Nutrition and Health
Series Editor: Adrianne Bendich

Riva Touger-Decker
Connie Mobley
Joel B. Epstein *Editors*

Nutrition and Oral Medicine

Second Edition

Humana Press

Nutrition and Health

Adrianne Bendich, Morristown NJ, USA, Series Editor

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On April 16, 2013 Dr. Dominick P. DePaola, author of the Foreword for the first edition of this textbook, passed away at the age of 70 at his home in Palm Beach Gardens, Florida. That the editors of this second edition of "Nutrition and Oral Medicine" so generously made the decision to dedicate this book to him is both fitting and proper, as very few people have influenced the study and the practice of the role of nutrition on oral health and disease as much as he. Through his advocacy, his leadership, and his research he was one of a handful of scientists, clinicians, and educators who propelled the evolution of the field from one based upon poorly substantiated folk medicine to an evidence-based discipline. In recognition of his role in this evolutionary, perhaps even revolutionary process, he received numerous honors during his lifetime; possibly the one he was most proud of was his being awarded honorary membership in the American Dietetic Association, the only dentist so honored.

Dom's contributions to health care and healthcare education went way beyond nutrition. As dean of three nationally prominent dental schools, as CEO and President of the nation's largest free standing dental research institute, and as past President of both the American Association of Dental Research and the American Dental Education Association, his influence is at least partially responsible for the adoption of concepts that today are considered basic tenets of healthcare education, including the interprofessional training of clinicians who are critical thinkers, who can adapt to a continuing changing environment and who not only care about the health of the individual patient but about the health of the public at large.

Upon hearing of the passing of Dom Depaola, Dr. Richard Valachovic, Executive Director of the American Dental Education Association, commented that "this is a sad day for dental education and research." I need to add that it was even a sadder day for those numerous individuals that he touched in a very personal way and, by so doing, transformed them and their careers. I feel extremely blessed that I was one of those individuals and who during my career knew Dom as a mentor, as a colleague and, most cherished by me, as a friend. He will be sorely missed. If consolation can be taken, it is from knowing that in some small way Dom DePaola lives on in those of us whose lives he influenced, both directly and indirectly, including many of the contributors to this textbook.

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Preface

This second edition of *Nutrition and Oral Medicine* addresses the complex, multifaceted relationships between diet/nutrition and oral health, explores proposed relationships among oral, systemic, and nutritional well-being and provides insights into interprofessional, comprehensive care for individuals. Chapters focus on diet, nutrition, and oral health promotion and disease prevention across the lifespan, oral and dental diseases and disorders, oral manifestations of systemic diseases, and discussions of the synergy between oral tissues and nutrients. Editors and authors include experts in nutrition and oral health from around the world. Oral and systemic diseases and orofacial pain syndromes are addressed with a focus on associations with and impact on nutrition status, the impact of medications and treatments on the head, neck, oral cavity and oropharynx and nutrition status. Oropharyngeal cancers are examined in light of nutrition etiologies, impact upon oral function, and diet intervention strategies. Suggested management strategies are paired with selected topics in oral health. Cutting edge research issues regarding the relationships between individual nutrients, other nutrient substrates, complementary and alternative medicine, and genetics and oral health/disease are covered. The links among compromised immunity, oral infections, and systemic disease and nutrient deficiencies in relation to oral diseases and systemic diseases are included as well as the impact of impaired host defense on oral and nutrition health.

The book is divided into five parts, synergistic relationships among nutrition, oral, and systemic health, between oral and systemic health, between nutrition and oral health, and between select diseases/conditions with nutrition and oral health interfaces and nutrition and oral medicine education and practice. Chapters examine the research and practice relative to the topic as well as address contemporary and proposed practices as appropriate. Several screening and education tools are included in the appendices for our readers to use for educational purposes. We hope our colleagues in oral, allied, and primary health and education and practice and students in the fields of nutrition/dietetics and dentistry as well as other disciplines whose research, practice, and education includes nutrition and oral medicine find the text a valuable resource.

Riva Touger-Decker
Connie Mobley
Joel B. Epstein

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The Series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Nutrition and Oral Medicine, Second Edition," edited by Riva Touger-Decker Ph.D., RD, CDN, FADA, Connie Mobley Ph.D., RD and Joel B. Epstein DMD, MSD, Diploma American Board of Oral Medicine, and FRCD(C) FDS RCS (Edin) clearly exemplifies the goals of the Nutrition and Health Series. The major objective of this comprehensive revised and updated text is to review the body of research on associations between diet/nutrition and oral health and disease as well as the growing importance of adequate dietary intake of the essential nutrients and sufficient calories to maintain normal weight, and improve indices of good health including oral health.

This updated volume includes chapters that discuss oral health as having healthy teeth as well as being free of chronic oral-facial pain conditions, oral and pharyngeal (throat) cancers, oral soft tissue lesions, birth defects such as cleft lip and palate, and scores of other diseases and disorders that affect the oral, dental, and craniofacial tissues. The book includes 20 up-to-date informative reviews of the current thinking about associations between oral health and diseases, systemic health, and diet/nutrition as well as the relationship between diet quality and the overall health of individuals as well as the importance of oral health in assuring the overall health of the individual. Of great importance, there are in-depth reviews by the leading researchers in the fields on the associations among chronic and infectious diseases, oral health, and diet and nutrition. Practicing health professionals, researchers, and academicians can rely on the chapters in this volume for objective data-driven sources about the complex interactions among oral health, systemic health, and nutritional status. This new comprehensive volume includes oral health and oral medicine as well as unique chapters that examine approaches to assessment of oral health and examination of the process

of curriculum development in the dental school. Thus, the book contains valuable chapters that are of great importance to the nutrition and oral health communities as well as for health professionals who have to answer patient, client, or graduate students questions about the newest clinical research on interactions and relationships among diet, nutrition, oral health, and overall health consequences.

"Nutrition and Oral Medicine, Second Edition" represents a thorough review of food consumption during the lifespan and how diet affects oral health and how the status of one's oral health can affect one's nutritional status. It is to the credit of Drs. Touger-Decker, Mobley, and Epstein that they have organized this volume so that it provides an in-depth overview of the critical issues involved in the determination of the best nutritional strategies for infants, toddlers, school-age children, adult, and senior populations that can be beneficial to their teeth, gums, and other structures within the oral cavity. The volumes' editors provide their in-depth knowledge and expertise to help the reader to understand the value of diet quality in the development of national dietary recommendations. Dr. Riva Touger-Decker Ph.D., RD, CDN, FADA is Professor and Chair of the Department of Nutritional Sciences—School of Health Related Professions and serves as the Director of the Division of Nutrition—Rutgers School of Dental Medicine, now part of the Rutgers University Biomedical and Health Sciences (formerly University of Medicine and Dentistry of New Jersey). Dr. Touger-Decker served as coeditor of the first edition of "Nutrition and Oral Medicine." She has been recognized by her colleagues and peers for her successful efforts to include nutrition in the dental school curriculum as well as her research findings. She has been awarded both the American Dietetic Association Medallion Award and Excellence in Dietetic Education Award; the American Society for Clinical Nutrition Dannon Institute Award for Excellence in Medical/Dental Nutrition Education and in 2008, the University of Medicine and Dentistry of New Jersey Excellence in Research Award, School of Health Related Professions and in 2012, she was elected a Fellow, New York Academy of Medicine. Dr. Joel B. Epstein DMD, MSD, FRCD(C) FDS RCS(Edin) is a consultant in the Division of Otolaryngology and Head and Neck Surgery at the City of Hope Hospital in Los Angeles, CA and is a Collaborative Member, Samuel Oschin Comprehensive Cancer Institute, and medical-dental staff at Cedars-Sinai Medical Center in Los Angeles, CA. He is a Fellow of the College of Dental Surgeons of Canada in Oral Medicine/Oral Pathology, a Fellow of the Royal College of Surgeons of Edinburgh, and a Diplomat of the American Board of Oral Medicine and was an examiner and President of the Board of Oral Medicine. He has been recognized for his expertise in oral cancer and oral complications of cancer therapy. Dr. Connie Mobley Ph.D., RD is Associate Dean of Research and Professor in the Department of Biomedical Sciences in the School of Dental Medicine at the University of Nevada Las Vegas, Las Vegas, NV. Dr. Mobley served as coeditor of the first edition of "Nutrition and Oral Medicine." She is internationally recognized for her leadership in interdisciplinary research in nutrition/diet, health promotion, and oral health. Along with Dr. Touger-Decker she is the coauthor of "Oral Health and Nutrition." She has held many positions of leadership in the Academy of Nutrition and Dietetics and is an active member of the International Association of Dental Research Nutrition Research Group.

The second edition of "Nutrition and Oral Medicine" contains 20 comprehensive chapters that are organized into five parts. Part I provides an overview and perspective on the importance of understanding nutritional terminology, diet quality, and the nutritional and overall health benefits of adopting high-quality diets for prevention of obesity before and during pregnancy and throughout childhood, adolescence, and adulthood. Focus is placed on the oral health consequences of the aging process and how these affect nutrient intakes and overall health. Chapter 1 presents a comprehensive review of the importance of diet quality and lays the foundation for understanding the basis of nutritional guidelines and recommendations. Chapter 2 examines the interaction between prospective mothers, parents, infants, and young children and the quality of foods consumed. The authors

have included over 140 references and eight tables and take an evidence-based approach to examine the underlying mechanisms contributing to the protective effects of nutritional adequacy on tooth development. We learn that maternal nutritional status directly impacts the development of both the enamel and dentin of the primary and permanent teeth during fetal growth. In addition, preconception nutritional status of the mother impacts the general health and birth outcomes of the infant. Topics include childhood caries, effects of diabetes, cystic fibrosis, and other childhood illnesses as well as birth defects involving the oral cavity. Chapter 3 reviews the relationship between nutrition and the aging process. There is a high prevalence of tooth loss with aging, especially in seniors at the poverty level, and tooth loss can directly affect diet via masticatory, sensory, salivary, and gastrointestinal changes. Declining oral health in aging adults is discussed with regard to malnutrition, oral surgery, periodontal disease, restorative oral care, temporal-mandibular joint disorders, and dysphagia. Chapter 4 in this part reviews the literature concerned with obesity and its role in oral health. There are potential links between certain oral bacteria and the risk of obesity that are discussed. The importance of an interdisciplinary team in the treatment of the obese individual is reviewed in-depth.

Part II looks at the interactions between oral health and systemic health and also contains a chapter that reviews the impact of certain medications on salivary glands, tooth structure, and other components of the oral cavity. Oral/systemic interactions that are discussed and tabulated include periodontal disease and diabetes and atherosclerotic cardiovascular disease; gingivitis and alterations in sex hormone levels; autoimmune diseases and salivary gland dysfunctions resulting in increased caries; cancer therapies and oral mucosal diseases; dysphagia resulting from neurogenic, myogenic, or other causes. Chapter 6 explores the interactions among prescription and over-the-counter (OTC) medications, nutrition, dietary supplements, and oral health and includes 12 relevant tables and over 100 references. Many of the drugs used by oral health care professionals can adversely affect nutrient absorption from foods as well as dietary supplements. Likewise, many prescription and OTC drugs can cause adverse effects in the oral cavity including oral lesions, stomatitis, reduced salivation, and decreased taste and smell sensations.

Part III of this volume contains four chapters that describe associations between nutrition and oral health. As indicated by the authors of Chapter 7 in this part: "Nutritional status and oral health are reciprocally related, and each one affects the other—a down-turn in nutrition impairs oral function." The chapter emphasizes the importance of fetal nutrition as calcification of the enamel on the deciduous teeth occurs early in fetal development and is dependent upon sufficient calcium in the pregnant mother's diet. The effects of deficiencies of vitamins A, D, C, B12, protein, and energy, calcium omega-3 fatty acids, and antioxidant nutrients on the oral cavity are examined in detail and well referenced. The interactions among the immune system, inflammation, nutrition, and the oral cavity as well as related systemic disease consequences are examined in a logical order in Chapter 8 that includes over 125 references and helpful tables and figures. The chapter describes the effects of autoimmune diseases, allergic reactions, infection, inflammation, with emphasis on periodontal diseases and immune responses on the structures and blood supply to the oral cavity. The next informative Chapter 9 reviews the numerous complementary and alternative medicine practices that may be used by patients either for reducing pain or other oral cavity symptoms or for systemic uses. The chapter includes overviews and useful tables on dietary supplements; both herbal and non-herb containing dietary supplements, homeopathy, Traditional Chinese Medicine, acupuncture, meditation and hypnosis, commonly used oral health drug–herb interactions, chiropractic and osteopathic medicine, and use of massage with reference to dental practices. Chapter 10 in this part contains a unique evaluation of the current state of the science linking genetic factors to oral health. The author informs us that the exploration of gene-based mechanisms in dental medicine is in its early stages. Genetic variations have been associated with caries development, enamel formation, gingivitis, and periodontitis. As an example, the new field of pharmacogenomics helps to predict patient responses

to medication. The chapter, which contains over 175 references, includes an in-depth discussion of the effects of changes in DNA at the molecular, cellular, organ, and organism levels and links these to effects in the oral cavity.

Part IV contains eight chapters that examine key disease conditions with nutrition and oral health relationships. Diabetes is the first systemic disease reviewed that has a strong association with oral health. Oral complications include increased risk of periodontal disease, root caries, and candidiasis as well as neuropathic conditions such as burning mouth and reduced salivary flow. Oral surgery in diabetics can be adversely affected by decreased wound healing. There are excellent discussions and tables that outline the management of the oral health as well as nutritional issues seen in diabetic patient in the dental office. Chapter 12 examines the epidemiological evidence for prevention of cancer of the lip, oral cavity, oropharynx, and salivary glands. Such cancers and treatment of cancer can result in pain, disfigurement, speech impairment, and chewing and/or swallowing difficulties leading to among other effects, nutritional compromise. The author describes the two major classifications of oral cancers, oral squamous cell carcinoma, and oropharyngeal cancer and their links with tobacco and alcohol abuse, nutritional compromise in developing countries, and association with human papilloma virus (HPV). The chapter reviews the survey data concerning fruits, vegetables, breads, grains and cereals, dairy, coffee and tea, fibers, vitamins, and minerals with regard to their associations with decreased risk of oral cancers. Chapter 13 reviews the effects of head and neck cancer and cancer treatment on the oral cavity as well as nutritional consequences of these effects. It is estimated that greater than 90% of head and neck cancer patients develop mucositis and oral complications during treatment. In addition, side effects of the tumor or treatment may impact mouth opening, biting, chewing, or swallowing, resulting in compromised oral consumptions of foods, fluids, and/or medications. Specific toxicities of the oral cavity include mucositis, hyposalivation, taste changes, mucosal sensitivity, odynophagia, dysphagia, mucous production, and edema. Potential nutritional impacts and considerations are tabulated for the reader.

Chapter 14 reviews in detail the effects of HIV infection on the oral cavity and head and neck areas. Oropharyngeal fungal infections, bacterial and viral diseases, along with stomatitis and periodontitis, are frequently associated with pain and can lead to reduced food intake. Esophagitis and oral and esophageal candidiasis can cause painful mastication, drinking, and swallowing, further compromising appetite and intake. Taste change due to infection or other causes such as medications may impact food selection. There are also tumors including lymphoma and Kaposi's sarcoma that can occur in the oral cavity and adversely affect oral intake. Oropharyngeal fungal infections may cause a burning painful mouth, taste change, and dysphagia. Inclusion of the oral health care provider in the treatment of the HIV-infected patient is critical to maintaining their nutritional status. Similarly, in patients with autoimmune diseases, there can be serious, painful manifestations in the oral cavity. Chapter 15 examines the impact on oral health and nutrition in patients with the following autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, and Sjögren's syndrome, and the mucocutaneous disorders of pemphigus vulgaris and mucous membrane pemphigoid. The chapter is well organized and provides a review of the pathogenesis, clinical features, diagnosis, treatment, a separate section on oral health and nutrition complications, and management for each included autoimmune disease. Osteoporosis is another disease that has manifestations in the oral cavity. Chapter 16 reviews the general characteristics of osteoporosis and also the newer thinking about the link between bone loss in the skeleton and bone loss in the head and neck areas. The connection is via alveolar bone loss. Alveolar bone loss occurs with tooth loss and is an outcome in periodontal disease. Alveolar bone is the type of bone that supports the teeth. In periodontal disease, bacteria can initiation an inflammatory response that leads to alveolar bone loss. It has been speculated that osteoporosis reduces alveolar bone quantity and quality, thereby exacerbating the periodontal disease process. Periodontal disease is the major cause

of tooth loss that impacts the ability to consume a varied diet containing foods such as meat, nuts, hard cheeses, etc. The chapter also describes the potential adverse effects of osteoporosis drugs on the oral cavity.

Chronic orofacial pain can be considered by the dental/medical community as a disease. Chapter 17 reviews chronic orofacial pain disorders and their diagnosis and treatments. Associations between chronic orofacial pain disorders and diet and nutrients are discussed and approaches to dietary management are included. Chronic orofacial pain is often classified by the symptoms and organ systems involved into four major types: musculoskeletal, neuropathic, vascular pain, and psychogenic/psychological pain and/or patients may suffer from pain from overlapping conditions. Effects of the medications used to treat chronic orofacial pain are reviewed with regard to their impact on nutrient intakes and diet. The last chapter in this part examines the effects of oral surgery and acute and postsurgical pain on food intake and nutritional status. The authors indicate that approaches to diet and feeding patients undergoing oral and maxillofacial surgical procedures, including dentoalveolar, maxillofacial trauma, and orthognathic surgical procedures as well as cleft lip and palate surgery are discussed in this chapter that includes several tables and 10 helpful figures. The chapter focuses on oral surgeries and known and postulated impacts on diet and nutrition and suggestions for nutritional support for individuals undergoing oral and dental surgeries.

Part V of this comprehensive volume includes two unique chapters that will be of great value to oral health care providers and their students. Chapter 19, written by the primary editor of this volume outlines the process of assessing nutritional risk in the oral care practice. Health and nutrition risk screening in the dental setting includes a combination of subjective questions relative to diet, oral health status, biting and chewing ability, and body weight history as well as objective assessment of height, weight, and the condition of the oral cavity. The chapter includes descriptions of screening tools, and relevant tables and figures. The last chapter describes the components that need to be included in the development of a curriculum for oral health care professionals that includes nutrition education. The chapter is written by two of the coeditors and they have both been recognized as leaders in the development of such curricula. The chapter emphasizes the importance of interprofessional education and training across all of healthcare providers and includes unique approaches to nutrition education. The chapter includes a historic perspective concerning the inclusion of nutrition topics in the pre-dental, dental, and continuing dental education curricula. Two valuable appendices are included in the volume. The first includes a comprehensive list of web resources for diet and nutrition-related information. The second appendix includes numerous diet education tools that will be most relevant to nutrition health professionals and their clients and patients.

The logical sequence of the Parts in the volume as well as the chapters within each Part enhances the understanding of the latest information on the current standards of practice in dentistry and the role of nutrition considerations in patient care. This comprehensive resource has great value for academicians involved in the education of graduate students and postdoctoral fellows, dental students and oral health care professionals, allied health professionals, and public health nutritionists and dietitians who plan to improve the diet quality for patients at risk for macro and/or micronutrient deficiencies due to health issues involving the oral cavity. Moreover, many of the chapters provide unique resources including lists of relevant websites, professional organizations, and other resources that are of value to any health professional interested in nutrition and oral medicine.

The volume contains over 100 detailed tables and figures that assist the reader in comprehending the complexities of food choices, quantification of intake and availability of essential nutrients, composition of diets, and the nutritional needs of infants and children, pregnant women, other healthy adults, and seniors. There are in-depth discussions of the behavioral aspects of eating and the effects of primary diseases of the oral cavity as well as secondary effects of chronic diseases including cancer, diabetes, osteoporosis, and HIV infection. The overriding goal of this volume is to provide the health professional including dentists, physicians, and nutrition professionals with

balanced documentation and awareness of the newest research and technical approaches to assessing the nutritional consequences of conditions that affect the head and neck structures and functions such as taste, swallowing, and chewing. A number of the chapters broaden one's appreciation of the complexity of the interactions among genetics, health and disease, nutrient deficiencies, and new issues of psychological aspects to food choice in the patient with tooth loss as one example. Hallmarks of the 20 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. There are over 1,600 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains two useful educational and practice-oriented appendices as well as a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics of determining the nutritional status of the dental patient, diet quality, historic perspectives, and descriptions of the most common conditions that affect the structures within the oral cavity that impact the capability to consume a diet that varies in textures, densities, and flavors. The importance of oral health and diet quality of pregnant women, infants, children, seniors, and other population groups is examined in-depth. The overarching goal of the editors is to provide fully referenced information to oral and related health professionals so they may have a balanced perspective on the value of patient nutrition evaluation by oral health professionals as an integral part of their practices.

In conclusion, "Nutrition and Oral Medicine, Second Edition," edited by Riva Touger-Decker Ph.D., RD, CDN, FADA, Connie Mobley Ph.D., RD, and Joel B. Epstein DMD, MSD, Diploma American Board of Oral Medicine, FRCD(C) FDS RCS (Edin) provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and comprehensive volume on the current state of incorporating nutrition into dental education and practices. Additionally, practice-oriented recommendations for the determination of diet and nutritional status using validated assessment tools are included along with relevant discussions of the management of clients' and patients' nutritional requirements. The updated second edition of this well-respected volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich Ph.D., FASN, FACN

About the Series Editor

Dr. Adrianne Bendich, Ph.D., FASN, FACN has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 120 volume editors that have developed the 60+ well-respected and highly recommended volumes in the Series.

In addition to "Nutrition and Oral Medicine, Second Edition" edited by Dr. Riva Touger-Decker, Dr. Joel B. Epstein and Dr. Connie Mobley, major new editions in 2012–2013 include:

1. "Nutrition in Kidney Disease, Second Edition" edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2013
2. "Handbook of Food Fortification and Health, volume I" edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
3. "Handbook of Food Fortification and Health, volume II" edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
4. "Diet Quality: An Evidence-Based Approach, volume I" edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
5. "Diet Quality: An Evidence-Based Approach, volume II" edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
6. "The Handbook of Clinical Nutrition and Stroke" edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
7. "Nutrition in Infancy, volume I" edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
8. "Nutrition in Infancy, volume II" edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
9. "Carotenoids and Human Health" edited by Dr. Sherry A. Tanumihardjo, 2013
10. "Bioactive Dietary Factors and Plant Extracts in Dermatology" edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013

11. "Omega 6/3 Fatty Acids" edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
12. "Nutrition in Pediatric Pulmonary Disease" edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
13. "Magnesium and Health" edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012
14. "Alcohol, Nutrition and Health Consequences" edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
15. "Nutritional Health, Strategies for Disease Prevention" third edition, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
16. "Chocolate in Health and Nutrition" edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
17. "Iron Physiology and Pathophysiology in Humans" edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included Vitamin D, second edition edited by Dr. Michael Holick; "Dietary Components and Immune Function" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; "Bioactive Compounds and Cancer" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "Modern Dietary Fat Intakes in Disease Promotion" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "Iron Deficiency and Overload" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "Nutrition Guide for Physicians" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; "Nutrition and Metabolism" edited by Dr. Christos Mantzoros; and "Fluid and Electrolytes in Pediatrics" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: "Handbook of Drug-Nutrient Interactions" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "Probiotics in Pediatric Medicine" edited by Dr. Sonia Michail and Dr. Philip Sherman; "Handbook of Nutrition and Pregnancy" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; "Nutrition and Rheumatic Disease" edited by Dr. Laura Coleman; "Nutrition and Kidney Disease" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; "Nutrition and Health in Developing Countries" edited by Dr. Richard Semba and Dr. Martin Bloem; "Calcium in Human Health" edited by Dr. Robert Heaney and Dr. Connie Weaver; and "Nutrition and Bone Health" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC, and is the editor of ten books including "Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fourth Edition" coedited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics, and Antioxidants*, and has served as Associate Editor for "Nutrition" the International Journal; served on the Editorial Board of the Journal of Women's Health and Gender-based Medicine, and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is an Adjunct Professor at Rutgers University. She is listed in the Who's Who in American Women.

Biography of Volume Editors

Dr. Riva Touger-Decker Ph.D., RD, CDN, FADA is a Professor and Chair of the Department of Nutritional Sciences—School of Health Related Professions and Director of the Division of Nutrition—Rutgers School of Dental Medicine at Rutgers University Biomedical and Health Sciences (formerly University of Medicine and Dentistry of New Jersey). Dr. Touger-Decker was a lead editor of the first edition of "Nutrition and Oral Medicine." She is a registered dietitian and is internationally recognized for her expertise and leadership in nutrition and oral health/dental education, nutrition focused physical exam, and advanced practice dietetics education. She has authored multiple peer reviewed publications on nutrition and oral health and clinical nutrition and is the co-author of the "Oral Health and Nutrition" position of the Academy of Nutrition and Dietetics. She is on the editorial board of *Topics in Clinical Nutrition* and the *Journal of the American Dental* Association where she represents the Nutrition Research Group of the International Association of Dental Research. She has been awarded the American Dietetic Association Medallion Award and Excellence in Dietetic Education Award; the American Society for Clinical Nutrition Dannon Institute Award for Excellence in Medical/Dental Nutrition Education and the UMDNJ SHRP Excellence in Research Award. She is also an elected Fellow of New York Academy of Medicine. Dr. Touger-Decker holds degrees from New York State University College at Buffalo and New York University.

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Part I
Synergistic Relationships Between Nutrition and Systemic and Oral Health

Chapter 1
Impact of Dietary Quality and Nutrition on General Health Status

Teresa A. Marshall and Connie C. Mobley

Keypoints

- Dietary excesses and inadequate physical activity increase risk of obesity and chronic diseases including cardiovascular disease, diabetes, and some cancers
- Protein energy malnutrition, nutritional anemia, nonalcoholic liver disease, and osteoporosis are associated with nutrient deficiencies that increase risk of oral diseases and conditions
- Government, health agencies, and health foundations define dietary guidelines and patterns supported by evidence-based research and presented in formats to increase health promotion and disease prevention
- Oral health care professionals and nutrition professionals can participate in healthcare teams to provide nutrition education and counseling to promote optimum oral health

Keywords Dietary quality · Nutritional status · Health status · Chronic disease · Dietary excess · Obesity · Cardiovascular disease · Dyslipidemia · Hypertension · Nonalcoholic fatty liver disease · Protein energy malnutrition · Insulin resistance · Dietary guidelines

Introduction

Dietary quality and nutritional status are important for the promotion and maintenance of health throughout the life span and inclusive among the multiple determinants of chronic diseases. They occupy a prominent position in disease prevention and health promotion. When combined with other modifiable risk factors, such as tobacco or physical activity, diet and nutrition may have an additive or multiplier effect on the prevalence of chronic diseases, including cardiovascular disease (CVD), diabetes, obesity, cancers, osteoporosis, and oral diseases [1]. Furthermore, nutritional status is a primary determinant of responses to medical therapies effective in the treatment of an array of physical and iatrogenic conditions.

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This chapter discusses the synergistic relationships between diet and nutrition and other determinants of health and provides a contemporary perspective of related nutrition research. Foundations for practices that include diet and nutrition with respect to both primary and secondary prevention and management of prevalent diseases are briefly reviewed.

Definition of Terms

Nutrition is the sum of dietary quality and physiological and biological activity necessary to maintain life. The multidimensional impact of nutritional status on health reflects the intricacies of nutrition. *Dietary quality* is often expressed in terms of agricultural or industrial sources of food, nutrient content, organoleptic appeal, variety, and adequacy. Food and foodstuffs are chemical compounds configured by nature or formulated by manmade processes to mimic nature. Beyond human milk for infants, there is no one food that meets all nutritional needs and thus it is a combination of foods and adequacy of the diet that defines quality. Dietary quality to a large extent determines health. Between 20 and 30 biologically distinct types of foods are required for healthy diets in the course of 1 week [1]. Diets evolve over time, are influenced by many factors, and represent complex sociodemographic and political/economic environments associated with availability and accessibility of food. Nutrition is a scientific term that describes how diets meet energy output and balance the needs and demands of cellular activity, growth, and tissue maintenance [2]. However as a discipline, it has been defined "as the study of food systems, foods and drinks and their nutrient and other constituents and of their interactions within and between all relevant biological, social and environmental systems" [2, p. 697]. An optimum diet, via biological processes, supports general health, health promotion, and disease prevention but has yet to be precisely identified for each individual.

Both undernutrition and overnutrition are forms of *malnutrition* [3]. Nutrient inadequacies as well as malabsorption, impaired utilization, or increased excretion of a nutrient, can result in undernutrition, whereas excessive intakes or decreased excretion of nutrients contribute to toxicities and overnutrition [3]. During several million years of human evolution, nutrients and physical activity have influenced gene expression and defined opportunities for both health and susceptibility to disease [4]. Environmental factors determine which individuals among those who are genetically susceptible will develop an illness or chronic condition [4].

Nutritional status is a measurement of the extent to which an individual's defined physiological need for nutrients is being met by his or her dietary patterns and choices [5]. Thus measurements of nutritional status entail review of dietary intake, biochemical markers of nutrient status, and anthropometric measures as well as assessment of clinical indices of health [5].

Dietary guidelines are developed based on available population-based nutritional status summaries within a specific country or region and their associations with indices of disease risk and a defined health status [6]. For example, number of food groups alone described in dietary guidelines in over 25 different countries within The European Food Council ranged between 4 and 12 distinct groups [7]. These food based guidelines are intended to be suited to a country's environmental, social, and cultural context and vary accordingly [7]. By providing markers for assessing health status, recommendations about lifestyle behaviors to enhance positive health outcomes designed to improve the public health status of a region or nation can be targeted [6, 7].

Diet, Physical Activity, and Chronic Disease

Five chronic diseases—Cardiovascular Disease (CVD), cancers, stroke, chronic obstructive pulmonary diseases, and diabetes—accounted for the majority of deaths in the United States in 2010 [8]. Approximately 75% of healthcare costs each year are attributed to treatment of chronic diseases [9].

Dietary Excess and Inadequate Physical Activity

Chronic diseases are largely preventable and associated with lifestyle behaviors—diet, physical activity, and tobacco use [10]. Excessive intakes of energy-dense, highly processed foods and a lack of physical activity contribute to overweight, obesity and obesity-related diseases (e.g., insulin resistance, hyperlipidemias, CVD, select cancers, nonalcoholic fatty liver disease) [10]. The prevalence of obesity has increased among all age groups, and obesity-related diseases are observed at increasingly younger ages [10]. Among adults living in the United States in 2009–2010, the prevalence of obesity was 35.5% among men and 35.8% among women with no significant change compared with 2003–2008 [10]. Adults 60 and older, particularly women, were more likely to be obese compared to younger adults in 2010 [10]. Among younger obese adults, decreased life expectancy is increased [11]. Social and economic costs of obesity and obesity-related diseases are enormous, and have increased from approximately 6.5% of US healthcare expenditures in 1998 to 9.1% in 2008 [12].

Obesity

Obesity is a heritable disease driven by complex interactions between genetic and environmental factors [13]. It is defined as excessive body fat, and typically assessed by evaluating the weight for height relationship expressed as the Body Mass Index (BMI; e.g., weight in kg/height in m^2) [14]. The National Heart, Lung and Blood Institute (NHLBI) guidelines categorize obesity using BMI of 25–29.9 to reflect overweight; 30–34.9 to reflect Class I obesity; 35–39.9 Class II obesity and over 40 Class III obesity [14]. Energy consumed in excess of expenditures is converted to fat and stored in adipocytes or fat cells. Adipocyte capacity is limited; once full, pre-adipocytes differentiate, increasing adipocyte numbers. During weight loss, adipocytes may decrease in size, but do not go away, making weight loss difficult [15]. Obesity-related diseases and conditions, such as diabetes, select cancers, CVD, gallstones, metabolic syndrome among others, are more closely associated with adipocyte size and location (e.g., central deposition) than with total body fat, thus reduction of adipocyte size is an appropriate weight-loss goal [15, 16].

Advances in our understanding of adipose tissue have identified significant metabolic activity within adipose tissue [17, 18]. Visceral or central adiposity is associated with release of numerous proinflammatory molecules [17, 18]. These inflammatory mediators contribute to chronic inflammation in obese individuals, particularly those with central adiposity, and may link obesity to systemic complications [17, 18].

Weight loss is achieved when energy expenditure exceeds energy intake. Achievement and maintenance of ideal body weight (i.e., a return to both normal number and size of adipocytes) is virtually impossible and not an appropriate goal for most obese individuals [19]. Contemporary research suggests that a 10% weight loss is sufficient to decrease risk of obesity-related diseases, and is reasonable to achieve and maintain [20]. The Diabetes Prevention Program demonstrated that less than 10% weight loss in overweight and obese individuals significantly decreased risk of developing type two diabetes [20] and was associated with reduction in inflammatory mediators [17, 18].

Table 1.1 Dietary Guidelines for Americans, 2010

1. Build a healthy plate (See ChooseMyPlate)
2. Cut back on foods high in solid fats, added sugars, and salt
3. Eat the right amount of calories for you
4. Be physically active your way

Reference [6] http://www.cnpp.usda.gov/Publications/MyPlate/DG2010Brochure.pdf. Accessed: 5/6/2013

Because loss of all excess body fat is not realistic, prevention of obesity through the establishment of appropriate dietary and physical activity patterns early in life is important. Food characteristics (e.g., energy-dense, processed), eating behaviors (e.g., binging, compulsive overeating), and environmental factors (e.g., marketing, portion sizes, and accessibility) contribute to increased energy intake, whereas excessive sedentary leisure activities (e.g., television, video games), safety issues (e.g., latchkey kids, absence of sidewalks or parks), and technological advances (e.g., automobiles, labor-saving devices) are thought to lower energy expenditure [21]. A diet based on low-fat, minimally processed foods, and adequate in plant foods consistent with the US Department of Agriculture (USDA) and the Department of Health and Human Services (HHS) Dietary Guidelines for Americans [6] is described in Table 1.1 and illustrated in Fig. 1.1. Chapter 4, **Obesity and Oral Health across the Life Span** addresses this topic in further detail.

Insulin Resistance

Insulin resistance is characterized by impaired insulin function. Removal of glucose and free fatty acids from serum is reduced with insulin resistance; excess insulin is secreted to compensate and maintain normal serum glucose and free fatty acid concentrations. If insulin resistance reaches the threshold where compensation is lost serum glucose levels increase and the individual meets criteria for Type 2 diabetes [22]. Insulin resistance without elevated glucose is not benign; resulting hypertension and dyslipidemia (e.g., small, dense low-density lipoprotein [LDL], hypertriglyceridemia and decreased high-density lipoprotein [HDL]) increase risk of CVD [23]. Individuals with central adiposity are at increased risk for insulin resistance and Type 2 diabetes. However, reduction of adipocyte size has been shown to improve insulin response.

Insulin resistance is improved or reduced by weight loss and physical activity [22]. High carbohydrate diets, particularly those high in simple sugars, appear to aggravate insulin resistance. Therefore, diets moderate in both carbohydrate and fat, with emphasis on complex carbohydrate and unsaturated fats are recommended [24]. Chapter 11 on **Diabetes** addresses diabetes and oral health in greater depth.

Cardiovascular Disease

CVD the primary cause of mortality in the United States, has been a focus of nutrition and physical activity clinical trials since the 1940s [25]. Beginning with the Framingham studies in 1967, physical activity was found to reduce the risk of CVD, whereas obesity was found to increase the risk [25].

CVD is characterized by atherosclerotic disease in the blood vessels supporting the heart [26]. Associated risk factors include obesity, insulin resistance, hypertension, and dyslipidemia [27]. The American Heart Association (AHA) diet and lifestyle goals for CVD risk reduction, prevention

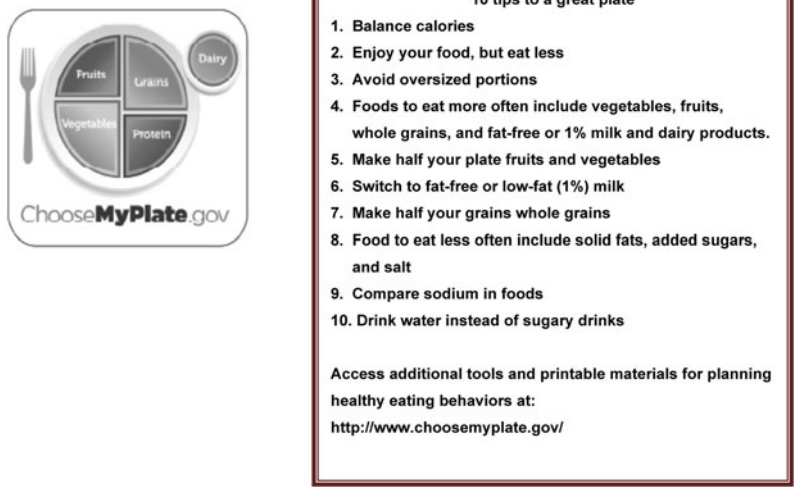

Fig. 1.1 US Department of Agriculture (USDA) ChooseMyPlate. (*Source* From Ref. [8])

Table 1.2 American Heart Association diet and lifestyle goals for CVD risk reduction

1. Consume an overall healthy diet
2. Aim for a healthy body weight
3. Aim for recommended levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides
4. Aim for a normal blood pressure
5. Aim for a normal blood glucose level
6. Be physically active
7. Avoid use of and exposure to tobacco products

Reference [28]

and management target risk factors and include reduction of energy intake and increased physical activity [27, 28]. See Table 1.2.

Dyslipidemia

Athrogenic dyslipidemia includes a spectrum of disorders characterized by abnormal serum lipid levels [5]. Serum lipid levels are subject to genetic and environmental influences; both diet and physical activity can modify serum lipid levels [29]. Four components typically are included in this condition because it does not result from a single metabolic defect but from the coexistence of several defects associated with obesity, diets high in fats leading to elevated serum cholesterol, physical inactivity, aging, and genetics [5]. Hypercholesterolemia, characterized by, elevated LDL cholesterol and low HDL cholesterol; hypertriglyceridemia associated with mild to moderate triglyceride levels; small and dense LDL particles, and low HDL-cholesterol are associated with an increased risk of CVD [29].

Weight loss and physical activity can lead to improvement in these serum lipid levels [29]. Additionally, a decrease in total dietary fat, saturated fat, and cholesterol will decrease LDL-cholesterol levels, and a diet containing moderate complex carbohydrates, low simple sugars,

Food Group	Daily Servings	Recommended Servings Size
Grains*	6-8	1 slice bread 1 ounce cereal ½ cup cooked cereal, rice or pasta
Vegetables	4-5	1 cup raw leafy vegetables ½ cup cut-up raw or cooked vegetables ½ cup vegetable juice
Fruits	4-5	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen or canned fruit ½ cup fruit juice
Fat-free or low-fat Milk or milk products	2-3	1 cup milk or yogurt 1 ½ ounce of cheese
Lean Meat, Poultry Or Fish	6 or less	1 ounce cooked meat, poultry or fish 1 egg
Nuts, Seeds, or Legumes	4-5 per week	1/3 cup or 1 ½ ounce nuts 2 Tablespoons Peanut Butter 2 Tablespoons or ½ ounce seeds ½ cup cooked legumes (dry beans & peas)
Fats and Oils	2-3	1 teaspoon soft margarine 1 teaspoon vegetable oil 1 Tablespoon mayonnaise 2 Tablespoons salad dressing
Sweets and Added Sugars	5 or less per week	1 Tablespoon sugar, jelly or jam ½ cup sorbet or gelatin 1 cup lemonade

*Whole Grains are recommended

Fig. 1.2 Following the Dash Diet Plan. References [33, 34]

moderate fat, and limited alcohol decreases triglyceride levels [29]. Hypertriglyceridemia, which often presents with insulin resistance among individuals at risk for or with diabetes, is also indicative of risk of CVD [30].

Hypertension

High blood pressure is defined by the National Heart Lung and Blood Institute (NHLBI) as a systolic pressure of 140 mmHg or greater, diastolic pressure of 90 mmHg or greater, or use of antihypertensive medication [11]. As the BMI of individuals has risen in the US, so has the prevalence of hypertension associated with insulin resistance and risk for CVD and stroke [29].

Lifestyle changes, including weight management, diet modification, and physical activity are recommended for management of hypertension [1, 31]. Researchers have shown that blood pressures can be reduced with the *Dietary Approaches to Stop Hypertension* eating plan, a plan that is low in saturated fat, cholesterol, and total fat and that emphasizes fruits, vegetables, and fat-free or low-fat milk and milk products [32]. Diets limited in sodium from processed foods, reduced in calories, but adequate in calcium, magnesium, and phosphorous may further lower blood pressure [33, 34]. See Fig. 1.2.

Cancer

Cancer, defined as a disease of deoxyribonucleic acid (DNA), is characterized by uncontrolled growth of cells secondary to initiating and promoting factors and failure of the body to inhibit the uncontrolled growth [35]. Dietary factors have been associated with initiation (e.g., aflatoxin, nitrosamines) and promotion (e.g., salt, fat) [1]. Obesity increases risk of certain cancers, including cancers of the breast in postmenopausal women, colon and rectum, endometrium, kidney and adenocarcinoma of the esophagus and pancreas as well as cancer of the gallbladder, liver, non-Hodgkin lymphoma, cancer of the ovary, aggressive prostate cancer and colorectal cancer [36]. Alcohol consumption is an established risk factor for cancers of the mouth, pharynx, larynx, esophagus, liver, colorectum, pancreas, and female breast [36]. Antioxidants (e.g., vitamins A, C, and E) and folic acid found in fruits and vegetables protect against a range of cancers including head and neck, stomach, lung, pancreas and prostate [36, 37]. Dietary recommendations to prevent cancer include: weight management; moderate energy and fat intakes; diets limited in red and processed meats and alcohol; and a diet rich in fruits and vegetables [36, 37]. Chapter 12 on **Oral Pharyngeal Cancer Epidemiology and Prevention** further addresses this topic.

Nonalcoholic Fatty Liver Disease

Primary Nonalcoholic Fatty Liver Disease (NAFLD), defined as the presence of hepatic steatosis in the absence of alcohol abuse, is associated with obesity and attributed to insulin resistance which promotes hepatic lipid accumulation [38, 39]. Untreated, NAFLD may progress to hepatitis with increased risk of cirrhosis, hepatocellular carcinoma, and liver failure. Treatment strategies target accompanying metabolic risk factors; both weight loss and improved insulin sensitivity are associated with improved liver function.

Dietary Deficiency and Diseases

Dietary deficiencies occur less frequently than dietary excesses in the US, yet remain a significant public health burden, particularly for vulnerable populations [40]. Poverty and environmental barriers are associated with insufficient food intake, reliance on highly processed foods, narrow food choices, and limited nutrient intakes. Young children and the elderly are particularly vulnerable [40].

Protein Energy Malnutrition

Protein energy malnutrition (PEM) is characterized by weight, stature, or weight for stature indices below the fifth percentile for age [41]. In children PEM is the result of inadequate energy or protein to maintain weight and support growth [41]. Diets characterized by insufficient energy and protein are typically deficient in multiple nutrients [23, 24]. The etiology of growth failure may be multifactorial [41, 42]. In addition to physical signs, individuals with PEM may exhibit cognitive delays, behavioral problems, and emotional problems secondary to PEM [41, 42].

Management of PEM includes identification and resolution of the underlying problem (e.g., access to food, dysphagia, and food preparation barriers). Provision of appropriate and adequate foodstuff, including a variety of foods from all food groups, vitamin and mineral supplementation when food acceptance is severely limited, and limitation of energy-dense beverages with structured meals and snacks are recommended [40].

Anemias

Anemia is characterized by reduced red blood cell volume, insufficient hemoglobin, and reduced oxygenation of body tissues. The World Health Organization defines nutritional anemia as a condition in which the hemoglobin concentration is below the level that is normal for a given individual, due to deficiency of one or more of the nutrients required for hemopoiesis, or a condition in which the hemoglobin concentration can be raised by increasing the amount of iron, folic acid or vitamin B_{12} that can be absorbed [43–45]. Iron-deficiency anemia is a public health burden of infants, young children, and pregnant women, particularly those living in poverty. In addition to anemia, iron deficiency is associated with growth failure, impaired immune function, learning difficulties, and behavioral problems [43]. Folic acid deficiency have been identified as a risk factor for neural tube defects and, through associations with elevated homocysteine levels, CVD [44]. Vitamin B_{12} deficiencies are associated with cognitive declines in the elderly and elevated homocysteine levels with increased risk of CVD [44].

Management of nutritional anemia requires careful identification of the deficient nutrient; folic acid supplementation will correct a vitamin B_{12} deficiency anemia, but not concurrent neurological damage associated with the vitamin B_{12} deficiency. Iron-deficient anemia may be treated with supplemental iron and iron-containing foods [43]. Folic acid-deficient anemia is treated with supplemental folic acid and folic acid-containing foods. Supplemental folic acid is recommended for women at risk for pregnancy [44]. Vitamin B_{12} deficiency is treated with supplemental vitamin B_{12} and vitamin B_{12}-containing foods (e.g., animal products) if the diet is inadequate; supplemental vitamin B_{12} if gastric hydrochloric acid production is reduced; and by injection of vitamin B_{12} if intrinsic factor, which is required for absorption, is limited [45]. Table 1.3 lists possible causes of nutritional anemia, associated oral health conditions, treatment options and dietary sources recommended to improve outcomes.

Osteoporosis

Osteoporosis is characterized by decreased bone density and quality and is associated with an increased risk of fracture [46]. Although fractures do not typically occur in younger adults, osteoporosis may be considered a pediatric disease because most bone accrual occurs during this life stage [46]. Bone accrual is influenced by genetic and environmental factors, including diet, physical activity, and body size. Inadequate dietary calcium and insufficient vitamin D (either dietary or sunlight exposure) are associated with reduced bone density [47].

Maximization of bone density is a primary strategy for prevention of osteoporosis [46]. Diets high in calcium and vitamin D (e.g., dairy products) and limited in low nutrient beverages (e.g., soft drinks) are recommended [1]. Chapter 16 on **Osteoporosis** covers this topic in greater depth.

Dietary Guidelines for Optimum Health

One of the greatest challenges in contemporary US health care is the shift from the management of acute episodes of illness toward the prevention and management of chronic conditions. Although the healthcare provider manages acute episodes, effectiveness of chronic disease management ultimately depends on the patient's lifelong adherence to diet and exercise regimens and response to symptoms [48]. Centers for Disease Control and Prevention (CDC) estimated that $92 billion in healthcare costs was associated with physical inactivity in 2009 [48]. Scientific evidence indicates that when clear and compelling health information is conveyed, the public is engaged [49, 50].

Table 1.3 Anemia associated with iron, folic acid and vitamin B_{12} deficiency

Nutritional anemia	Cause	Relative oral health conditions in untreated anemia	Treatment	Recommended dietary sources
Iron deficiency anemia	Blood loss	Angular Cheiliosis	Blood transfusion	Meat
	Poor diet		Iron injections	Turkey
	Inability to absorb iron	Pallor of lips and oral mucosa	Intravenous iron therapy	Seafood
		Glossitis	Increased intake of dietary iron	Iron-fortified foods Beans
		Sore, burning tongue	Iron supplementation per healthcare provider instructions	Tofu
		Atrophy, denudation of filiformpapillae		Whole Egg
		Pemphigus		Dried fruits
		Candidosis		Spinach and other dark green leafy vegetables.
		Increased risk for periodontitis		
Folic acid deficiency anemia or megaloblastic anemia[a]	Increased need for folic acid due to growth and development	Angular Cheiliosis	Dietary supplements	Bread, pasta, and rice fortified with folic acid
		Mucositis	Increased intake of dietary folic acid	
	Poor absorption	Sore or burning tougue		Spinach and other dark green leafy vegetables
	Poor diet inadequate in dietary sources of folic acid	Glossitis		Black-eyed peas and dried beans
		Pemphigus		
	Drug nutrient interactions	Candidosis		Beef liver
	May mask a Vitamin B_{12} deficiency and diagnosis requires test that assess status of both vitamins	Aphthous-stomatitis		Eggs
		Aphthous-ulcers		Bananas, oranges, orange juice, and some other fruits and juices

(continued)

Table 1.3 (continued)

Nutritional anemia	Cause	Relative oral health conditions in untreated anemia	Treatment	Recommended dietary sources
Vitamin B_{12} deficiency anemia or Prenicious Anemia (may be macrocytic or megaloblastic)[a]	Lack of intrinsic factor necessary for Vitamin B_{12} absorption	Angular Cheiliosis	Vitamin B_{12} injections or supplements depending on presence of intrinsic factor	Foods fortified with vitamin B_{12}, such as breakfast cereals, soy-based beverages and vegetarian burgers
	Poor diet inadequate in dietary sources of Vitamin B_{12}	Sore/burning mouth Glossitis Pemphigus	Increased intake of dietary sources of Vitamin B_{12}	Meats such as beef, liver, poultry, and fish
	Secondary to surgery, intestinal diseases or drug nutrient interactions	Candidosis		Eggs and dairy products (such as milk, yogurt, and cheese)
		Apthous Stomatitis/ mucositis Hemorrhagic gingiva Halitosis Epithelial dysplasia of oral mucosa Aphthous-ulcers Neurological weakness including face tremors (numbness, tingling) Taste distortion Delayed wound healing Xerostomia		

[a] Describes alteration in the size of the red blood cells

References [5, 43–45]

Table 1.4 American agency and health-based organization dietary guidelines

Dietary Guidelines for Americans[a]	American Heart Association[b]	American Cancer Society[c]
Build a healthy plate (See ChooseMyPlate)	Achieve a Body Mass Index <25 kg/m^2	Achieve and maintain a healthy weight throughout life
Cut back on foods high in solid fats, added sugars and salt	Increase vegetable and fruit intake	Consume a healthy diet emphasis on plant foods
Eat the right amount of calories for you	Increase whole grain intake	Choose foods and beverages that help maintain a healthy weight
Be physically active your way	Decrease fats including saturated, trans, and dietary cholesterol	Limit consumption of process meat and red meat
	Decrease sugar, especially sugar-sweetened beverages	Eat at least 2.5 cups of vegetables and fruits each day
	Decrease salt	Choose whole grains instead of refined grain products
	Maintain a physically active lifestyle	If you drink alcoholic beverages, limit consumption

[a] *Source* Reference [6]
[b] *Source* Reference [28]
[c] *Source* Reference [37]

Communication strategies to inform and influence individual and community decisions on health promotion and disease prevention depend on documented evidence-based physical activity and dietary guidelines as given in Table 1.4. Longitudinal multicenter clinical trials, epidemiological evidence, and the expert opinion of government agencies, researchers, and academicians have led to a better understanding of the role of dietary and physical activity in health promotion [51, 52]. Evolving guidelines serve as a framework and set policy for the interpretation and implementation of healthy choices [52].

Comparative Overview of American Health Agency Guidelines

Benchmarks used to determine the direction and framework for establishing dietary practices appropriate for decreasing risk for disease and for health promotion have been expressed in a variety of formats. Dietary guidelines (See Table 1.1) or messages for dietary choices (See Fig. 1.1) are generally broad, may include food groups and are designed primarily to increase awareness of choice and establish guiding principles for populations [53]. Other specific guidelines, such as food pattern guides and daily recommendations for specific nutrients, are more targeted to either be inclusive or specific to a nutrient need. See Table 1.4.

General Guidelines

Dietary and physical activity concepts based on significant population-based research have been published by a variety of government agencies and health-based organizations. The *Dietary Guidelines for Americans*, the cornerstone for diet and nutrition messages, was first published in 1980, followed by five intermittent revisions [54]. The most recent version, published in 2010, reflects an evidence-based evaluation of epidemiological, clinical trials and observational studies in humans to identify how dietary intake may reduce risk for major chronic diseases and how a healthy diet may improve nutrition [55]. Conceptual statements are designed to increase awareness and promote action related to associations between lifestyle behaviors and chronic disease risk. Examples of dietary guidelines addressing chronic disease risk are noted in Table 1.4.

Table 1.5 Daily recommendations for major nutrient intakes by percentage of calories or by gram weight

Nutrient components	US Dietary Guidelines[a]	Institute of Medicine[b]	World Health Organization[c]
Protein	10–35%	10–35%	10–15%
Carbohydrate	45–65%	45–65%	50–70%
Added and simple sugars	NS[d]	<25%	<10%
Dietary fat	20–35%	20–35%	15–30%
Dietary fiber	25–34 g	25–38 g	NS[d]

[a] *Source* Reference [8]
[b] *Source* Reference [35]
[c] *Source* Reference [1]
[d] Not Specified

Food Pattern Guidelines

The clinician is encouraged to translate general guidelines to meet the needs of individuals. *ChooseMyPlate* [6] presents recommendations for selecting a variety of foods leading to successful implementation of the dietary guidelines, and was developed simultaneously with the *2010 Dietary Guidelines for Americans*. The *ChooseMyPlate* graphic (http://www.choosemyplate.gov/downloads/GettingStartedWithMyPlate.pdf) is primarily a nutrition education tool and is an expansion of the food guidance system designed to communicate moderation, variety, balance and gradual improvement of food choices based on scientific nutrition evidence. The website includes weight management, physical activity monitoring, and a *Super Tracker* for entering foods and beverages consumed and converted into personalized dietary intake reports. It is presented in both text and interactive web-based formats allowing for individualization of food choices based on age, gender, and body size, and offers strategies to guide changes in food choices. It recognizes special groups, like children and the elderly, with age appropriate guidance [6]. It was concluded that recommendations for individuals should encourage consumption of large amounts of fruits, vegetables, and grains and moderate amounts of meats, milk, and dairy products. Food patterns represent not only daily food choices but also food combinations that collectively meet dietary guidelines recommendations. Tailored food plans to meet individual caloric and nutrient needs can be found and reviewed on the MyPlate website http://www.choosemyplate.gov/supertracker-tools/daily-food-plans.html.

Nutrient Intake Recommendations

Researchers and health professionals can define dietary quality in terms of nutrient composition in addition to food patterns. The evidence to support recommendations for both macronutrients and micronutrients represents a growing body of diet and nutrition knowledge known to be specifically associated with risk of a variety of diseases [52].

The Institute of Medicine of the National Academy of Sciences [56–61] and the World Health Organization [1] have published an extensive variety of documents in support of dietary recommendations for health promotion. An example is provided as a summary of these guidelines for caloric distribution from energy nutrients in Table 1.5. Recommendations for protein, carbohydrate, and fat distribution in the daily diet are similar. Additionally, recommendations for specific nutrients like simple and added sugars and types of fat are not specified by all agencies. The unequivocal scientific evidence to clearly identify what is described as optimum nutrition remains undefined. However, scientific findings continue to support food guide recommendations based on a variety of food categories broader in scope. Essentially, diets need to provide adequate protein for tissue regeneration and maintenance plus a variety of carbohydrates to support cellular and systemic functions. Dietary fat intake determinations define the importance of the unsaturated fatty acids in health promotion.

Table 1.6 Guidelines for practice

	Prevention	Intervention
Oral health care professional	Assess dietary patterns and body mass index as part of initial and periodic oral exams and checkups	Conduct dietary assessment and nutrition education with dental patients/clients
	Provide messaging to patients about the synergy between general, nutritional and oral health	Develop a referral protocol to a Registered Dietitian for comprehensive dietary counseling and follow-up
Nutrition professional	Provide guidelines that promote oral health and support dietary changes necessary to decrease risk for chronic and disabling diseases	Conduct oral screening as part of nutrition focused physical exam
		Tailor dietary counseling to include guidelines to promote optimum oral health and disease risk reduction
		Develop a referral protocol to a dental professional for oral health maintenance

The *Dietary Reference Intakes*, in addition to addressing energy nutrients, offer standards for recommended amounts of specific elements, macronutrients, and vitamins to be included in a dietary pattern [56–61]. These multiple sets of values include (Estimated Average Requirements, Recommended Dietary Allowances, Adequate Intakes, and Tolerable Upper Intake Levels) for designated age groups, physiologic states, and sexes. Like the former *Recommended Dietary Allowances* these values replace, they are intended to meet the needs of healthy individuals over time.

Summary

General health status can have an impact on oral health diagnoses and treatment outcomes. Diet and nutrition are major indicators of health status and can mediate the course of oral health outcomes. Likewise, oral health status has an impact on nutritional status and ability to eat. The synergy among oral health, general health, and nutritional well-being is dynamic and should be viewed from a global perspective to provide clinical and community interventions targeted toward health promotion. The similarities among dietary guidelines and recommendations specific to the major chronic conditions and diseases help to create oral health and nutrition messages with multiple intents and outcomes. Guidelines for the prevention and health promotion of oral health and nutrition are listed in Table 1.6 for oral health care professionals (OHCPs) and nutrition professionals. Chapters in this book provide both additional supporting evidence and specific guides that expand on this introductory chapter.

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Chapter 2
Pregnancy, Child Nutrition, and Oral Health

Jane Ziegler and Connie C. Mobley

Keypoints

- Adequate nutritional status prior to and during pregnancy supports the development of oral health in infants and children
- Recommended infant feeding practices, introduction of foods, and healthful dietary choices promote optimum growth and development and decreased risk of early childhood caries
- Caries in children is associated with multiple dietary factors including frequent fermentable carbohydrate consumption
- Poor oral health in children with childhood disorders and diseases is associated with possible increased risk for malnutrition and growth impairment

Keywords Prenatal nutrition · Perinatal nutrition · Tooth development · Maternal oral health · Maternal protein energy malnutrition · Vitamin nutrition · Mineral nutrition · Oral health · Infant feeding practices · Early childhood feeding practices

Introduction

Adequate nutrition is imperative during pregnancy as nutrition is an important factor in the health, growth, and development of the mother and the fetus [1–3]. Appropriate prenatal weight gain is associated with a lower risk of complications during the pregnancy and the birth process [1, 4–6].

Growth and development of the fetus begins during pregnancy and continues as the child grows into early adulthood. Physical growth is defined as increases in cell size caused by processes of cell multiplication involving hyperplasia, hypertrophy, and accretion occurring in set patterns. However,

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this can occur at different rates and ages. The effects of nutrition are expressed throughout this process of growth and development and demonstrated throughout the tissues and structures of the developing body [7].

Since the consequences of poor oral health can impact lifelong health, pregnancy and childhood are key periods to access oral healthcare [8]. According to the Surgeon General's Report on Oral Health, oral health is defined as having healthy teeth as well as "being free of chronic oral-facial pain conditions, oral and pharyngeal (throat) cancers, oral soft tissue lesions, birth defects such as cleft lip and palate, and scores of other diseases and disorders that affect the oral, dental, and craniofacial tissues, collectively known as the *craniofacial complex*" [9]. Nutrition is the intake of food, considered in relation to the body's dietary needs [10]. Diet refers to what we eat and drink and has a local effect on the oral cavity. Depending on the diet's composition, it can impact risk of dental caries and enamel erosion. Nutritional status impacts an individual's tooth and soft tissue development and resistance to infections, particularly periodontal disease and caries. A nutritious diet is essential for the development and maintenance of healthy teeth and soft tissue which in turn are needed to consume a varied and healthy diet throughout life [11]. Nutrient deficits can impact tooth development, including the integrity of the tooth and enamel, as well as the soft tissue and composition of saliva. Protein–calorie malnutrition and deficiencies of vitamins C, A, D, and iodine have been documented in human studies to have an impact on tooth development and maintenance [12–15].

This chapter explores relationships between oral health and nutritional status and dietary intake from conception through adolescence according to the developmental stages of pregnancy, infancy, early childhood, and school-aged children. Oral health and nutritional disorders among individuals with special needs are reviewed.

Prenatal and Perinatal Nutrition and Tooth Development

Adequate nutrition prior to and during pregnancy can impact the dentition of the infant. During fetal development, the primary teeth begin forming at about 6 weeks post conception with cells in the oral cavity of the fetus differentiating to form the dental lamina, the site of tooth bud formation. Tooth mineralization begins in the late bell stage of tooth development or about 4 months gestation with the formation of dentin, the foundation for the deposition of enamel [14, 16] and continues throughout adolescence [9]. Nutrition directly impacts the development of enamel and dentin of the primary and permanent teeth during fetal growth. In addition, preconception nutritional status of the mother as well as access to adequate nutrition during pregnancy has an impact on the general health and outcomes of the infant and may impact the infant's future health as an adult [17]. Nutrient deficiencies or insults from teratogens during pregnancy can impact the development of the primary and permanent teeth [17]. Upon birth, all primary and many unerupted permanent teeth are in various stages of development [9]. Early childhood caries (ECC) and hypoplasia found in infants and children in developing countries are associated with malnutrition or undernutrition during the perinatal period [18]. Individual nutrients are related to critical periods of calcification and poorly calcified teeth resulting in reduced caries resistance [19].

Maternal Oral Health Concerns in Pregnancy

During pregnancy the diet provides sufficient calories and other nutrients to meet the requirements of the mother as well as support the needs of the growing fetus. This allows the mother to establish nutrient stores required for ongoing fetal development and for future lactation needs [1]. Despite

available prenatal care for mothers and their fetuses, approximately 5% of infants born in the USA are diagnosed with intrauterine growth retardation (IUGR) [20]. Epidemiological studies have linked IUGR with the etiology of many chronic diseases in adults [20]. Energy and nutrient intake during pregnancy, along with prenatal weight gain, affect overall and oral fetal development and the child's gestational age and birth weight [21].

Routine oral healthcare is important to a pregnant woman's overall health status and to the future oral health of her child [22]. Both periodontal disease and dental caries are preventable through evidence-based interventions [23]. Educational interventions prior to and during pregnancy can promote disease prevention and positive, oral health behaviors and nutrition habits. The presence of periodontal disease and/or dental caries during the preconception period and during pregnancy will influence the mother's oral health conditions, may affect the outcome of the pregnancy, and the child's future risk of developing early and severe dental caries [24]. Periodontal disease in the mother has been associated with adverse pregnancy outcomes including premature birth [11, 25, 26], preeclampsia [27, 28], gestational diabetes [29], fetal loss [30], and small for gestational age infants [26]. Several investigators have demonstrated a relationship between treatment of periodontal disease during pregnancy and a reduction in risk of preterm birth [7, 32, 33].

During pregnancy the mother experiences changes in hormonal activity, in gastrointestinal anatomy and physiology [33], and alterations in blood flow, blood pressure, and respiratory function [34]. Some of these symptoms include nausea, vomiting, gastroesophageal reflux, changes in taste and food cravings, as well as fatigue; all of which may vary in presentation by trimester. Pregnancy-related gastric acid reflux, experienced during nausea and vomiting, can lead to dental enamel erosion. Morning sickness, which may be experienced early in pregnancy and acid reflux, common in latter stages of pregnancy, can also contribute to dental erosion [35]. Physiologic changes in the oral cavity due to shifts in estrogen levels can result in tooth mobility and maternal gingivitis [35–38]. Estrogen metabolism by gingival tissue and the synthesis of prostaglandins contribute to increased incidence of gingivitis during pregnancy [39]. An increase in estrogen levels results in a decreased production of collagen and keratinization of the gingival epithelium reducing the ability to repair and maintain gingival tissue [40]. In pregnancy higher levels of progesterone results in increased vascular permeability of gingival tissues [40]. Studies have demonstrated an association between periodontal infection and adverse outcomes of pregnancy including preterm birth and low birth weight of the infant [41, 42].

Dental caries during pregnancy is of unique concern because of the maternal-child linkage. Caries occurs when cariogenic bacteria in dental plaque metabolize fermentable carbohydrates and produce acid that can be transferred between mother and child through direct salivary transmission. Mothers who have extensive tooth decay are more likely to have high titers of *mutants streptococci*, a known oral bacteria, resulting in a higher risk of ECC in their children [23]. Levels of cariogenic bacteria in maternal saliva and transmission of bacteria from mother to child is facilitated by kissing, sharing of eating utensils, and cleaning pacifiers with mother's saliva [23]. The age of the child on exposure to cariogenic bacteria, the composition of the child's diet, and the child's salivary flow rate and composition can also impact transmission of cariogenic bacteria [23].

Oral pregnancy tumors may occur in up to 5% of women during pregnancy [43]. They are caused by combined effects of increased levels of progesterone and oral bacteria, are primarily located on the gingiva and have a smooth and erythematous appearance. The tumors can present after the first trimester with associated bleeding and may interfere with eating, but usually recede after delivery [43].

Table 2.1 Daily recommendations for increased energy and protein by trimester for women with a preconception BMI of 18.5–24.9 [45]

Trimester	Energy (K cal)	Protein (g)
First	No increase	25
Second	340	25
Third	452	25

Note Adjustments of these recommendations are needed for women with a BMI $\leq$ 18 or $\geq$25

Maternal Protein Energy Malnutrition

In order to optimize the health of the pregnant woman and to reduce risk of complications, women should enter pregnancy in good nutritional status and maintain optimal nutritional status throughout the pregnancy. Weight gain during pregnancy provides for the fetus, placenta, and amniotic fluid as well as tissue accretion in the mother [44]. Maternal protein energy malnutrition (PEM) can have significant effects on both the mother and the fetus. Ideal weight gain during pregnancy enhances pregnancy outcomes. Weight gain recommendations are individualized in relation to prepregnancy body mass index (BMI). Recommended weight gain during pregnancy for a woman at a normal BMI of 18.5–24.9 is between 25 to 35 pounds [45]. A woman with a BMI of less than 18.5 has a desirable weight gain of 28–40 pounds, an overweight woman (BMI 25–29.9) a desirable weight gain of 15–25 pounds, and an obese women (BMI $\geq$ 30.0) should gain between 11–20 pounds [45]. Table 2.1 [45] lists recommended increases in energy and protein needs by trimester for a woman with a normal BMI preconception. Energy intakes will differ by trimester and should be adjusted based on a woman's preconception BMI.

The 2002 Daily Recommended Intake (DRI) for protein necessary to provide adequate needs for the developing fetus and the pregnant women is 1.1 g/kg/day of body weight for a woman aged 20–39 years or an additional 25 g/day. (See DRI in the Appendices.) When evaluating the protein intake of a pregnant woman consider total protein needs and quality, as well as total energy intake. Low birth weight or preterm birth is associated with inadequate weight gain during pregnancy [45]. PEM of the mother is associated with a child's delayed tooth eruption [46], with tooth size and with possible decreased enamel solubility, as well as salivary gland dysfunction, all of which influences a child's caries risk [47]. Low birth weight and preterm delivery are associated with enamel hypoplasia of the child's primary and permanent teeth [47].

Maternal Vitamin and Mineral Nutrition

Maternal nutrition status impacts tooth development of the fetus pre-eruptively; whereas post-eruptively the impact is due to the local effects of diet [48]. See Table 2.2 for a list of effects of nutrient deficiencies on infant/child tooth development [49] and Table 2.3 for a list of vitamins and minerals recommended during pregnancy. Deficiencies of vitamins A and D along with PEM are related to a child's risk for enamel hypoplasia and salivary gland atrophy leading to reduced ability to buffer plaque acids and increased susceptibility to dental caries [50]. Maternal intake of vitamins A, C, and D and the minerals calcium, phosphorus, fluoride iron, and iodine impact developing dentition [9] of the fetus. Frank vitamin A deficiency is rare in developed countries, but typically occurs along with PEM in developing countries [51]. Sources of vitamin A, such as fortified milk and dark yellow/orange and dark green fruits and vegetables, when limited in the maternal diet, increase risk of vitamin A deficiency. A vitamin A deficiency during pregnancy can influence an

Table 2.2 Effects of prenatal nutrient deficiencies on tooth development [49]

Nutrient	Effect on tissue	Effect on caries	Human data
Protein–calorie malnutrition	Tooth eruption delayed Tooth size Enamel solubility decreased Salivary gland dysfunction	Yes	Yes
Vitamin A	Decreased epithelial tissue development Tooth morphogenesis dysfunction Decreased odontoblast differentiation Increased enamel hypoplasia	Yes	Yes
Vitamin D/calcium/ phosphorus	Lowered plasma calcium Hypomineralization (hypoplastic defects) Tooth integrity compromised Delayed eruption patterns	Yes	Yes
Ascorbic acid	Dental pulpal alterations Odontoblastic degeneration Aberrant dentin	No	No
Fluoride	Stability of enamel crystal (enamel formation) Inhibition of demineralization Stimulation of remineralization Mottled enamel (excess) Inhibition of bacterial growth	Yes	Yes
Iodine	Delayed tooth eruption Altered growth patterns Malocclusion	No	Yes
Iron	Slow growth Tooth integrity Salivary gland dysfunction	Yes	No

infant's risk of impaired development of epithelial tissues, affect odontoblast differentiation, result in defective tooth enamel and dentin [52], and may reduce the extent of tooth mineralization [53]. Vitamin A deficiency in pregnancy is associated with preterm birth, IUGR, and low birth weight [54] as well as antepartum hemorrhage secondary to abruption placentae [55].

Vitamin D, calcium, and phosphorus deficiencies in pregnancy will have a substantial impact on a child's tooth development and integrity, particularly related to enamel hypoplasia and hypomineralization and eruption of teeth. These deficiencies impact both primary and permanent teeth [12, 52]. Vitamin D deficiency occurs when dietary consumption of this nutrient is inadequate or when the pregnant woman is not exposed to adequate sunlight [56]. Hypomineralization of primary teeth related to inadequate intake of Vitamin D, calcium, and phosphorus can increase susceptibility to ECC in the infant [12, 16].

Ascorbic acid (Vitamin C) deficiency in pregnancy is associated with defective dentinal tissue development [13]. Ascorbic acid is involved in maintaining the integrity of the osteoblasts, fibroblasts, chondroblasts, and odontoblasts [13, 57] and is needed for collagen synthesis. Collagen supports the organic matrix for the deposition of calcium phosphate crystals that form during bone mineralization [13, 58]. Ascorbic acid deficiency in rats resulted in a reduction in dentin formation in laboratory studies [58]. Requirement for ascorbic acid increases during pregnancy and can be met through ingestion of fresh fruits and vegetables. Scurvy, the chronic deficiency disease of ascorbic

Table 2.3 Daily vitamin and mineral recommendations for pregnant women

Vitamin	Recommended intake[a]	Quantity in standard prenatal supplement	Some recommended food sources	Supplementation recommended?
A	770 RE		Fish oils, dark green leafy vegetables, and deeply colored fruits	No
B_1	1.4 mg		Green leafy vegetables, lean pork, soy milk, enriched whole grain breads and cereals	No
B2	1.4 mg		Green vegetables, eggs, milk, meats	No
B6	1.9 mg	2 mg	Wheat germ, pork, cereals, legumes	No
B12	2.6 μg		Meats, poultry, fish, shellfish, milk, eggs, cheese	No
C	85 mg	50 mg	Dark green vegetables, citrus fruits	No
D	5 μg	5 μg	Fortified milk, egg yolks, fatty fish	No
E	15 mg		Polyunsaturated plant oils, wheat germ, tofu, avocado, sweet potatoes	No
K	90 mg		Leafy green vegetables, cabbage, cheese	No
Folate	600 μg	400–600 μg	Dark-green leafy vegetables, beans, peas, lentils	Yes
Niacin	18 mg NE		Peanut butter, lean ground beef, chicken, tuna, shrimp	No
Mineral				
Iron	27 mg	30 mg	Red meats, spinach, broccoli, tofu, shrimp, iron-fortified cereals	Yes
Calcium	1000–1300 mg	250 mg	Dairy products including milk, yogurt and cheese; leafy vegetables; almonds; calcium-fortified foods	No[b]
Phosphorus	700–1250 mg		All animal foods (meats, fish, poultry, eggs, milk)	No
Zinc	11–12 mg	15 mg	Lentils, shrimp, crab, turkey, pork, lean ground beef, eggs, tofu	No[c]

[a] *Source* Institute of Medicine [12, 15, 63]
[b] Supplementation is recommended if food high in calcium are not consumed
[c] Both iron and copper compete with zinc at absorption sites; therefore, zinc supplementation is recommended when elemental iron supplementation exceeds 60 mg/d
RE Retinol equivalents; *NE* Niacin equivalents

acid, is characterized by swollen, bleeding gingiva and tooth loss. Vitamin A and ascorbic acid, through the effects of calbindin and collagen, promote mineralization and development of teeth [13].

Fluoride promotes mineralization of teeth and assists in resistance of teeth to caries by inhibiting demineralization and stimulating the remineralization of enamel of teeth [52]. Fluoride supplementation during pregnancy does not appear to be of benefit to the developing fetus [59]. The uptake of fluoride into teeth is most prominent during infancy and thereafter decreases with age [12, 52].

The fluoride content of breast milk is relatively low [9]. The primary sources for fluoride include community water supplies, some foods and beverages, and dental products [9]. A key role of fluoride is to maintain the stability of the tooth enamel [9]. Fluoride is most effective when ingested during infancy, beginning at 6 months of age, through ingestion of fluoridated community drinking water [60, 61]. In the absence of a fluoridated water supply, the child's physician may prescribe fluoride-containing vitamin supplements (Table 2.4).

Dental fluorosis characterized by white opaque flecks or white or brown staining and in extreme cases, pitting of the enamel is caused by excessive fluoride ingestion. Multiple sources of fluoride especially from supplementation and toothpaste can contribute to fluorosis in the young child.

Table 2.4 Recommended dietary fluoride (F) supplementation for infants and children based on levels in fluoridated water [60, 61]

Age	Fluoride content of water supply		
	<0.3 ppm F	0.3–0.6 ppm F	>0.6 ppm F
Birth-6 months	0	0	0
6 month–3 years	0.25 mg	0	0
3–6 years	0.50 mg	0.25 mg	0
6 year up to at least 16 years	1.00 mg	0.50 mg	0

Note: ppm = part per million

Excess systemic fluoride effects on tooth structure are limited to between the ages of infancy to 14 years of age as the permanent teeth are formed within this time period [60, 61].

Intake of the minerals iron and iodine play a role in tooth development. Iodine deficiency can result in delayed tooth eruption and malocclusion and iron deficiency can impact the integrity of the tooth structure [15]. In addition to effects on dentition, both minerals are fundamental for growth and development of the fetus. A demand for increased iron during pregnancy is due to maternal blood volume expansion and the fetal iron requirements for normal development. Ingestion of adequate iron from food sources during pregnancy may be difficult for some women; therefore, iron supplementation of 30–60 mg/day is suggested [62]. Adequate iodine intake is readily achieved through use of iodized salt in the diet.

Infant and Early Childhood Feeding Practices and Oral Health

To ensure the growth, health, and development of children, adequate nutrition during infancy and early childhood is essential to avoid risk of illness, and malnutrition leading to childhood obesity, an increasing public health concern worldwide [64]. The first 2 years of life offer a critical window of opportunity for ensuring that children experience adequate and appropriate growth and development through optimal feeding practices. During the first 6 months of life, exclusive breastfeeding meets the energy and nutrient needs for most infants [65]. However, only approximately 34.8% of infants are exclusively breastfed during this period of time [66].

Breastfeeding provides short-term and long-term advantages for both child and mother [67], including protection against a range of acute and chronic diseases. See Table 2.5 [67–74]. The potential long-term advantages of breastfeeding are increasingly acknowledged as imperative [68, 69].

Obesity in later childhood and adolescence is less common among breastfed children than formula-fed children; a longer duration of breastfeeding is associated with a lower risk of obesity [75, 76]. However, breastfeeding duration of greater than 1 year is associated with decreased iron stores [77].

Children fed with commercial formulas have an increased risk of chronic diseases with an immunological basis. These include asthma and other atopic disorders [70, 71], type 1 diabetes [72], celiac disease [73], ulcerative colitis, and Crohn's disease [74]. Published evidence links formula feeding with risks to cardiovascular health, such as changes in blood pressure [78], blood cholesterol levels [79], and resulting atherosclerosis in later adulthood [80].

After the age of 6 months, the requirements for energy and other nutrients begins to exceed what is provided by breast milk [81] and additional or complementary foods are required to meet dietary needs [82] and to promote development of masticatory efficiency and gastrointestinal tract function.

Table 2.5 Advantages of breastfeeding for infants and mothers [67–74]

	Advantages of breastfeeding to infant	Advantages of breastfeeding to mother
Short-term advantages	Lower morbidity of diarrheal, respiratory, and allergic diseases, lower risk of otitis media and ear infections, and development of type 1 diabetes	Reduced post-partum bleeding
Long-term advantages (adulthood)	Associated with lower mean serum cholesterol, systolic and diastolic blood pressure, overweight and obesity risk, type 2 diabetes	Lower risk of ovarian and breast cancer and development of rheumatoid arthritis

Table 2.6 Guidelines for introducing solid or complementary foods into an infant's diet [84]

Child should be able to sit upright with good head control
Child should reach for food and seem eager to be fed
Child should be able to move the food from a spoon to his/her throat
Generally infants need to have doubled their birth weight or weigh about 13 pounds to be ready for solid foods
Introduction of foods has typically been by tradition with single grain cereals introduced first, followed by vegetables then fruits although no evidence exists that demonstrates an advantage of one food over another when introducing
Provide one new food at a time and wait 2–3 days before introducing another new food to allow assessment of allergy symptoms
Within a few months of introducing foods to the child's diet, the diet should contain breast milk or infant formula, cereals, vegetables, fruits, meats, eggs, and fish

Once complementary foods have been introduced, breastfeeding continues to be a major source of nutrients for the infant, providing about 50% of energy needs up to the age of 1 year [83].

Complementary foods include several categories of foods and assist in transition from a liquid-based diet (breast milk, or infant formula) to a diet including foods offering a wide range of tastes and textures. It is recommended the complementary foods in an infant's diet be limited in the amount of salt, saturated fats and sugar, and adequate in proteins, carbohydrates, fiber, vitamins, and minerals are included [66].

In order to meet the nutritional needs of young children, complementary foods need to be nutritionally adequate, safe from food-borne pathogens or toxins, and fed in a manner that is appropriate to meet the child's energy and nutrient needs. Potential concerns with complementary feeding include offering calorie dense and nutrient-poor foods, offering foods too frequently or not often enough, and replacing breast milk with beverages of inferior quality [60].

Guidelines from the American Academy of Pediatrics regarding the introduction of solid or complementary foods are addressed in Table 2.6 [84].

Health Consequences of Early Childhood Caries

The combined presence of cariogenic microorganisms, fermentable carbohydrate, and a susceptible tooth and host initiate the infectious and transmissible disease known as dental caries. Although preventable and reversible, ECC is the most common chronic infectious disease of childhood. When left untreated it results in pain, bacteremia, high treatment cost, reduced growth and development, speech disorders, and premature tooth loss. Consequently, ability to bite and chew can be compromised and children may exhibit loss of self-esteem, and harm to permanent dentition [85, 86]. ECC may reduce a child's ability to consume a varied diet.

Table 2.7 Recommended dietary guidelines and practices for oral health promotion of infants and young children [92–94]

Birth to 6 months
•Whether breast- or bottle-feeding is the method of choice, infant feeding schedules should encourage routine consumption of milk rather than on-demand feeding
•Discourage bedtime bottles and nocturnal feeding after eruption of first tooth
•Diminish transmission of bacteria from caregiver to infant by wiping the gums after feedings and implementing oral hygiene when the first tooth erupts
•Promote introduction of water in bottles as appropriate but not until routine feeding is well established
•Instruct mothers to avoid introduction of food until the infant doubles the birth weight or weighs at least 13 lbs or reaches 6 months of age
6–12 months
•Promote weaning from the bottle in combination with the introduction of a cup and spoon
•Promote introduction of food to encourage self-feeding
1–3 year
•Stress the value of mealtime and snacks and the importance of variety and moderation. Offer no more that 1 cup/d of fruit juices and only at meals and avoid all carbonated beverages during the first 30 months of life

Dietary data from the Healthy Eating Index for 2- to 5-year-old children found those with the best dietary practices were 44% less likely to display severe ECC compared with children with less desirable eating habits [87]. Increased consumption of readily available sugar-sweetened beverages, candies, chips, and cookies adds excessive calories to the diet and increases the risk of caries. Inadequate intake of fruits and vegetables deprives the child of nutrients essential to growth and development [88, 89].

Extensive ECC may be associated with low weight for age; Acs et al. [90] found a significant difference in baseline weights between preschool children with ECC and those who were caries free. In addition, those with ECC met failure to thrive weight criteria at baseline measurement. Children treated for ECC experienced significant increases in their age-adjusted percentile weights ($p < 0.01$) [90]. Since ECC is associated with underlying nutritional deficiencies in the perinatal period [91], it seems probable that as the disease progresses, developmental eating behaviors and nutritional status are vulnerable.

Recommended Infant and Early Childhood Feeding Practices to Promote Oral Health

Breast milk or formula is supplemented and partially replaced with complementary foods as the infant is developmentally ready (refer to Table 2.6). The introduction of pureed and solid foods is recommended to coincide with developmental, cognitive, and physiological needs. Feeding guidelines promote adequate nutritional intake to support continued growth and development as well as oral health for infants and young children (Table 2.7) [92–94].

School-Age Children and Oral Health

Oral health is critically important for the overall health and development of children of all ages. Approximately 42% of children (2–11 years) have had dental caries in their primary teeth and 21% of children (6–11 years) have had dental caries in their permanent teeth [95]. Caries remains one of

the most common infectious diseases in children, occurring five times more than asthma [96]. Disparities exist for children from low- and moderate-income households and children of color are more likely to have caries compared to white children [95]. Children with special healthcare needs are at increased risk of caries, particularly those with cognitive disabilities, developmental or neuromuscular disorders, chronic illnesses, immune compromising diseases, certain cardiac, kidney, or liver diseases, and those who are homeless or living among migrant populations [97]. Untreated dental caries can result in serious consequences that impact self-esteem and social functioning, ability to chew and consume a varied diet, failure to gain weight, and causes for pain and discomfort. All of these circumstances can disrupt the child's ability to function successfully in school and in society [85].

Diet and caries are closely related. Cariogenicity of a food or a constituent of a food is relative to and interdependent with multiple dietary factors, including diet composition, frequency of eating, food components of the meal, and sequencing of foods at a meal, and duration of exposure [98]. A variety of nutrient-dense foods including grains, dairy, fruits, vegetables, and protein foods should comprise the base of a child's diet. Fermentable carbohydrates including those found in simple sugars, naturally in foods, and as part of processed foods can contribute to incidence of dental caries [98]. Energy-dense, low-nutrient food examples of such carbohydrates include candies, cookies, and chips which in small quantities can be included within an individual child's diet and within their desired energy requirement allowance. In contrast, there are nutrient-dense fermentable carbohydrates, including fresh fruits, which also have an important role in the diet. The frequency and consistency of meals and snacks are as important in the caries process as is the food composition. Oral bacteria continue to metabolize fermentable carbohydrates for 20–40 minutes following each eating episode. Demineralization occurs until acid production ceases. The more frequently fermentable carbohydrate containing foods are consumed, the more sustained is the production of acids leading to demineralization and allowing less time for remineralization to occur. Saliva production provides protection against dental decay through its buffering capacity thus providing the opportunity for remineralization of the tooth enamel to occur. Conditions which result in decreased saliva production or xerostomia can result in increased dental caries risk [99].

Children and Youth with Special Health Care Needs, Nutrition and Oral Health

Approximately 13.9% of children in the United States have special healthcare needs [100, 101] and are at increased risk for oral diseases. A variety of medical conditions are associated with risk of poor oral health (Table 2.8) [102, 103]. Chronic childhood disorders may require dietary modifications that impact oral health. The need for frequent feedings, parental overindulgence with cariogenic foods and beverages, long-term use of cariogenic medications, and xerostomia are common issues that contribute to dental caries risk in this population [102]. Children with special healthcare needs may have higher levels of dental plaque, increased occurrence of gingivitis, and higher calculus index [103, 104] than their counterparts. Poor oral health status among children with special needs has been attributed to inadequate dental hygiene behaviors and diets high in fermentable carbohydrates [103–105]. Lui et al. [106] reported that risk factors associated with decay in the population were the frequency of intake of sweets, plaque scores, and the ability of the child to brush their teeth.

Common medical issues that affect children with special healthcare needs including gastroesophageal reflux disease (GERD), motility disorders of the oral, pharyngeal, and esophageal structures, sialorrhea, sensory processing disorders, failure to thrive, use of enteral feedings and medications, and feeding problems [107]. These conditions may affect oral health and impact tooth

Table 2.8 Medical conditions in children associated with increased risk for poor oral health [100, 101]

Asthma
Autism spectrum disorders
Cancers
Cerebral palsy
Congenital heart disease
Critical illness
Cystic fibrosis
Down syndrome
Gastroesophageal reflux disease
Gastrostomy feeding
Hemophilia or other clotting disease
Immune dysfunction
Type 1 diabetes mellitus
Juvenile idiopathic arthritis
Renal/liver failure
Seizure disorder
Sickle cell anemia
Special needs children

development as well as affect risk of dental caries, periodontal disease, and fungal infections [107]. GERD, commonly observed in infants and children, has been associated with higher levels of salivary *mutants streptococci* [108]. A higher rate of erosion is seen in these children with GERD due to the combination acid reflux, higher levels of salivary *mutants streptococci*, and possible conditions of bruxism and/or hyperactive bite [109].

Motor disorders among children with special health care needs attributed to a variety of neurological disorders, mental retardation, traumatic brain injury, cerebral palsy, cleft lip/palate, and even disruption of the extra-oral integrity due to cancer therapies can impact feeding ability and oral health [110]. Loss of muscle tone of the cheeks, lips, and tongue contributes to sialorrhea, and prolonged exposure of food in the mouth resulting in increased caries risk [111]. Sialorrhea frequently seen in children with cerebral palsy, those being fed via gastrostomy tube, those prescribed multiple medications, and those with GERD can result in dehydration, bad breath, chapped skin and lips, and fungal infections. Excessive salivation results in difficulty forming a cohesive bolus, impairing the swallowing process, increasing risk of aspiration, and prolonging oral clearance time [112]. Oral hypersensitivity can result in facial or oral defensiveness presenting as biting, lip pursing, grimacing, gagging, emotional outbursts such as crying, or defensive techniques including turning of the head or pushing at food or utensils as they come close to the mouth. Dental hygiene, such as brushing and flossing as well as interventional dental care, may be difficult to achieve [113].

Many children with special healthcare needs require a wide range of medications typically provided in liquid form and containing significant amounts of sucrose [114]. Children who require sucrose-containing medications over an extended period of time are at increased risk for dental caries. Other side effects of medications such as xerostomia or sialorrhea may further increase the risk of decay [115]. Hospitalized children potentially develop poor oral hygiene secondary to lethargy or malaise. Medications, medical treatments, and intubation make these children vulnerable to poor oral health outcomes [116].

Children with the diagnosis of failure to thrive may require a higher calorie diet to meet needs for catch up growth [117]. Added calories in the forms of fats, oils, and proteins as well as high-calorie liquid nutrition supplements and sources of fermentable carbohydrates are commonly recommended. Parents who add snacks and juices high in carbohydrates or added sugars may increase calories but may also increase caries risk [102]. Enteral nutrition provided via gastrostomy feeding tubes is the

most common approach to the care of the child who cannot meet their nutritional needs orally [102]. Although evidence is limited, children with gastrostomy feeding tubes have a tendency to have increased levels of plaque and calculus buildup compared to gender- and age-matched special needs children who do not require a feeding tube and thus may require vigilant oral hygiene intervention [118].

Children with Diabetes

Diabetes, including Types 1 and 2, is associated with increased risk of oral infectious diseases and is further addressed in Chapter 11. Despite the increased incidence of Type 2 diabetes in children, much of the oral health research in the area of diabetes and pediatrics has focused on type 1 diabetes mellutis (T1DM) [119–125]. Children with T1DM are more prone to calculus accumulation and gingivitis even with comparable oral hygiene habits practiced by children who do not have a diagnosis of diabetes [124].

Children with Eating Disorders

Oral healthcare professionals (OHCPs) may be among the first healthcare professionals to recognize signs and symptoms of an eating disorder (e.g., anorexia nervosa, bulimia) in a child or adolescent. Hence, they are in an ideal position to screen for eating disorders during routine office visits [128]. Perimolysis, swelling of the parotid gland, salivary amylase concentrations, tooth erosion, and dental caries may occur in children with eating disorders [128]. Enamel erosion and parotid gland swelling are the most common oral manifestations associated with chronic vomiting, occurring predominantly along the lingual surfaces of the anterior teeth and buccal and occlusal surfaces of the posterior teeth [129–133]. The incidence of dental caries in this population is variable with conflicting results [129, 131–134]. Individuals with eating disorders are at risk for osteopenia and hence should be referred to a physician for evaluation of bone health [128]. When an eating disorder is suspected, further probing questions should be explored with the child and parent depending on the age of the child. A referral to the child's primary care provider for further evaluation and a registered dietitian (RD) for evaluation is warranted. Nutrient deficiencies may occur in children with eating disorders and may be evidenced in the condition of the oral mucosa, indicating that an oral exam could lead to early diagnosis of an eating disorder [128].

Children with Cystic Fibrosis and Other Chronic Respiratory Disorders

Management of the child with cystic fibrosis includes medications, a high-calorie high-fat diet, and other therapies. Foods high in fermentable carbohydrates, in particular added sugars, are often included in the diet to assist in maintaining the increased caloric demands. In such instances, frequent brushing is needed to reduce risk for caries. Narang et al. [137] reported a lower prevalence of caries in individuals with cystic fibrosis; however, a universally higher prevalence of dental defects and calculus accumulation compared to normal children. Pancreatic enzyme replacement and long-term antibiotics, common interventions in children, with cystic fibrosis have been associated with caries reduction [137].

Children with Inborn Errors of Metabolism

"Inborn errors of metabolism" is an inclusive term for a variety of disorders which result from hereditary deficiency of a specific enzyme necessary for a specific metabolic pathway [138]. Included in this group are disorders of protein, carbohydrate and lipid metabolism and defects in organelle function. Treatment and management of some of these disorders requires complex medical nutrition therapy with adherence to specialized diets, many of which are highly cariogenic. Some diseases, such as glycogen storage diseases may require frequent feedings of high carbohydrate snacks or beverages and in some cases nighttime feedings high in carbohydrate must be provided during sleep. Although this type of dietary pattern is indicative of a high caries risk, the prevalent oral pathology is unknown in this cohort of children. A challenge to achieve optimal dental health in these children is confounded by their dietary needs and requirements. Treatment of dental and oral disorders may also be compromised due to metabolic derangements. An interprofessional team approach is needed to address appropriate care for these individuals with any of these complex disorders [139].

Children with Cancer

The oral health needs of the differing types of childhood cancer differ according to cancer type and treatment [140]. Children under the age of 3.5 years who are treated with chemotherapy are at risk for microdont teeth in the adult dentition when compared to older children receiving chemotherapy [140]. Complication of cancer treatments can lead to mucositis and xerostomia; caries risk may be higher if children are consuming greater quantities of fermentable carbohydrates more frequently without oral hygiene interventions [102].

Children with HIV

Oral lesions that affect children with HIV include fungal lesions caused by Candida strains, herpes simplex, linear gingival erythema, parotid enlargement, and oral ulcerations [141]. Children with HIV may experience reduced appetite and decreased food intake, impaired absorption and higher nutrient requirements requiring an energy dense diet, high in calories and protein. Frequent snacks and meals and nutritional supplements are provided to meet the nutrient requirements exacerbated by needs to support growth and development. The prevalence of caries is higher in children with HIV especially in advanced disease [102]. Chapter 14 on HIV provides more detail on oral health problems of children with HIV.

Children with Asthma

Asthma, a leading cause of hospitalization in children, places them at risk for oral infections of *candida albicans* due to use of corticosteroid inhalers. In addition, the use of inhaled steroids has been associated with increased risk of gingivitis and tooth decay [102, 142]. These children should be identified as needing preventive oral care and encouraged to consume a diet that reduces caries risk.

Children with Congenital Heart Disorders

Malnutrition and growth impairment are typical in children with congenital heart disorders secondary to poor appetite, early satiety, malabsorption, fluid restriction associated with increased calorie needs, and hypoxemia-induced fatigue [102]. These children have been shown to have an increased level of dental decay, enamel hypoplasia, and periodontal disease [143–145]. The higher prevalence of decay and untreated decay compared to healthy children [143–145] is of concern in this group of children because of their susceptibility to infective endocarditis as a result of oral bacteremia. In order to meet increased energy demands, dietary recommendations for individuals with congenital heart disorders include small frequent meals secondary to hypoxemia-induced fatigue and frequent vomiting [146].

Children with Craniofacial Anomalies

Of all craniofacial anomalies, cleft lip with or without cleft palate and cleft palate are the most common resulting from failure of the first branchial arches to fuse [9]. Structural anomalies may require multiple surgeries and alterations in both speech and dental development may occur. Caries risk may increase due to difficulties removing plaque and these children may experience oral aversions making dental hygiene efforts difficult [147].

Children with special healthcare needs require special attention to oral hygiene to help reduce risk of dental caries and other oral health diseases that occur in this population. Table 2.8 lists medical conditions in children, including those discussed in this chapter, associated with increased risk for poor oral health. Cleaning the gingiva and mouth with moist gauze prior to tooth eruption and use of appropriate-sized toothbrushes with assistance in brushing can enhance oral hygiene behaviors. An electric toothbrush may be needed for plaque removal since manual dexterity may be limited.

Summary

Throughout pregnancy, infancy, and childhood, nutrition and diet play a significant role in oral health status. Assuring adequate nutrition of the mother and fetus throughout pregnancy and into childhood will increase the likelihood of establishing health behaviors that will promote positive health outcome. Malnutrition can contribute to adverse pregnancy outcomes to include preterm delivery, failure to thrive, obesity, and altered growth patterns, all of which are associated with increased risk for oral diseases. OHCPs should address diet, nutrition, and oral health concerns specific to the stage of growth and development and promote positive parenting behaviors that promote health and development. Pregnant women and children who have experienced unintentional weight change, or who have problems meeting their nutritional needs via their regular diet or those for whom a nutrient deficit is suspected should be referred to a Registered Dietitian (RD).

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Chapter 3
Age-Related Changes in Oral Health Status and Diet and Nutrition Status

Connie C. Mobley

Keypoints

- Diet, nutrition, and oral health have a dynamic relationship and are determinants of active aging
- A plant-based diet rich in vegetables, fruits, fish, and whole grains supports cardiovascular health, oral health, and the unique demands of healthy aging
- The prevalence of tooth loss with aging can affect diet and nutrition if dietary adaptations are not identified relative to masticatory, sensory, salivary, and gastrointestinal changes
- Declining oral health in aging adults associated with malnutrition, oral surgery, restorative oral care, temporomandibular joint disorders, and dyspahgia can be addressed with special dietary guidance

Keywords Aging and oral health · Diet and nutrition · Aging and nutritional status · Age-related changes · Oral health

Introduction

The number of Americans aged 45–64 years increased by 33% from 2010 to 2011; there were 41.4 million Americans over the age of 65 years in 2011 projected to increase to 79.7 million in 2040 [1]. Over the past several years the average life expectancy has increased by approximately 19–20 years [1]. The majority of over 65 years of age were community dwellers [1]. Between 1980 and 2010, the centenarian population experienced a larger percentage increase than did the total US population [1]. This demographic is projected to grow in numbers in the future and to represent a growing cohort of individuals with healthcare needs modulated by healthy aging, age-related diseases, and longevity.

Genetic and environmental factors, including dietary intake, have altered the aging trajectory [2]. There are compelling observational data demonstrating links among eating patterns, nutritional well-being, satisfaction associated with eating, and overall aging [3]. Over the last 150 years, improved medical care and prevention associated with increasing life expectancy parallel with health-related best practices, has led to a major shift in causes of death for all age groups, including older adults [3, 4].

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The leading causes of disability and mortality in old age have changed from communicable diseases to noncommunicable chronic diseases that share common risk factors with most oral diseases [5]. The Centers for Disease Control and Prevention (CDC) have identified four common causes of chronic diseases that include lack of physical activity, poor nutrition, tobacco use, and excessive alcohol consumption [6]. Poor nutrition affects oral health and in turn oral health may influence dietary intake and nutritional status [7].

This chapter discusses the role of diet and nutrition as major determinants of active aging, synonymous with successful aging [8]. It includes a review of strategies to address the dynamic relationships between nutrition and oral health changes in older adults, and acknowledges prevention, early detection, and treatment of oral conditions and diseases that contribute to quality of life in a growing aging human demographic [9].

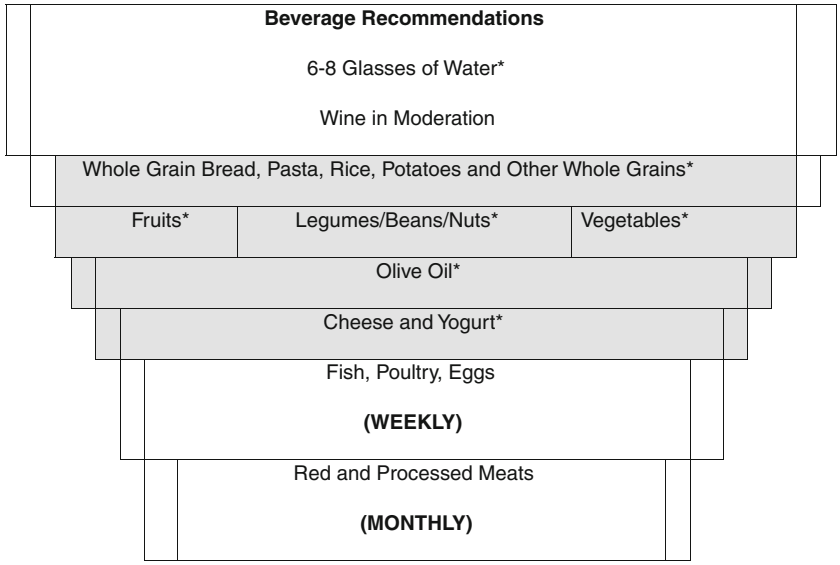
Diet Quality, Nutritional Status, and Aging

Prior research has demonstrated that dietary patterns during adulthood increase risk of chronic diseases in older adults, including those associated with cardiovascular disease (CVD), diabetes, cancer, and other conditions such as musculoskeletal disorders [10–13]. Akbaraly et al. reported that older adults whose diets were most representative of higher intakes of fats, processed foods, sweet foods, and red meat were diets associated with higher odds of cardiovascular and noncardiovascular mortality compared with diets lower in fats, processed foods, sweet foods, and red meat [14].

Several studies have identified a positive association between the Mediterranean diet and health and aging, showing positive effects of increasing dietary intakes of vegetables and fruits, fish, and whole grain cereals, while decreasing animal products in the diet, such as some dairy foods and meats [15, 16]. A 4.8-year study of the associations between adherence to an energy-unrestricted Mediterranean diet, supplemented with olive oil or nuts, and evidence of cardiovascular risk among the study participants, was observed. This plant-based diet contributed to reduced cardiovascular risk among 30% of study participants [17]. The evidence supporting a Mediterranean Diet pattern for adoption as an acceptable approach to successful aging and health indicates significant benefits [11, 18]. Table 3.1 provides a general overview of the typical Mediterranean Diet.

Changes in nutrient needs occur due to both physiologic and functional changes in the natural course of aging. Energy requirements decrease progressively with age [19]. This is due to normal changes in body composition reflected in loss of skeletal muscle mass accompanied by gains in both total and visceral body fat mass [19]. Associated diminishing energy requirements can also make it difficult for the aging adult to meet increased vitamin and mineral needs [20]. Calcium and Vitamin D requirements that support bone health in aging are discussed further in Chapter 16. Vitamin B_{12} needs may be compromised in older adults if malabsorption or inadequate dietary intake is present [20] (See Chapter 1, Table 3.3 for a list of recommended dietary sources of Vitamin B_{12}). A deficiency of this B vitamin is manifested as macrocytic anemia and presents with neurological and sensory symptoms [20, 21]. An excessive intake of Folic Acid, available in most fortified foods, can mask a Vitamin B_{12} deficiency in the older adult [8, 21, 22]. Diets adequate in dietary fiber, high quality protein, and antioxidants derived from fruits, vegetables, legumes, and grains contribute to successful aging [8]. Age-specific recommendations for both macro and micronutrients can be found in the Appendix.

Table 3.1 Food groups recommended in a Mediterranean Diet



*Daily. *Source* Refs. [10, 11]

Dentate Status Affects Diet and Nutrition

Fifty-three percent of adults aged 25–44 and 29% of adults aged 45–64 had a full set of permanent teeth (excluding third molars) according to results of the National Health and Nutrition Examination Survey (NHANES) conducted in 2009–2010 [23]. The prevalence of complete tooth retention was significantly higher among adults aged 45–64 living above the poverty level compared with those living in poverty [23]. Complete tooth loss was significantly higher among adults aged 65–74 with one in four adults over 65 having lost all their teeth [23]. Fifteen percent of adults aged 65–74 and 22% of adults aged 75 and greater were edentulous in 2009–2010 [23]. The prevalence of complete tooth loss was more than twice as high for those living at or below 100% of the federal poverty level (34%), compared with those living above the poverty level (13%). For adults aged 75 and over, there was no significant difference in the prevalence of edentulism; differences observed by race and ethnicity status were not statistically significant [23].

In older adults, caries and its sequellae, along with periodontal disease, are the most common reasons cited by dental professionals for tooth loss [24]. Although the percentage of older adults with removable dentures (approximately 44% of those aged 75 or older) is not increasing, as the population of older adults increases in number, so do the total number with removable dentures [25]. Removable prostheses—ranging from overdentures, complete dentures, implant-supported dentures, or removable partial dentures are used to replace natural teeth in individuals with tooth loss [26]. Subsequently, changes in mastication of foods and alterations in taste and salivary flow occur that may lead to alterations in dietary choices possibly influencing nutritional intake and dietary quality [26–28]. Studies designed to determine the success rate of the variety of possible dental prostheses relative to these alterations remain equivocal and subject to further study [27, 28].

Masticatory Ability

Research consistently has demonstrated that reduced chewing efficiency is associated with decreasing numbers of teeth, removable partial dentures as compared with a similar number of natural teeth, and complete dentures as compared with natural dentition [29]. The number of natural teeth and their function, particularly that of the posterior teeth; the occlusal force or functional tooth units; salivary flow; and oral motor function or muscle strength are thought to be the most accurate indicators of masticatory or chewing ability [30]. Aging is associated with changes in oral architecture and possible muscle weakness; however, the literature suggests that dental impairment rather than age is a major determinant of masticatory performance [31–33].

Changes in dentition can have a profound impact on perceived and actual ability to eat, although perceived chewing efficiency seems to be a more likely determinant of food acceptance than measured function based on chewing strokes required for swallowing, a methodology used as a gold standard in masticatory studies [34]. According to a systematic review of the literature, chewing ability seems to be sufficient with at least 21 teeth and significantly impaired when greater than seven teeth are missing, however, the number of functional tooth units appear to be a critical factor [35]. Reviews addressing comparisons of types of removable prostheses relative to chewing ability reported contradictory results, but there has been an overall slight improvement with implant-supported dentures noted in the literature [36, 37]. Awad et al. studying patients 65 years and older fitted with either implant-supported overdentures or traditional complete dentures, suggested that neither treatment had a more positive effect on nutritional status at 6 and 12 months posttreatment, but that those patients wearing overdentures were significantly more likely to eat fresh, whole fruits and vegetables [38, 39].

Sensory Perception

Taste of foods depends on both the structure of the food's chemical composition and the binding to the 28 taste receptors expressed on the surface of the tongue [40]. Reports of declining taste function among aging adults leading to changes in food selection have been noted in the literature. However, this may be associated with other conditions such as age-related diseases and health status rather than aging per se [41]. Medications, smoking, lack of tongue cleaning, dental diseases and oral infections and lesions, salivary gland dysfunction, and poorly fitting dentures can alter both senses of taste and smell [42].

Since the 1950s, oral health care professionals (OHCPs) have recognized that taste sensitivity is reduced when an upper denture covers the hard palate which contains taste receptors, making it difficult for a person to determine the location of food in the mouth and thus making swallowing less well coordinated [43–45]. Unusual odor perception and risk of choking are additional conditions that may accompany altered taste perception among older adults [46].

Salivary Flow, Digestion, and Gastrointestinal Function

A decline in salivary flow is associated with reduced masticatory performance in older adults [47]. The estimated prevalence of perceived dry mouth ranges from 20 to 40% in most community dwelling older adults, with a higher prevalence reported in women than men [48]. Although use of select medications is associated with decreased salivary flow, aging per se is not [49]. Adequate

saliva plays a significant role in bolus formation of food suitable for swallowing and in retention, stability, and tissue protection of removable dentures [30].

The chewing of foods is important for the initiation of food digestion. Tosello demonstrated that subjects with "a natural set of teeth" had significantly less gastrointestinal pathology than did partially edentulous subjects [50]. Heartburn, chronic cough, hoarseness, asthma, and idiopathic pulmonary fibrosis have all been associated with gastroesophageal reflux disease (GERD), leading to possible dental erosion, taste alterations, chronic duodenal ulcers, and vomiting [51]. GERD in older adults is a common symptom of the aging gut, particularly in those individuals with an increased susceptibility to gastrointestinal complications of comorbid illnesses [52].

Diet Quality, Nutritional Status, Aging, and Oral Health

Aging of the population, together with prolonged retention of teeth, has brought new challenges to OHCPs. In the past, oral care for the elderly was restricted to provision of restorations or partial or complete dentures, but now patients who are older adults are presenting with ongoing dental caries or other oral infectious diseases, failed restorations, and comorbid diseases such as type 2 diabetes mellitus, peptic ulcers, and CVD [53]. These problems may be associated with masticatory, salivary, and olfactory functions and possibly associated pain, reflected in changes in general health, dietary quality, nutritional status, and quality of life [53, 54]. When adults aged 60–71 years in Australia responded to a survey to assess compliance with dietary guidelines in relation to fiber, sugar, fat, and salt reported diminished chewing efficiency, it was associated with lower compliance with those guidelines, reflecting risk behaviors that impact health status [55].

Declining oral health status in older adults has been shown to adversely affect dietary intake and subsequently nutritional status. Deterioration in diet quality due to lack of adherence to dietary guidelines for management of some chronic diseases including diabetes and gastritis may lead to exacerbation of the diseases and negatively impact systemic health [53, 56].

Malnutrition and Nutritional Status

Oral health is associated with malnutrition in older adults [56]. However, malnutrition is independently a complex and multifactorial condition usually representing low quality food intake, possibly reduced food intake, and associated with other concurrent negative systemic health conditions [57]. It may alter homeostasis which can lead to oral disease progression, reduced resistance to oral biological infectious agents, and compromised tissue healing capacity [7]. Evidence that suggests this independent association between malnutrition and oral health requires extensive examination in future research [57].

Study participants 70 years and older when screened using the *Mini-Nutritional Assessment* were dissatisfied with their gingival ("gum") health and at risk of malnutrition [58]. Specifically, those who were edentulous were at higher nutritional risk due to insufficient energy intakes and deficits in vitamins and micronutrients than those with teeth [58]. Frail edentulous elders in a Swiss study presented with malnutrition as measured by low serum albumin and weight loss associated with not wearing their dentures due to their ill-fitting condition [59]. An insufficient number of functional tooth units associated with inadequate intake of vitamin C, calcium, riboflavin, and zinc, explained a further association with poor oral health status in noninstitutionalized older adults in Brazil [60]. In the US, data from NHANES revealed lower serum beta carotene, folate, and vitamin C levels in individuals with the most impaired dentition compared to those with a functional dentition [61].

Food Choices and Dietary Patterns and Quality

Aging is associated with possible declines of physiological and cognitive functions that contribute to overall health [62]; nutrition is considered a major determinant of successful aging [62]. Food choices and dietary patterns in combination, as compared to intake of individual nutrients, reflect the total diet and represent targets for change that may improve the influence of diet and nutrition on both oral and general health outcomes of older adults. Two dietary patterns, ranging from healthful to lower quality, were identified based on analysis of 24 hours dietary recalls from over 400 older adults in a study on aging [62]. Using the Healthy Eating Index-2005 scores for analysis, a more healthful dietary pattern was considered a stronger predictor of diet quality [62]. It included higher intakes of fruits, vegetables, whole grains, nuts, legumes, and dairy, and was associated with lower energy density and higher intakes of fiber, folate, vitamins C and B_6, calcium, iron, magnesium, and zinc [62]. The alternative pattern of lower quality was depicted as diets low in produce (fruits, vegetables, etc.), and high in sweet foods, high in saturated fat, and low in dietary fiber and vitamins [62].

Dietary studies examining dietary quality for all adults, including older adults, reported similar findings when dietary data were reviewed relative to oral health status [63–65]. The Department of Veterans Affairs Longitudinal Aging Study with 625 community dwelling men age 65 and older reported that an adequate intake of good to excellent sources of total fiber was linked with lower risk of alveolar bone loss progression associated with periodontal disease [63]. Edentulous participants in the United Kingdom Low Income Diet and Nutrition Survey consumed lower intakes of fruits and vegetables compared to their dentate counterparts even after the data were controlled for lack of means to acquire these foods [64]. After controlling data for socioeconomic factors, less than 1% of adults with tooth loss (0–10 teeth remaining) participating in a North Carolina study met recommended intakes for total vegetables, dark green and orange vegetables, energy from solid fat, alcohol, and added sugar compared to those adults with greater than 10 teeth [65]. Adults with fewer than 28 natural teeth reported significantly lower intakes of foods such as carrots and salads, as well as total dietary fiber in the US [61].

Aging affects both hard and soft oral tissues; negative oral tissue changes can cause pain, difficulty in speaking, mastication, swallowing, and poor dietary intake, in addition to aesthetical considerations leading to anxiety and depression [66]. The interactions among nutrition, dietary patterns, and oral health play a significant role in successful aging and the possible decreased risk of oral health difficulties over time.

Dietary Guidance

Prior to receiving dental care to improve oral health, individuals may have developed poor dietary habits associated with tooth loss, poor occlusion, oral infection, and other pathological conditions [67, 68]. Dietary choices, including avoidance of foods that are difficult to chew or cause pain or irritation can lead to the possible avoidance of fruits, vegetables, whole grains, and nuts that contribute to a healthy diet. The consistency, temperature, and dryness of foods have been associated with food-avoidance behaviors of people with either conventional dentures or implant-retained overdentures as well as those with pain and discomfort [25, 26]. Food modifications including steaming and moistening foods, as well as altering consistency by chopping or pureeing to various consistencies, can accommodate temporary oral discomfort and act as a transitional step to improving the dietary quality in an effort to achieve or maintain dietary guidelines associated with successful aging [26].

Table 3.2 Questions to guide dietary interview of adult patient

1.	Is it more comfortable to chew small pieces of chicken or ground beef than to chew pieces of meat?
2.	Do you prefer to eat softer foods rather than harder, crusty foods?
3.	Are you comfortable chewing foods with nuts and seeds?
4.	Is it necessary to add juice, sauce, or gravy to your food or to soak your food before you eat?
5.	Can you eat fresh fruits and vegetables that you enjoy with ease?
6.	Is it necessary to drink liquids when you eat to help you either chew or swallow?
7.	Do you experience excessive coughing or choking when you swallow foods?
8.	Does your mouth feel dry most of the time?
9.	Do you experience an unusual or different taste when you eat certain foods?
10.	Have you gained or lost weight in the past few months?

Answers can be explored further and correlated with suggestions for dietary modifications listed in Table 3.3

Source Ref. [26]

Patient satisfaction with oral health care, empowerment to achieve a quality diet and adaptation to changes in oral health status due to the insertion of an oral prosthesis are enhanced when OHCPs include suggestions for dietary strategies to help discourage avoidance of foods important in healthful dietary patterns [25, 69, 70]. Table 3.2 lists questions to guide OHCPs when interviewing adult dental patients about oral health conditions associated with dietary behaviors. Table 3.3 provides suggestions for modifications of dietary choices to support oral adherence to dietary recommendations and support of oral and general health status.

Oral Healthcare Interventions and Diet and Nutrition

In 2000, the Surgeon General's Report on Oral Health in America stated [71]: "Oral diseases are progressive and cumulative and become more complex over time. They can affect our ability to eat the foods we choose, how we look, and the way we can communicate. These diseases can affect economic productivity and compromise our ability to work at home, at school, or on the job. Health disparities exist across population groups at all ages." Oral health care includes interventions targeted to prolonging a positive oral health status and quality of life. However, interventions can alter dietary intake and possibly nutritional status (http://www.nidcr.nih.gov/datastatistics/surgeongeneral/report/executivesummary.htm).

Oral Surgery and Maxilomandibular Fixation

Oral surgery and maxilomandibular fixation temporarily alter food intake and may contribute to weight loss [72]. Nutritional requirements increase as a result of surgical stress simultaneously with the time when eating well becomes most difficult. After tooth extraction surgery or immobilization of fractured jaw surgery, patients may avoid eating for a short time because of local pain or fear that eating will cause pain. Numbness and swelling of the hard and soft palates may cause pain or soreness, but within a few hours post surgery, patients usually begin oral fluid intakes to avoid dehydration [72]. Chapter 18 addresses diet and nutrition recommendations for individuals following oral surgery.

Table 3.3 Modifications of dietary choices to support oral adherence to dietary recommendations for adults with special needs associated with oral conditions

Food choices to accommodate need for	Dairy	Meat, fish, eggs, and meat alternative	Fruits and vegetables	Grains and cereals	Other
Soft or liquid alternatives	Low-fat milk and milk drinks	Broths, soups, low-fat or Nonfat egg nogs, or custards	Juices, nectars, sauces, gelatins	Cooked cereals/grains soaked in liquid	Moderate use of fats and oils
	Low-fat yogurt and cottage cheese	Baked, poached and broiled fish, chicken, or turkey	Pureed, mashed, canned, and cooked fruits/vegetables	Mash potatoes	Avoid excessive use of sugars and sweeteners
	High protein breakfast drinks	Tofu, lentils, soybeans, eggs	Avoid seeds and peels	Soft breads without crust	Ensure daily intake of water
	Low-fat spreadable cheese products	Avoid nuts and nut butter or spreads		Add crackers to soups or stews	
Impaired taste issues	Enriched milk products in favorite flavors	Use spices seasonings and herbs to enhance flavor	Combine juices and purees with meats and other foods	Enriched and fortified breads such as whole grain	Seasonings, flavoring agents, and herbs to be used as desired
			Avoid bitter and sour fruits and vegetables unless tolerated	Avoid seeds if not tolerated	
Mastication and swallowing issues	Moisten dry foods with fat-free or low-fat milk or yogurt	Cut meat into small pieces and serve in sauce or gravy	Peel and cut fresh fruit and vegetables into smaller pieces	Pasta, rice, and other cooked grains	Not applicable
	Combine fat-free or low-fat cottage cheese with fruit/vegetables	Avoid stringy meats	Blend fruits and vegetables into hardy drinks and sauces	Serve with gravy, or broth or season with flavorful condiments	
		Chew slowly and thoroughly			
Impaired salivation	Eat small pieces of hard cheese before a meal if tolerated	Use spices and seasonings	Choose fresh juicy and ripe produce	Chew slow and thoroughly	Not applicable
		Drink clear liquid before and after meals		Combine liquids with cereals and grains	
Rationale	Bone and cardiovascular health (major source of calcium, protein, and B vitamins)	Repair and maintenance of oral soft tissue (major source of vitamins and minerals and protein to maintain immune system health)	Provides dietary fiber (major sources of B vitamins, minerals, and phytochemicals [antioxidants])	Provides dietary fiber (major sources of B vitamins and minerals)	Moderate intake of essential fats and oils (olive, safflower, canola, etc.)
					Sugars interact with oral bacteria and can promote caries

Source Ref. [25]

Tooth Replacement

The overall risk for caries in individuals aged 45 and older has not decreased appreciably [29, 67]. The increased need for restorative care is projected to be higher in adults over the age of 44 years by 2030. The prevalence of root caries and the number of restored teeth in the adult population along with plaque index are the primary risk indicators for adult caries [73]. Dietary recommendations to decrease caries risk will need to be tailored to the adult and if there are comorbidities influenced by dietary management, this will need to be addressed. See Chapter 7 for caries risk factors.

The associations and relationships among tooth loss, dentures, and diet and nutritional status are discussed throughout this chapter [8, 23–30]. Replacing poorly fitting dentures with new ones does result in greater stability and improved occlusion, while replacing posterior teeth with fixed or removable prostheses improves swallowing and limited masticatory function [44, 61–68]. Implant-supported dentures have been shown to improve masticatory function, particularly bite force [69]. However, tooth replacement alone, no matter which approach is taken, has not been shown to markedly improve dietary intakes without instructions on food choices and modifications tailored to meet patient needs [24–26, 61–67].

Temporomandibular Joint Disorders

Dysfunction of the temporomandibular region, where the mandible joins the temporal bone, can result in pain, discomfort, and the inability to open the mouth widely. These impediments can limit biting and chewing ability and may alter food choices [74]. Chapter 17 on orofacial pain addresses temporomandibular joint disorders along with other orofacial pain disorders.

Dysphagia

Dysphagia (difficulty swallowing) is commonly associated with stroke or other neurological disorders, but can occur with poor dentition (natural or artificial), head and neck radiation or other anticancer therapy, surgery involving oral structures, esophagitis, or severe trauma to the oral facial area [75]. It can influence nutrient and energy intake in adults and aging adults due to attention to restricted consistency of dietary options if not well managed [75]. Chapter 5 discusses dysphagia in greater detail.

Summary

Oral health status in aging adults can affect food choices and ultimately impact dietary adequacy and quality. The associations between poor oral health and malnutrition in older adults may primarily be due to tooth loss associated with decreased chewing efficiency. Reduced masticatory ability, even when augmented with partial or complete dentures, can cause great difficulty with eating and can lead to increased risk for compromised dietary quality. Interventions to address food choices and dietary need can enhance the role of the OHCP in the promotion of successful aging among all adults.

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Chapter 4
Obesity and Oral Health Across the Lifespan

Diane Rigassio Radler and Connie Mobley

Keypoints

- Oral health care professionals' roles in health promotion and disease risk reduction includes addressing overweight/obesity in oral health even though the magnitude of association is unclear
- Environmental factors influencing risk of overweight/obesity and oral health status are comparable and can be addressed in the dental setting
- Approaches to screening strategies for overweight and obesity in both children and adults for oral health care professionals include as outcomes patient referral to registered dietitians and provision of health education resources to address findings
- Oral health care professionals should confer and consult with all health professionals, including registered dietitians, to educate, refer, and counsel those seeking to achieve a healthy body weight

Keywords Obesity · Oral health · Environmental factors · Interprofessional practice · OHCP · Oral health care providers

Introduction

Nutrition, physical activity, and obesity have been identified as leading health indicators to achieving health in the United States (US) according to Healthy People 2020 [1]. These areas of focus are a result of data that show the quality of everyday dietary choices and food habits in the US are not optimal and physical activity levels remain inadequate. In 2013 the American Medical

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Table 4.1 Body mass index (BMI) Categories [10]

Underweight	BMI less than 18.5
Normal weight	BMI 18.5–24.9
Over weight	BMI 25–29.9
Obesity	BMI equal to or greater than 30
Class I obesity	BMI 30–34.9
Class II obesity	BMI 35–39.9
Class III obesity	BMI equal to or greater than 40

Table 4.2 Waist circumference values for risk of chronic disease [10]

Men	Greater than 40 inches (102 cm)
Women	Greater than 35 inches (88 cm)

Association officially recognized obesity as a disease [2]. In the US, one out of every three adults, including older adults, and one out of every six children and adolescents are obese making excess body weight a serious public health concern [3, 4]. Obesity increases the risk of several chronic diseases that may lead to premature death and contributes to shortened life expectancy and increased health care costs. As the causes of the growing epidemic of obesity are multifactorial, the strategies to reverse the trends in weight status include actions by individuals, communities, and health professionals, including oral health care providers (OHCPs) [1, 5, 6].

Obesity and overweight can be defined by Body Mass Index (BMI) that is calculated based on a person's weight relative to the stature reported as kilograms/meters, squared (kg/m^2) [7]. While BMI does not account for body composition, it can be used as a gross marker for overweight and obesity and used to evaluate risk of chronic disease (See Table 4.1). In adults, overweight is defined as BMI equal to or greater than 25 and less than 30 and obesity is defined as BMI equal to or greater than 30; children and adolescents (ages 2–19 years) at or above the 85th percentile of BMI on the Centers for Disease Control and Prevention (CDC) growth charts are considered overweight and those at or above the 95th percentile are obese [7, 8]. Flegal et al. completed a systematic review and meta-analysis of associations between overweight, obesity and all-cause mortality and reported that class 2 (BMI $\geq$ 30 but $<$ 35) and class 3 (BMI $\geq$ 35 but $<$ 40) obesity were associated with higher rates of all-cause mortality when compared to normal weight [9]. Measurement of waist circumference (WC) is another screening tool to determine risk of chronic disease as high values may be considered a marker of abdominal obesity [10]. Values associated with increased risk of type 2 diabetes, hypertension and cardiovascular disease (CVD) are sex-specific; a WC greater than 40 inches in men and greater than 35 inches in women should be considered in addition to BMI as risks for related chronic diseases (see Table 4.2) [10].

This chapter will address the associations between overweight, obesity and oral health, some environmental factors that may impact oral health and disease, and, suggest roles for OHCPs in weight status screening, provision of education relative to oral health, and appropriate and timely referral of patients to other health care providers for counseling.

Associations Between Overweight/Obesity and Oral Health

While obesity is of concern for overall systemic health and risk of chronic diseases, it is important for OHCPs to be concerned with the associations between obesity and dental and oral health. The possible role of oral bacteria as a contributor to obesity has been investigated via measures of

salivary bacterial populations in overweight and normal weight subjects [11]. Composition of salivary bacterial changes in overweight subjects was evident when compared to healthy weight subjects; the results suggested that oral bacteria may contribute to development of obesity via several hypothetical propositions that need further investigation before stating definitive tenets. When 15,538 subjects in Sweden were assessed and followed from birth for 19 years to explore risk factors for caries development, the investigators found that overweight during pregnancy, as well as smoking habits, were risk factors for development of proximal caries in their offspring in their teen years [12]. Analysis of three cycles of National Health and Nutrition Examination Survey (NHANES) data collected between 2001 and 2006 noted a significant and positive association between obesity and timing of tooth eruption [12]. Teeth erupted earlier in obese children who on average had 1.44 more erupted teeth than non-obese children by 11 years of age [12]. The implications suggest that early and periodic oral health evaluation and preventive measures including dietary guidance may be needed as early as possible because, on average, obese children compared to non-obese children had significantly more erupted teeth for a more extended length of time exposure in the oral cavity, subsequently increasing risk for dental caries [13]. A meta-analysis of 14 studies examining the relationship between obesity and dental caries in children reported mixed and inconclusive results in general, but did indicate a significant relationship between obesity in children with permanent dentition and dental caries when parameters were standardized [14]. For example, Ziegler et al. noted an association between obesity and the sum total of bacterial cells (23 bacterial species derived from subgingival biofilm), in approximately threefold higher amounts, on average, in obese adolescents compared with normal weight controls, thus indicating a possible link between increases in oral microbiota indicative of caries risk and obesity in adolescents [15].

Suvan et al. conducted a systematic review to explore associations between overweight/obesity and periodontitis in adults [16]. The investigators concluded that there was an obesity-periodontal disease relationship mediated by chemicals (cyctokines and hormones resulting in low-grade inflammation and insulin resistance) secreted by adipose tissue and implicated in periodontal disease. This finding supports an association between BMI, overweight and obesity [16]. Dental plaque and infection were associated with a high BMI and obesity, independent of dietary patterns and insulin resistance, when investigators analyzed associations between number of teeth, periodontal status, and plaque index (15). A systematic review of 41 epidemiologic studies examining the evidence of an obesity-periodontal disease relationship supported by the National Institutes of Health suggested greater mean clinical attachment loss among obese individuals and an increase in periodontal disease with increasing BMI [16]. However, the magnitude of these associations remains unclear in cross-sectional studies due to confounders that have not been categorically defined. Thus, clinicians should continue to stress the importance of maintaining a healthy weight [17] for overall health and disease risk reduction.

Environmental Factors Related to Obesity and Oral Health

While there is controversial evidence regarding the associations between obesity and dental caries and periodontal disease [14, 18], there is an association between incidence of caries and increased sugar-sweetened beverage (SSB) intake and greater levels of inflammation, larger WC, and decreased HDL cholesterol in children age 3–11 years of age [19]. The authors reported associations between SSB and cardiometabolic markers in children, and suggest that prospective studies are warranted to determine if SSB may be one of the food and nutrition targets leading to deleterious systemic health effects. According to the CDC, SSBs include sodas, soft drinks, fruit drinks/ades, sports drinks, tea, coffee, energy drinks and milk drinks that contain caloric sweeteners or syrups [20]. These beverages are also a source of fermentable carbohydrates associated with caries risk.

Similarly, Skinner et al. [21] reported significant associations between inflammatory markers and increasing weight in a cross-sectional study among children age 1–17 years old. While the identified association cannot be assumed to be causal, SSB may be independently associated with obesity, obesity-related chronic diseases, and dental caries. As part of health promotion and treatment efforts, OHCPs can advise patients on the impact of cariogenic foods and beverages, including SSB, on oral, nutritional and systemic health and healthful approaches to reducing risk of oral and systemic diseases and maximizing health.

Dietary patterns refer to food choices, portion control, and frequency of food intake that includes meals and snacks. Snacking among Western populations has resulted in a nearly doubled intake of energy-dense, low-nutrient-dense snack foods in the past two decades [22, 23]. In the US, potato chips, fried potatoes, whole milk and fruit drinks were identified as snack preferences among individuals with incomes below the poverty level; high-income groups prefer grain-based salty snacks, fruits, skim milk, soft drinks, coffee and tea [22]. Among 44,754 adults aged 19 years and older, the five most common sources of snack foods were desserts, salty snacks, sweetened beverages and fruit juices [23]. In either case, one can identify available fermentable carbohydrates in these foods that may contribute to caries risk. Caries development in children and adults has become significantly associated with the increasing role that snacking plays in dietary patterns [24]. Additionally, a prominent dietary trend has been the increasing frequency with which meals are consumed outside of the home in fast food establishments, restaurants, from street vendors, convenience stores and vending, all of which have implications for diet quality, obesity and chronic disease risk including oral diseases [25]. Both dietary food and beverage choices and patterns of consumption including frequent intake of energy dense low nutrient quality options can contribute to risk of overweight and obesity [24, 26].

The environment includes both food and physical activity factors responsible for modulating behavioral decisions associated with the prevalence of overweight and obesity in both children and adults. Figure 4.1 illustrates a synergistic environmental model that identifies primary influences on individuals, families, communities, and societies that may impact access to and availability of a spectrum of food choices. Larson et al. surveyed 2,793 adolescents and concluded that infrequent family meals, a higher proportion of friends who were overweight, television viewing, and lower physical activity among female friends were associated with higher BMI z-scores [27]. Inequitable access to healthy foods is one mechanism by which socioeconomic factors influence the diet and health of a population where obesity may follow a social gradient [28]. As income declines, energy-dense, nutrient-poor foods provide daily calories at an affordable cost whereas nutrient-rich foods and high-quality diets may cost more and be consumed by more affluent groups [28]. School children in rural areas have been reported to have a higher prevalence of obesity as compared to children in urban schools due to socioeconomic distress where parents are single, possibly unemployed and have lower educational attainment [29]. Associations between overweight and obesity and longer work hours and shift hours have been identified among adults. Much of this has been attributed to the environmental shifts in employment from agriculture and physical labor to automated, labor-saving environments and to after-work hours spent on social networks [30].

Interprofessional Practice

Obesity is a disease that is prevalent globally. This disease is associated with increased risk for several chronic diseases with oral health implications. Although there is no causal evidence of the impact of obesity on oral disease, studies cited throughout this chapter speak to associations between obesity and oral diseases. Collaboration across disciplines including networking with physicians, pediatricians, and registered dietitians (RD) to foster health promotion and disease prevention and

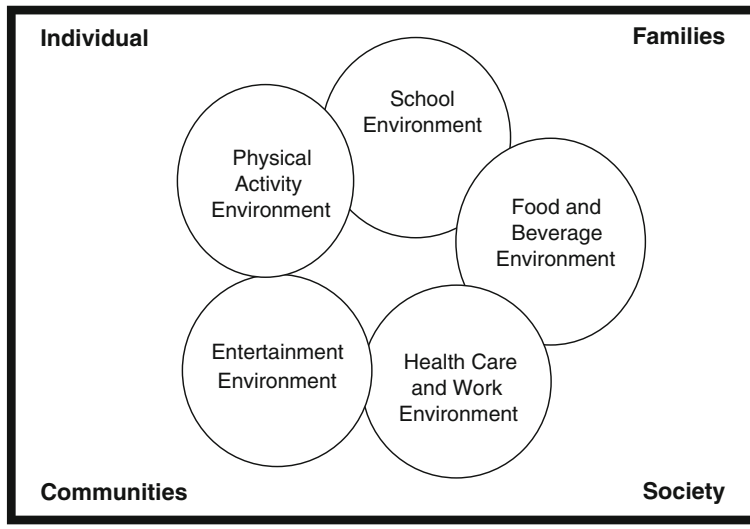

Fig. 4.1 A model of synergistic environmental influences on obesity and oral health status [27–29]

intervention through weight screening, education and referral may help reduce the prevalence of obesity [31, 32]. The American Dental Association's "Call to Action for Oral Health" aims to reduce oral health disparities while "advocating for healthier lives, through guidelines on healthy nutrition…" and that to make an impact OHCPs must identify the needs of the patient populations and remove barriers that may impede action [33, p. 96]. This section addresses approaches for OHCPs in weight screening, education and referral. Although weight loss counseling is outside of the scope of practice for OHCPs, awareness with scientifically sound approaches may be valuable in directing patients for care. Weight management resources and strategies are presented in an effort to familiarize OHCPs with recommended approaches to patient care in the context of interdisciplinary collaboration to reduce obesity prevalence.

Role of OHCPs in Weight Screening

Oral health affects overall health and wellness [34]; OHCPs have a role like other health professionals in screening patients for overweight and obesity, providing basic health promotion and disease prevention education and referring accordingly to other health professionals [32, 35, 36].

All health care providers are encouraged to serve as role models and advocate for health. The Patient Promise is an initiative aimed at health professionals to encourage them to partner with patients and clients in adapting healthy lifestyle examples. It encourages health professionals to "lead by example" by practicing healthy behaviors for diet, physical activity and stress management to reduce risk of and manage chronic diseases including obesity, CVD, hypertension and diabetes (http://www.thepatientpromise.org/index.html). Students and clinicians can adopt the Patient Promise to make a commitment to their patients to practice the same healthy behaviors that they espouse (http://www.thepatientpromise.org/index.html).

Awareness of the associations between overweight/obesity and systemic and oral health, can prepare OHCPs to screen and provide pertinent education on the role of diet and oral health and disease, and as necessary provide referrals to RD for weight management counseling, or other health care providers for chronic disease management.

Screening for Overweight and Obesity

Knowledge and confidence have been identified as barriers to screening and counseling on dietary intake and obesity [37, 38] and diabetes and oral health [39] among OHCPs. OHCPs are increasingly adopting screening practices for chronic diseases including diabetes and CVD [35, 36, 40]. They may also recognize their role in weight screening and questioning patients about their use of weight control diets, dietary intake patterns, and dietary supplements in the context of the dental office as part of routine care for patients of all ages [41, 42]. Since overweight and obesity increase risk and associated comorbid conditions of both CVD and diabetes hence the integration of weight screening would expand their screening practices in a comprehensive manner. Both future and currently practicing OHCPs may benefit by continuing professional education and accessing resources to confidently screen for overweight and obesity and provide referrals to their patients for best possible outcomes. Chapters 11 and 19 on diabetes and approaches to oral nutrition health risk assessment respectively provide additional insight into screening strategies.

However, while excess body weight carries social stigma in the US [43], OHCPs and other healthcare providers may feel uncomfortable and uncertain in their approach to screen and discuss the topic with their patients and the caregivers of pediatric patients, especially if the provider is overweight or obese himself/herself [44, 45]. The Weight Control Information Network recommends addressing the patient's primary concern first and then having an open discussion regarding weight control, and encourages using terms such as "excess weight" or reference to BMI, rather than using the terms "overweight" and "obese" (Table 4.3) [46]. Volger et al's research findings further emphasized avoiding undesirable terms such as "heaviness", "fatness" and "large size" [47]. Tseng et al. [31] offer practical guidelines for addressing obesity in the dental practice, and they emphasize that the context of the discussion should relate obesity to oral health and disease. The messages should be delivered in a culturally appropriate manner and sensitive to the wellbeing of the patient or caregiver. Explaining the rationale behind recommendations may increase the likelihood of attaining change.

Approaches to screening may also involve ancillary office personnel who are trained in weight screening and providing patients with reading materials (print or other media) in the waiting area. The treating OHCPs may then have a more focused discussion of what their BMI or weight status reflects, associated risks and approaches to referrals for management. In some settings OHCPs may place signage in waiting areas indicating that their office provides weight screening and referral as part of comprehensive care so the patient is aware of the practice. Positive promotion of screening practices can help the patient to understand the added value of this service.

Health Education and Promotion by OHCPs

Health promotion and disease prevention are within the scope and competence of the OHCPs in regards to general dentistry [32, 35]. OHCPs may educate patients on dietary intake with regards to risk of oral infectious diseases and their management, diet modifications following restorative or reconstructive procedures, and management of oral soft and hard tissue disease relative to diet. Screening, basic education, and referral for counseling by a RD in the dental setting may be expanded to address the issues of overweight/obesity and systemic health and the interface with oral health and disease.

Tavares et al. [48] reported a successful pilot program for weight intervention in a pediatric dental setting. The Healthy Weight Intervention (HWI) program was an office-based protocol in which the dental hygienist screened weight status and dietary intake and physical activity patterns. As a result of the health report card, recommendations were provided and goals were set. Based on follow up at the next dental appointment, children and caregivers reported making healthier food choices and working

Table 4.3 Weight screening, sample questions, and resources for clinicians [46]

Purpose	Question/action	Resources/outcome
Screen for overweight and obesity by measuring height and weight. If a scale (to measure weight) and stadiometer (to measure height) are not available, screen based on patient recall	Calculate BMI (note different tools for adults and children/ adolescents)	http://www.cdc.gov/healthyweight/assessing/bmi/index.html or download the smartphone app
Start the discussion in a respectful, culturally-sensitive manner; be aware of body language of both the clinician and patient	"Ms. Brown, your BMI is above the healthy range. Excess weight could increase your risk for some health problems. Would you mind if we talked about it?"	If the patient is receptive to the conversation then continue to ask about dietary intake and physical activity. If the patient is resistant to a discussion then emphasize the importance of weight management in context of reduced risk of chronic disease and impact on oral health
Find out what a patient's eating habits are like on a typical day	"What kinds of foods do you eat on a typical day?" "What does 'healthy eating' mean to you?"	www.choosemyplate.gov offers resources for weight management that a OHCPs and patients may access and use http://myplate.gov/weight-management-calories/weight-management.html
Find out what a patient's physical activity habits are like in a typical day/week	"How much time do you spend sitting down each day?" "Do you know how much physical activity you should do each week to stay healthy?"	Aim for 150 minutes of moderate intensity physical activity a week. http://myplate.gov/weight-management-calories/weight-management/better-choices/increase-physical-activity.html
If a patient is ready to adopt a healthier lifestyle, refer them to a registered dietitian for weight management counseling or to a primary care clinician with expertise in treating patients with overweight and obesity	Refer to www.eatright.org for a RD in you area by zip code; Refer to http://www.obesity.org/membership/clinician-directory.htm to find a clinician certified by the American Board of Obesity Medicine (ABOM)	Refer patient. Follow up on outcomes at 6-month recall (or sooner if actively treating patient)

towards their goals. As this was a pilot intervention long term outcomes are not published, however with repeated follow up visits, OHCPs can monitor progress and revise goals as needed.

OHCPs are encouraged to be part of the interprofessional team that can support weight management for general health promotion [32]. To do so, OHCPs can look towards other health care providers for examples and strategies to incorporate nutrition, physical activity, and obesity screening and referral into patient care encounters. Perrin et al. [49] demonstrated that pediatrician confidence was improved after they received training and resources for obesity-related counseling. A pre-intervention questionnaire was administered to 67 pediatricians to elicit their perceived confidence and frequency of counseling on weight, physical activity and nutrition. The questionnaire was followed by a training session that included instruction on how to use a color-coded BMI chart to screen for risk of overweight and obesity and a guide to discussing weight with parents including assessing readiness to change, how to tailor counseling, and goal setting. After a period of implementation (2–4 months) the pediatricians reported improved confidence, more ease in counseling, and increased frequency with which they discussed nutrition and physical activity. The authors concluded that when equipped with the training and resources, clinicians might change practices regarding counseling that may have a long-term impact on overall health.

Weight Management Interventions and Resources

Balancing dietary intake (nutrition) and physical activity is the core principle in energy balance and hence, weight management. Lifestyle modification approaches that integrate a balanced, healthful diet and physical activity are supported by strong evidence and the Academy of Nutrition and Dietetics [50], the American Heart Association [6], and the American College of Sports Medicine [51]. The strong evidence-based conclusions are a reflection of studies conducted using a sound research design and scientific rigor that have been subjected to critical review and consensus leading to a defined and stated and agreed upon tenet of the strength of the evidence supporting reported outcomes [52]. For weight loss, energy intake must be less than energy expended from the basal metabolic rate and physical activity [1]. Thus the cornerstones of weight management are dietary intake and physical activity recommendations. However, the approaches to change the diet and physical activity patterns are often packaged in behavior therapy [6, 8, 53]. The combination can also promote improved cardiac and respiratory fitness and loss of abdominal fat. Wadden et al. provide a comprehensive review of diet, physical activity, and behavior therapy to modify habits and promote weight management [53]. The authors review the research on diets that vary in macronutrient composition (e.g. low carbohydrate, low fat), the use of meal replacements (e.g. meal bars, liquid shakes), the role of physical activity in weight loss and maintenance, and several behavioral therapy interventions. The general guidelines are outlined in Table 4.4. Despite the various approaches published on macronutrient distributions best for weight loss, and advocacy of dietary approaches to reduce risk of CVD [54] and blood pressure [55], overall energy (caloric) restriction is the primary factor in achieving weight loss [53]. According to the Academy of Nutrition and Dietetics, goals should be set for a loss of 1–2 pounds per week, achieved by a combination of caloric deficit (of 500–1,000 calories/day) and increased physical activity [6, 50]. It is likewise important to note that energy needs for weight loss need to be periodically reassessed and adjusted, as energy needs change with changes in body weight. For example, an individual weighing 180 pounds will lose weight faster on an 1,800 calorie diet than an individual weighing 150 pounds as the heavier person needs more calories to maintain their weight. Table 4.4 provides guidelines for general calorie levels for weight loss; however, these should be tailored to an individual's current weight and physical activity by a RD.

When behavior therapy alone fails to change dietary intake and physical activity habits, patients have the options of medically supervised prescription medication (pharmacotherapy) and surgical interventions (bariatric surgery) for weight management [56]. Clinicians and patients can use BMI and presence of comorbid conditions (hypertension, type 2 diabetes, dyslipidemia) to determine the appropriate treatment options according to the guidelines set forth by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery. (Table 4.5) [57]. For a BMI greater than or equal to 25, the frontline therapy should be dietary modification, physical activity, and behavior therapy. For a BMI greater than or equal to 30, or a BMI 27–29.9 with comorbidities, pharmacotherapy may be considered in addition to diet, physical activity, and behavior therapy. For patients with a BMI greater than or equal to 40 who present with a favorable surgical risk, bariatric surgery may be a treatment option. Bariatric surgery may also be considered in patients with BMI greater than or equal to 35 with comorbidities or in people with a BMI 30–34.9 with diabetes or metabolic syndrome [57]. The Obesity Society has a campaign entitled "Treat Obesity Seriously" (http://treatobesityseriously.org) that may serve as a resource for OHCPs and their patients [58]. The website has information on the burden of the disease, tools to calculate BMI, and links for resources on medical weight loss procedures and referrals.

Pharmacotherapy options are presented in Table 4.6. Orlistat which is a lipase inhibitor may potentiate the anticoagulant effect of anticoagulant medications; for patients taking Orlistat and anticoagulant medications, OHCPs may want to check recent (or order if not available) INR

Table 4.4 Key components of comprehensive approach for weight loss and maintenance [53]

Components	Weight loss	Weight maintenance
Frequency and duration of treatment contact	•Weekly contact, in person or by telephone for 20–26 weeks	•Every other week contact for 52 weeks or longer; monthly contact may be adequate
Dietary prescription	•Reduced calorie diet (1,200–1,500 kcal for individuals <250 pounds or 1500–1800 kcal for those >250 pounds) •Typical macronutrient composition <=30% fat, 15–25% protein, remainder from carbohydrate	•Group or individual contact. Consumption of a hypocaloric diet to maintain reduced body weight •Macronutrient composition similar to that for weight loss
Physical activity prescription	•180 minutes/week of moderately vigorous activity; strength training desirable	•200–300 minutes/week of moderately vigorous activity
Behavior therapy prescription	•Daily monitoring of food intake and physical activity by use of paper or electronic diaries •Weekly monitoring of weight	•Occasional to daily monitoring of food intake and physical activity •Twice weekly to daily monitoring of weight

Table 4.5 Treatment options according to BMI category [57]

Treatment	BMI category
Diet, physical activity and behavior therapy	BMI >= 25
Pharmacotherapy	BMI = 27–29.9 with comorbidities BMI > 30
Bariatric surgery	BMI = 30–39.9 with comorbidities BMI >= 40 and acceptable surgical risk

(international normalized ratio) values. Those that are central nervous system stimulants suppress the appetite but have possible practice management implications for the OHCP. The side effects of these are outlined in Table 4.6; OHCPs should ask patients about use of weight loss drugs and be aware of those that impact the transmission of norepinephrine, serotonin and dopamine in the central nervous system. Although there is a paucity of evidence at this time, blood pressure and pulse should be monitored when using local anesthesia with vasoconstrictors, especially in patients with hypertension and CVD. OHCPs should inquire about all medications, even short-term medications before commencing treatment or prescribing medications for oral conditions or post-treatment therapy. In addition to pharmacotherapy as a treatment option, OHCPs should be aware that many over-the-counter dietary supplements are marketed for weight loss and increasing energy, however as these are dietary supplements patients may take dietary supplements unbeknownst to the OHCP or any other member of the health care team. This may be of concern as dietary supplements may not be risk free. Refer to Chapter 9 for more on dietary supplements.

Summary

Screening for overweight and obesity may be done with a simple calculation of BMI. Given the prevalence of overweight and obesity and the evidence of associations between obesity and oral and systemic health effects, health care providers, including OHCPs should be prepared to start the conversation with patients regarding the consequences of excess body weight. Scientific evidence supporting the linkage and interaction between oral disease and overweight and obesity in

Table 4.6 Food and drug administration approved short-term (12 week) pharmacotherapy for weight loss in adults [59]

Generic name	Drug type	Side effects
Phentermine	Appetite suppressant; CNS stimulant	Increased blood pressure and heart rate, sleeplessness, nervousness, dry mouth
Phentermine + topramate	Appetite suppressant; CNS stimulant plus anticonvulsant	Increased blood pressure and heart rate, mood changes, forgetfulness, sleepiness
Diethylpropion	Appetite suppressant; CNS stimulant	Increased heart rate, blood pressure, dizziness, headache, sleeplessness, nervousness, dry mouth
Phendimetrazine	Appetite suppressant; CNS stimulant	Increased blood pressure and heart rate, sleeplessness, nervousness, dry mouth
Orlistat (may be used for up to 1 year; approved also for children age 12 and older) Over-the-counter version (Alli) approved for adults 18 years and older	Lipase inhibitor	Must follow a low-fat diet to reduce gastrointestinal issues (cramping, diarrhea, oily spotting); rare cases of severe liver injury reported

observational studies strongly suggests OHCPs can assume a significant role in addressing the growing obesity epidemic in both children and adults. A concerted effort by all health professionals can reinforce messaging and hopefully reduce the prevalence of this disease, shown to be associated with chronic diseases that may manifest in the oral cavity. OHCPs with adequate education and training may interface with the patient and the interprofessional team to promote healthy lifestyle choices for optimal outcomes.

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Part II
Synergistic Relationships Between Oral and Systemic Health

Chapter 5
Bidirectional Associations Between Oral and Systemic Health

Judith E. Raber-Durlacher, Joel B. Epstein, Riva Touger-Decker and Lisette van der Molen

Keypoints

- Many systemic diseases have associated oral manifestations
- Systemic inflammatory processes are associated with oral inflammatory disease
- Dysphagia may occur due to locoregional diseases, vascular, neurologic, and autoimmune diseases and medical management
- An interprofessional approach is important for dysphagia screening and management
- The preservation of periodontal health is a key component of oral and overall health

Keywords Synergistic relationships · Oral and general health · Periodontal disease · Caries · Oral mucosal disease · Dysphagia · Diet management

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Introduction

The mouth is "the gateway to the body" and is thus challenged by invaders, including bacteria, viruses, parasites, and fungi [1]. Further challenging the functions of the oral cavity are oral infectious diseases, notably caries and periodontal disease, temporomandibular joint disorders, cancers of the head and neck, trauma, and other oral diseases. A potential relationship of oral infections and distant, nonoral diseases was first described in 1891, when Miller published the theory of "focal infection" which hypothesized that oral infections were responsible for a number of regional and systemic diseases, such as tonsillitis, pneumonia, endocarditis, and septicemia [2]. This concept was propagated until early in the twentieth century [3], but the lack of scientific evidence condemned this theory to dormancy. In recent years, there has been renewed interest with studies directed to periodontal disease and a potential relationship with various chronic systemic diseases and conditions. Most data indicating an association between periodontal infections and systemic diseases originate from epidemiological studies. Prospective cohort studies, which indicate that periodontal disease is associated with an increased risk of premature death from any cause, prompted the hypothesis that periodontitis may be a risk factor for several diseases [4, 5]. However, while outcomes support associations and biological plausibility, well-designed future studies using uniform definitions of periodontitis are necessary to obtain more insight in the role of periodontal infection and inflammation in systemic diseases and in the efficacy of interventions.

In turn, systemic diseases may have oral manifestations and minimizing the impact of these oral sequelae of systemic diseases and their treatments is one of the global goals of the World Health Organization [6]. Although there are still many questions to be answered, the preservation of periodontal health is seen as a key component of oral and overall health and is important in all patients [7]. Reciprocal oral and systemic interactions require a multiprofessional approach to patient care, research and collaboration among dental, medical, as well other healthcare professionals including dietitians. It is essential for health professionals to ensure that patients receive appropriate and timely oral health care, which includes oral health education. Table 5.1 summarizes a broad range of oral-systemic problems that may have bidirectional impact and should prompt the primary care provider to consider evaluation by the dentist, dental hygienist, registered dietitian, or physician. The current knowledge of bidirectional associations and relationships between periodontal disease and caries and selected systemic illnesses are reviewed in this chapter. Diabetes mellitus, cancers of the head and neck, autoimmune diseases, orofacial pain, and functional disorders are addressed elsewhere in this book.

Periodontal Disease

Gingivitis and periodontitis ("periodontal disease") are complex multifactorial inflammatory diseases caused by microorganisms in the biofilm (dental plaque) and the host response that effect the supporting tissues surrounding the teeth. In gingivitis, inflammation is limited to the gingiva, and the condition is characterized by the absence of attachment loss and is reversible by practicing good oral hygiene. Clinical signs of gingivitis include erythema, edema of the gingiva, changes in contour, consistency, texture, and bleeding on provocation. In periodontitis, the inflammation extends into the tissues affecting the attachment apparatus of the tooth and is a major cause of tooth loss in adults. Gingivitis and moderate periodontitis are rather common, and prevalence increases with age. Moderate periodontitis is estimated to affect 40–50% of adults and approximately 10% of the adult population of western countries suffers from severe forms of periodontitis [8]. Similar figures for the prevalence of severe periodontitis were reported in a Swedish study, although recently more individuals have a healthy periodontium as compared to reports in the early 1970s [9].

Table 5.1 Selected disorders or events for which a clinical pathway including referral among oral health, medical, and nutrition/dietetics clinicians should be considered

Systemic
- Diabetes mellitus
- Autoimmune disorders (Sjogren syndrome, lupus erythematosus, rheumatoid arthritis, pemphigus vulgaris, cicatricial pemphigoid)
- Cardiovascular disorders (risk for infective endocarditis, atherosclerotic cardiovascular disease and screen for periodontitis and periapical infections)
- Coagulation disorders
- Eating disorders (anorexia nervosa, bulimia)
- Malnutrition and obesity
- End stage renal disease
- Greater than 10% unexplained weight changes in the past 6 months
- Inflammatory bowel diseases
- Neurodegenerative disorders affecting physical ability
- Systemic immunosuppressive therapy (organ transplant, primary immunologic disorders)
- Osteoporosis
- Pathologic immunosuppression (HIV, AIDS, malignancy)
- Pregnancy (for periodontal disease assessment and care)
- In vitro fertilization
- Likely to undergo mechanic ventilation (aspiration pneumonia)
- Tobacco use

Oral
- Dysphagia
- Orofacial pain
- Oral or pharyngeal cancer (pre-, intra-, and post-therapy)
- Chronic or recurrent oral mucosal lesions
- Poor oral hygiene (plaque and calculus)
- Gingivitis and periodontitis (inflamed gingival tissues)
- High caries risk (three or more carious lesions in the past 12 months)
- Xerostomia
- Taste alterations
- Halitosis

Although microorganisms, particularly Gram negative facultative or strictly anaerobe bacteria are needed for initiation, maintenance, and progression of periodontal diseases, the immune/inflammatory response of the host to the microbiological challenge is a critical element in determining the expression of periodontal disease. The genetic make-up of the host has a major influence on this response. An important corollary is that any systemic condition that is able to modulate the fine balance between the microbial composition of the dental plaque and the host response to this challenge can constitute a risk factor for periodontal diseases. Responses include vascular changes and involvement of various inflammatory and immune cells, which are coordinated by proinflammatory mediators including interleukin IL-1, IL-6, and tumor necrosis factor (TNF)-α, and anti-inflammatory mediators including IL-10. Eventually, the effectors of periodontal inflammation and destruction such as proteinases and osteoclasts are activated. Additionally, environmental factors including lifestyle factors such as nutrition and diet contribute to the development and progression of periodontal diseases. Some of the most frequent conditions and environment factors identified as modifying the expression of periodontal diseases are diabetes mellitus, immunosuppression, hormonal changes, smoking, stress, and dietary factors. Discussion of systemic diseases and conditions in relation to periodontal disease in this chapter is limited to cardiovascular disease; Chapter 11 addresses diabetes and periodontal disease in greater depth; Chapter 8 on nutrition and inflammation also addresses periodontal disease.

Periodontal Disease and Alterations in Sex Hormones

Hormonal shifts occurring during puberty, the menstrual cycle, and pregnancy are proposed as one of the mechanisms responsible for increased expression of gingivitis during these physiological states [10]. Studies suggest that the prevalence, severity, and extent of gingivitis increase in adolescents reach a peak around the age of 12–14 years and decrease thereafter, with significantly lower values by the age of 16–17 years [11]. The increase in the severity and extent of gingivitis appear to parallel sexual maturation rather than plaque index, suggests an enhanced response of gingival tissues to the presence of dental plaque and supporting the role of puberty in the pathogenesis of gingivitis [12]. During puberty, the hormonal changes vary between girls and boys. In girls, there is a significant increase in estrogen and progesterone; in boys, testosterone reaches significantly higher values. The main mechanisms by which sex hormones affect periodontal tissues include host-related alterations such as angiogenesis and increased vasodilation, decreased epithelial keratinization, reduction in neutrophil chemotaxis, and changes in T cells and signal transduction molecules [13].

Changes in gingival appearance may also occur throughout the menstrual cycle. The menstrual cycle is associated with surges in progesterone and estrogen, although less dramatic than those seen in pregnancy. Gingival changes may manifest as increases in gingival crevicular fluid [14]. It appears that this increase occurs particularly during ovulation and pre-menstruation. A 2012 study concluded that while ovarian hormones have a negligible effect on a clinically healthy periodontium, these hormones may exaggerate pre-existing inflammation in gingival tissues [15].

More pronounced gingival inflammation has also been observed with the use of oral contraceptives. However, most studies on birth control pills were performed when the medication contained much higher levels of hormones compared to the medications in use today. A literature review concluded that current oral contraceptives no longer place users at increased risk for gingivitis or periodontitis [16].

In vitro fertilization in which women are treated with high levels of female sex hormones may increase the severity of gingivitis and pre-existent periodontitis [17]. In addition, it has been speculated that sex hormones administered for gender transformation may affect the periodontium.

During pregnancy, there is a significant increase in gonadotropins in the first trimester and in progesterone and estrogens in the second and third trimesters. It is well documented that pregnancy is associated with an increase in the prevalence and the severity of gingivitis which is reported in between 30 and 100% [18, 19]. During pregnancy, gingivitis increases in severity as early as the second month of pregnancy, increases further as the pregnancy advances, reaches a maximum around months 7 and 8, decreases in month 9, and returns to pre-pregnancy values in the postpartum period. The clinical signs of pregnancy gingivitis include increased gingival redness, bleeding, and swelling [18, 20]. These changes are independent of the amount of plaque present [21], but studies suggest that the bacterial composition of dental plaque shifts during pregnancy. A significant increase in the proportion of anaerobic bacteria has been reported, particularly of *Prevotella intermedia* which may be associated with the ability of these bacteria to use progesterone as a growth factor [22, 23]. In addition to direct effects of sex hormones on the gingival vascularization, shifts in immunological responses may be involved in the pathobiology of pregnancy gingivitis [24, 25]. Periodontitis may exacerbate during pregnancy, particularly in multiparous women [26]. Occasionally, pregnant women develop a "pregnancy epulis" or tumor of granulation tissue. This benign tumor often bleeds easily and can appear red and inflamed. In general, a pregnancy epulis is not painful and does not have the potential to become malignant. Usually it will become smaller and resolve after childbirth, but in some cases surgical excision is required.

Maternal periodontitis has a potential to influence the health of the fetal–maternal unit and has been associated with adverse pregnancy outcomes, including low birth weight, pre-term birth, growth restriction, pre-eclampsia, miscarriage, and stillbirth [27]. However, the strength of the

observed associations is modest and seems to vary according to the population studied and with the definitions of periodontal disease. Maternal periodontitis represents a potential source of microorganisms that are known to routinely enter the circulation, and directly or indirectly may influence the health of the fetal–maternal unit [28]. Periodontal pathogens or their byproducts may reach the placenta and spread to the fetal circulation and amniotic fluid. Their presence can stimulate fetal immune and inflammatory responses characterized by the production of antibodies against the pathogens and the secretion of elevated levels of inflammatory mediators, which may cause miscarriage or premature birth [29]. Moreover, systemic infection and inflammation may cause structural placental changes leading to pre-eclampsia and impaired nutrient transport causing low birth weight. Finally, the systemic inflammatory induced response due to periodontitis may exacerbate local inflammatory responses at the fetoplacental unit and further increase the risk for adverse pregnancy outcomes.

Periodontal therapy has been shown to be safe and leads to improved periodontal conditions in pregnant women. However, periodontal therapy, with or without systemic antibiotics, does not reduce overall rates of pre-term birth and low birth weight [30, 31]. Future research should focus on various treatment strategies as well as timing and intensity of treatment. Nevertheless, as an important component of prenatal care, oral health and periodontal health, should be maintained or re-established in pregnant women, with specific attention to reduction of the periodontal microbial infection and related inflammatory responses.

Periodontal Disease and Atheriosclerotic Cardiovascular Diseases

Cardiovascular disease (CVD) encompasses several pathological conditions involving the heart and vascular system including coronary heart diseases, hypertension, cerebrovascular diseases, and peripheral vascular diseases. The most common pathologic basis for these diseases is atherosclerosis, which is a pathological condition affecting the mid- and large-sized arteries. Its lesions are characterized by accumulation of lipids and fibrous elements formed within the intimal layer of the vessels. Inflammation has emerged as an integrative factor for atherosclerosis and can operate in all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis [32]. The major risk factors for atherosclerolerotic cardiovascular disease (ACVD) include dyslipidemia, hypertension, obesity, smoking, physical inactivity, poor diet, and diabetes. Obesity alone is associated with mortality as well as being a risk factor for diabetes, metabolic syndrome, ACVD, coronary heart disease, and stroke. Along with the growth in prevalence of obesity, the prevalence of diabetes, both diagnosed and undiagnosed, and prediabetes have also increased in adults and children. Similarly, the prevalence of metabolic syndrome has also increased. Combined, the prevalence of all these risk factors, in the end, increases risk for ACVD [33].

Both mechanistic and clinical studies have been published examining the possible role(s) of periodontal disease in the pathogenesis of CVDs and associations between the two diseases [34]. The first study that found positive epidemiological evidence for an association between periodontitis and ACVD was reported in 1989 [35]. Thereafter, remarkable pathological and epidemiological associations between these two diseases have been presented [36]. Bahekar and coworkers performed a systematic review on the association between periodontitis and ACVD revealing five prospective cohort studies, five case-control studies and five cross-sectional studies. Meta-analysis of the cohort studies (86,092 patients) indicated that individuals with periodontitis had a 1.14 times higher risk than the controls (relative risk 1.14, 95% CI 1.074–1.213, $P < 0.001$). The case-control studies (1,423 patients) showed an even greater risk (OR 2.22, 95% CI 1.59–3.117, $P < 0.001$). The prevalence of CVD in the cross-sectional studies (17,724 patients) was significantly greater among individuals with periodontitis than in those without periodontitis (OR 1.59, 95% CI 1.329–1.907,

$P < 0.001$) [37]. The studies were adjusted for confounding factors shared by periodontitis and CVD which include increasing age, male sex, race and ethnicity, education and socioeconomic status, stress, smoking, alcohol abuse, diabetes mellitus, physical inactivity, and overweight [38, 39].

Although a causal relationship is debated and presently not demonstrated [34], the recent joint workshop of the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP) reported that there is consistent epidemiologic evidence that periodontitis increases the risk for future ACVD [40]. However, epidemiological evidence does not address causality or the mechanistic nature of the associations.

Several pathophysiological pathways have been suggested to explain the association between periodontitis and atherosclerosis. Periodontitis is associated with increased systemic levels of IL-1, IL-6, IL-8, TNF-α, C-reactive protein (CRP), fibrinogen, and other acute phase reactants [41]. CRP and other inflammatory reactants promote systemic inflammation and are associated with atherosclerosis. Endothelial cells stimulated by these inflammatory reactants increase their expression of various leukocyte adhesion molecules. Once adherent to the activated endothelial layer, the monocyte penetrates into the inner layer of arteries and initiates an atherosclerotic lesion. Subsequently, monocytes become macrophages undergoing a series of changes that ultimately lead to foam cell formation. These foam cells contain large amounts of a fatty substance, usually cholesterol and characterize the early atherosclerotic lesion. Macrophages within atherosclerotic plaques also secrete a number of growth factors and cytokines involved in lesion progression [42]. In addition, recent evidence suggests that periodontitis is associated with increased platelet activation [43]. Periodontal bacteria may induce activation of endothelial cells and platelets, which contributes to a procoagulant state and constitutes a risk for atherothrombosis. In addition, bacteremia originating from the mouth is a common event that occurs not only with invasive dental treatment, but also from activities of daily living including chewing and tooth brushing, especially in patients suffering from gingivitis and periodontitis [44]. Periodontal pathogens (i.e., *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia, Treponema denticola, and Eikenella corrodens*) enter the circulation via the gingival sulcus. These periodontal pathogens adhere to and invade the vascular endothelial cells. Infection of these endothelial cells by the periodontal pathogens induces a procoagulant response that might contribute to formation of an atherosclerotic plaque. Moreover, periodontal pathogens have been found in atherosclerotic plaques [45].

Mechanisms described above may act in concert to increase systemic inflammation associated with periodontal disease and to promote or exacerbate atherogenesis. However, proof that the increase in systemic inflammation attributable to periodontitis impacts inflammatory responses during atheroma development, thrombotic events, or myocardial infarction or stroke is presently lacking [46].

With respect to interventions, there is moderate evidence that periodontal treatment reduces systemic inflammation as evidenced by reduction of CRP and improvement of both clinical and surrogate measures of endothelial function. Limited evidence shows improvements in coagulation, biomarkers of endothelial cell activation, arterial blood pressure, and subclinical atherosclerosis after periodontal therapy. Nevertheless, there is no effect on serum lipid profiles [47].

Continued research is necessary to determine what factors in individuals with periodontal disease additionally predict risk for ACVD as well as alternate explanations for the observed epidemiological associations [48]. Future studies should explore common genetic susceptibility factors present in both diseases leading to increased inflammatory responses, as well as other shared risk factors for periodontal and cardiovascular diseases. Additional prospective, case-controlled studies are needed to clearly demonstrate that proposed associations are real and independent of common risk factors and intervention trials on the impact of periodontal treatment on prevention of ACVD are needed.

Although evidence for a causal relationship is lacking, practitioners should be aware of the emerging and strengthening evidence that there are strong associations between periodontitis and ACVD. In the light of these associations, patients with either disease should be screened for the other one. Based on the evidence presently available, individuals with periodontitis and other risk factors for atherosclerosis, such as hypertension, diabetes mellitus, overweight and obesity, smoking, etc., who have not seen a physician within the last year, should be referred to their primary care provider for evaluation of systemic health including ACVD. Early diagnosis of ACVD, coupled with secondary prevention strategies such as lifestyle changes, has been shown to have a favorable effect on the course of the disease. In addition, individuals with CVD and periodontitis should be referred to an oral healthcare professional for treatment of their periodontal disease [40].

Caries

Caries is one of the most common chronic infectious diseases in the world [49, 50]. Dental caries is an infectious microbial disease that results in dissolution and destruction of calcified tooth structure. Host (bacteria, saliva) and environmental (intake of fermentable carbohydrates in foods and fluids, oral hygiene, other dietary factors) influence the demineralization and remineralization processes occurring on tooth surfaces [51, 52]. The current incidence and prevalence data for caries is limited; the most recent as of 2013 are data from 1999–2004 [50]. For 2–11-year-old children, the prevalence of caries in the permanent dentition for 1999–2004 was 21 and 42% in the primary dentition of this age group. For adults during this same time period, the incidence is approximately 90% for coronal caries and 14% for root caries [50]. Up to 80% of the caries observed in children are only in about 25% of the children; this cohort represents children with primarily socioeconomic risk factors for disease. In particular, there is increased risk for root caries in these older individuals who have experienced varying degrees of gingival recession because of periodontal disease [53, 54]. Although fluoridation has had the single largest impact on the incidence of caries followed by dental sealants, improved oral hygiene, diet, education, and overall health have also played major roles [50, 55].

While the most common risk factors for caries are poor oral hygiene, diet (frequency of carbohydrate intake), low income, low education, and lack of community fluoridation, any systemic or local disease or medical therapy that results in salivary hypofunction may dramatically increase the risk for and incidence and progression of dental caries [56, 57]. Impaired salivary gland neurosecretory action caused by pharmacologic blockade is a common side effect of many medication classes (particularly antihypertensive, antihistaminic, antianxiety, and antidepressant medications), and any person with three or more carious lesions in one area who is taking a new medication should be evaluated for possible drug side effects [58] (see Chapter 6 on Medications). Several autoimmune disorders (e.g., Sjogren syndrome) can result in salivary gland damage, hyposalivation, leading to increased caries incidence (see Chapter 14 on Autoimmune disorders). Radiation therapy for the treatment of malignancy in the head and neck, when the major salivary glands are included in the treatment field, can result in profound hyposalivation leading to rampant dental demineralization and dental breakdown [59] (see Chapter 13 on Management of Cancer Therapies). Chemotherapy for cancer may also result in hyposalivation, which may recover with time from treatment and is typically less profound than that of other etiologies listed above.

Apical periodontitis, subsequent to the presence or restoration of deep lesions or fractured teeth, may result in inflammatory processes in the periodontal tissues that are initiated and maintained by an endodontic source of irritants [60]. Acute apical periodontitis is characterized by vascular dilatation, an exudate of neutrophil leucocytes, and edema in the apical periodontal ligament. Clinically, symptoms such as pain, tenderness, and swelling may be present [61]. Although these lesions most often confined to the oral region, they may extend to both nearby and distant body compartments

along the anatomical pathways. Hence, an acute periapical abscess may spread and reach the brain, the cavernous sinus, the eye, or the mediastinum. [62].

Chronic apical periodontitis is characterized by an inflammatory cell infiltrate rich in lymphocytes, plasma cells, macrophages, and granulation tissue. Most teeth with chronic apical periodontitis are asymptomatic. They are revealed most often by routine radiographic examination. It must be realized that the tissue reaction to irritation is a dynamic response, often fluctuating between acute and chronic inflammation. In root infections, bacteria are present not only in planktonic cells but also in biofilms, which are more resistant to host defense mechanisms and disinfectants.

It is well documented that bacteremia with oral bacteria, particularly streptococci, may lead to endocarditis [63]. In addition, in compromised hosts with cancer, unregulated diabetes, or immunodeficiency bacteria may multiply in the blood, resulting in potentially life-threatening bacteremia. In an epidemiologic study during a maximum follow-up of 32 years with 708 male adults, lesions of endodontic origin among those younger than 40 years old were statistically significantly associated with risk of ACVD after controlling for known risk factors [64], but as compared to periodontitis few studies are directed to a potential link between endodontic infection and inflammation and systemic diseases.

Guidelines for caries risk assessment (CRA) in both pediatrics and adults [51, 52, 65] are available. Risk assessment approaches look at the frequency of consumption of fermentable carbohydrates (including sucrose, glucose, fructose, and cooked starches) not the total volume [51]. Any patient with three or more carious lesions in the past 2 months is considered at high risk for future caries and should be evaluated for underlying causes (diet, hygiene, hyposalivation, and medications). Despite the continually high consumption of sugars and other sugar-based products, the widespread availability of fluoridated tap water and its use in other fluids has dampened the impact of dietary sugars consumption on the incidence of caries. The American Academy of Pediatric Dentistry [65] CRA addresses several factors relative to diet for children up until the age of 5 years and under including intake of more than three sugar-containing snacks or beverages between meals and going to bed with a bottle that contains sugared beverages. Featherstone's CRA includes between meal food/beverage snacks containing fermentable carbohydrates more than three times a day. Caries prevention strategies include attention to dental mineralization (fluoride, calcium, and phosphate supply), assessing levels of cariogenic flora, and diet intervention addressing healthy eating patterns and what the patient/client consumes between meal and bedtime with regard to fermentable carbohydrates [51, 52, 65]. Xylitol containing gums and mints have been promoted as anti-cariogenic measures [51, 65, 66]. Xylitol is a five-carbon sugar alcohol seen in the USA as one of several sweeteners used in some gums and mints, however its use is limited due to cost. When consumed in solution, xylitol does not cause a drop in plaque pH since oral bacteria do not metabolize it to organic acids. Xylitol also has an antimicrobial effect and can reduce mutans streptococci counts in plaque [67]. The American Academy of Pediatric Dentistry Caries Management Protocol for children aged 6 years and older recommends postprandial xylitol as gum or mints for those at high risk of caries [65].

Oral Mucosal Disease

Painful oral mucosal lesions can result in several local, systemic, and nutrition-related problems: impaired oral intake because of pain, damaged epithelial integrity as a portal for infection, altered taste, and a variety of complications related to treatment of the mucosal disorder may affect oral function). Representative oral mucosal disorders include local (oral cancer, aphthous stomatitis, reactive or traumatic lesions, recurrent [herpetic] viral lesions, candidiasis) and systemic disorders with oral manifestations (immune mediated, inflammatory conditions e.g., lichen planus, pemphigus

vulgaris, mucous membrane pemphigoid, lupus erythematosus, Graft-versus-host disease). Oral mucositis due to cancer therapy has a significant impact on quality of life, is associated with significant pain, and affects oral function, including oral intake. This section addresses cancer therapy induced oral mucositis. Chapter 13 addresses diet and nutrition management strategies for individuals with head and neck cancers in-depth.

Cancer Therapy Induced Oral Mucositis

Oral mucositis is defined as inflammation of oral mucosa commonly resulting from cancer therapy typically manifesting as erythema, ulceration, and pain. The condition may be exacerbated by local factors, such as microbial colonization or trauma from teeth. Trauma to the oral mucosal tissues may also result from eating or drinking hard or abrasive foods or hot liquids. The term stomatitis refers to any inflammatory condition of oral tissue, including mucosa, dentition/periapices, and periodontium. Stomatitis thus defines a broader range of pathoses of oral tissues, including mucositis. A number of instruments to evaluate the observable, subjective, and functional dimensions of oral mucositis are available, which may be used to facilitate patient care and in clinical trial research [68]. In addition, patient-reported outcomes of mouth and throat soreness have been developed [69, 70]. Traditionally, mucosal toxicities have been separated by site of occurrence and studied accordingly. However, new insights have led to the realization that cancer chemotherapy-induced mucosal damage affects the entire alimentary tract. Therefore, it has been proposed to use the term alimentary mucositis [71].

By virtue of their rapid mitotic rate, mucosal cells become targets of cancer cytotoxic regimens. This collateral damage affects treatment delivery and is often a dose-limiting toxicity, particularly for (chemo) radiation for head and neck cancers, and conditioning regimens for hematopoietic stem cell transplantation (HSCT). A significant number of patients report oral mucositis as the most debilitating and troublesome adverse effect of cancer therapy [72]. Considerable progress has been made in unraveling the pathobiology of mucositis [73]. A biological model for chemotherapy- and radiotherapy-induced oral mucositis was proposed by Sonis [74]. It became clear that mucositis is a complex phenomenon that does not only affect the epithelium, but also affects the connective tissue. The model includes events that have been described in five overlapping stages: initiation, upregulation, message generation, ulceration, and healing. Initiation involves the generation of reactive oxygen species, direct damage to cells, tissues and blood vessels, and the initiation of other biological events that create a cascade of reactions contributing to tissue damage. Activation of transcription factors such as nuclear factor-kappa B leads to an increase in proinflammatory cytokines including IL-6 and TNF. Feedback mechanisms result in amplification of the process, which finally leads to ulceration. Oral bacteria may colonize these ulcerations and their cell wall components activate macrophages to produce additional inflammatory cytokines. All these events lead to pain and particularly in neutropenic patients, bacteria may invade into the systemic circulation causing bacteremia and sepsis. Following cessation of cytotoxic therapy, healing occurs, and the epithelium appears clinically normal; however, ongoing alterations may persist predisposing to future complications.

Newer targeted agents such as tyrosine kinase inhibitors (TKi) and mammalian target of rapamycin inhibitors (mTORi) may also cause mouth ulcers [75, 76]. These advances in cancer therapy result in continuing prevention and treatment needs of mucositis and stomatitis in oncology care [77].

At present, little information is available on the pathobiology of oral lesions induced by targeted cancer therapies. Selected interventions have met some success and these include excellent oral care, oral cryotherapy using ice [78], exposure to low level laser therapy [79], and systemic administration of keratinocyte growth factor [80]. Each of these approaches has its limitations and while a number of agents are currently under development, what we currently have to offer to patients to manage mucositis and oropharyngeal pain is still inadequate.

Table 5.2 Causes of Dysphagia

Neurogenic	*Myogenic*	*Other*
Stroke	Muscular dystrophy	Connective tissue disorders
Multiple sclerosis	Myasthenia gravis	Rheumatologic and connective tissue disorders[a]
Amyotrophic Lateral Sclerosis (ALS)	Aging	Vagotomy
Diabetic neuropathy	Gastrointestinal resection	Medications
Cerebral palsy		
Guillain-Barré	*Latrogenic*	
Dementia	Medication side effects (chemotherapy, radiation therapy)	
Head trauma		
Obstructive		
Candidiasis		
Head and neck cancer, esophageal cancer		

[a] Rheumatoid arthritis, scleroderma, systemic lupus erythematous

Expansion of the current knowledge of the pathobiology of mucositis including the pharmacogenomics of toxicity is an important future goal. Ideally, this will lead the identification of the most appropriate targets for therapeutic interventions and opens avenues for toxicity risk prediction and personalized interventions to patients who are at risk.

Dysphagia

Swallowing dysfunction or difficulty (dysphagia) is characterized by difficulty with moving food, liquids, secretions, or medications from the oral cavity to the stomach. It can occur as a result of a variety of congenital abnormalities, structural damage, neurologic or muscular disorders, and/or medical conditions or complications of medical therapy [81]. Table 5.2 addresses causes of dysphagia. Locoregional cancer, postsurgical complications of head and neck, and oropharyngeal cancer have profound effects on dysphagia. This may be complicated by fibrosis associated with radiation or chemoradiation where late effects can have significant impact upon swallowing [82]. This section briefly addresses causes, consequences, screening, and nutritional management of dysphagia. References cited provide the reader with resources of more in-depth discussion of dysphagia. A review by Ney et al. [81] comprehensively addresses causes, consequences, and management of dysphagia with a focus on aging.

Clinical characteristics of dysphagia include coughing before, during, or after a swallow; frequent coughing toward the end or immediately after a meal, voice changes or a wet voice after a swallow, abnormal lip closure and tongue movement, lingual dis-coordination, delayed oral and pharyngeal transit times, incomplete oral clearance, (nasal) regurgitation, pharyngeal pooling, delayed or absent trigger of swallow, abnormal volitional cough, dysphonia and dysarthria [81, 83], and recurrent pneumonia [84].

There are two main types of dysphagia: *oropharyngeal* and *esophageal dysphagia*. Oropharyngeal dysphagia can be related to neurogenic disorders, decreased salivation (hyposalivation), oropharyngeal lesions, weakness of lips, decreased oral sensitivity, locoregional tumor, or cognitive disorders [81]. Symptoms may include excessive drooling due to limited swallowing of oral secretions, difficulty with initiation of a swallow (poor bolus formation, tongue weakness), coughing or choking, and changes in voice quality. Esophageal dysphagia can be related to obstructive disorders (e.g., stenosis or tumors), motility disorders, or motor dysfunction. Associated symptoms

include a sense of food "sticking" in the chest, coughing when lying down after eating, regurgitation of foods or medications in pill or capsule form, or dysphagia to solids that can progress to liquids and heartburn.

Consequences of Dysphagia

Dysphagia can result in numerous complications including aspiration of food, chest infection, aspiration pneumonia [85] compromised nutritional status, hospital admission and increased length of stay, overall disability, and increased mortality [84, 86–89]. Other negative outcomes include decreased functional status and rehabilitation potential, and decreased quality of life [90–93]. Silent aspiration accounts for 40–70% of aspiration in patients with dysphagia and is often associated with pneumonia and chest infections [94].

Nutritional Implications of Dysphagia

Dysphagia may result in insufficient food and fluid intake and/or dehydration. This is often because consuming an adequate volume is difficult or unsafe. Malnutrition occurs secondary to inadequate intake of calories, macro and micronutrients [81]. Dietary intake may be affected for long periods of time [83, 86, 91], and malnutrition significantly impedes the recovery process from medical or surgical therapy. Food choices often include low nutrient density foods and fluids that are soft, easy to swallow, and low in dietary fiber. Individuals with dysphagia are also at high risk for dehydration due to drooling of saliva and reduced fluid intake.

Dysphagia Screening

Dysphagia screening is defined as "a procedure designed to detect any symptoms of dysphagia or clinical indication of potential neurological deglutition dysfunction" [83] by nurses, dietitians, physicians, or other (oral) healthcare professionals [89, 94, 95]. Early screening and treatment of dysphagia leads to more cost-effective treatment, improves quality of care, and ensures optimal outcome [91, 96]. Screening can reduce risk of aspiration pneumonia in patients who have had a stroke. After identifying patients at risk for dysphagia, a referral can be made to a credentialed speech and language pathologist for dysphagia evaluation and assessment of swallowing and underlying anatomic or physiologic abnormalities using clinical diagnostic assessments such as videofluoroscopy [84].

Dysphagia screening tools typically include a patient interview, a questionnaire regarding diet and medical history, review of the medical record, observation of eating, cranial nerve screening assessment of cranial nerves V, VII, IX, X, and XII, and a brief swallow test [89]. Often a "dry swallow" test is used as a "wet" swallow would require administration of fluids and there is the risk of aspiration. The *Eating Assessment Tool (Eat-10)* [95] (http://www.nestlenutrition-institute.org/Documents/test1.pdf) is a 10-item self-administered questionnaire for assessing risk of dysphagia. Although it is subjective in nature and based on the patient's perception of their swallowing dysfunction, it can assist clinicians in determining dysphagia risk and initiating early referral to a speech and language pathologist. Belafsky et al. [95] have validated this tool and proven reliable for use in adults. Its advantages include its simplicity, applicability for use by a variety of healthcare

Table 5.3 Health professional's guide to dysphagia screening

WARNING SIGNS

- Pocketing food/medications
- Poor tongue control
- Drooling/increased secretions
- Gargly voice
- Delay or absence of elevation of thyroid cartilage
- Inadequate intake/weight loss
- Poor head control
- Tongue thrusting
- Slow oral transit
- Choking/coughing
- Mealtime resistance
- Regurgitation of food or liquids
- Altered level of consciousness
- Facial weakness

HISTORY TAKING: WHAT QUESTIONS TO ASK?

1. Presence of cough before, after, or during a swallow
2. Frequent swallowing to clear food or liquids
3. Frequent clearing of throat
4. Change in voice quality around eating
5. Feeling of something caught in the throat
6. Swallowing difficulties in the past
7. Avoidance of any foods or beverages
8. First symptoms of dysphagia, progression of symptoms

NUTRITION FOCUSED PHYSICAL EXAM TO IDENTIFY DYSPHAGIA RISK

Cognition:	Is the patient awake, alert and able to follow basic directions? Ask the patient to open their mouth and stick out their tongue. Ask the patient their name, date, and location.
Cranial Nerve Exam:	
Trigeminal (V)	Apply sensation of dull and sharp to face along the maxilla, mandible, and forehead (alternating sides). Test ability to move jaw and strength of jaw.
Facial (VII)	Ask patient to imitate facial expressions. Check for equal nasolabial folds. Test taste sensation in anterior 2/3 of tongue.
Glossopharyngeal (IX) and Vagus (X):	Test IX and X together. Touch posterior pharynx with cotton swab to test gag reflex. Should see elevation and tongue retraction. Have patient say 'Ah.' Look for bilateral elevation of the soft palate with midline uvula.
Hypoglossal (XII)	Ask patient to protrude tongue. Should be midline. Test strength of tongue with tongue depressor or gloved hand pressing against sides of tongue.
Conduct:	Ask the patient to cough. Ask the patient to perform a dry swallow.

R. Brody @ 2011

professionals and its coverage of swallowing difficulty (liquids, solids), symptoms (cough, pain, sticking), and consequences (weight loss, decreased quality of life). *The Registered Dietitian Dysphagia Screening Tool*, designed by Brody et al. [89] utilizes a medical record review, patient questioning, and observation of a meal to assess dysphagia (Table 5.3). Observation includes assessment for drooling of liquids and solids, cough during or after a swallow, facial or tongue weakness, difficulty with secretions, pocketing, changes in voice quality, posture and head control,

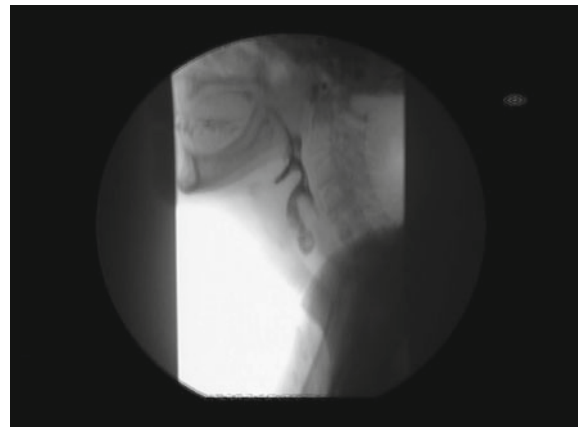

Fig. 5.1 Videofluoroscopic swallowing recording of aspiration

percentage of meal consumed, eating time, and presence of voluntary and dry cough. The tool was tested in hospitalized patients.

To define the abnormalities in anatomy and physiology causing the symptoms of dysphagia a clinical dynamic (diagnostic) assessment is essential [84].

Videofluoroscopy (VFS) (Fig. 5.1) is a frequently used technique to study the physiologic function of the swallow. By radiographic exposure the movement patterns of all four phases of the swallowing (oral preparatory, oral-, pharyngeal-, and esophageal phase of the swallow) can be visualized and examined in slow motion and frame by frame. This assessment also provides information on the presence and etiology of aspiration or penetration, and more than normal residue (efficiency of bolus movement). Another frequently used technique is *Fiberoptic endoscopic examination of swallowing* (*FEES*). FEES assessment is conducted using a flexible endoscope and a light source, and allows direct visualization of the structure and function of the oropharynx and larynx during swallowing.

Other dynamic assessment tools that can be used include *Manometry* (to measure the pressure in the pharynx and esophagus during swallowing), *Electromyography(EMG)* (to measure the amount of electrical energy generated by muscle contractions; most frequently used as a biofeedback technique during swallowing therapy), and *pH-metry* (monitoring of the pharynx and esophagus with naso-gastric sensors to evaluate the PH to evaluate the occurrence of reflux).

Nutrition and Diet Management

Team management of individuals with dysphagia is essential. The oral healthcare professional has a central role in identifying dental and oral problems that may impede ability to eat and posing suitable treatment options. The registered dietitian can identify strategies to manage diet in concert with the individual dysphagia symptoms of patients in consultation with the speech and language pathologist. Nutritional management of patients with dysphagia is a critical part of the comprehensive treatment plan to help prevent malnutrition and to maximize safe eating. The suggested diet or meal plan should be individualized to meet the specific needs required. Cultural and religious factors related to meal preferences should be addressed along with the emotional and social connection to eating. Some individuals may be embarrassed that they drool or choke when eating. Reassuring patients and providing foods to eliminate negative symptoms of dysphagia when possible is essential.

The key to diet management is to identify dysphagia symptoms that may be affecting food and fluid intake. Patients with dysphagia are prone to dehydration as they may avoid liquids due to fear of

choking or aspirating or they may dislike the taste or consistency of thickened beverages if they are prescribed for safety purposes. Individuals may self-restrict fluid intake due to advanced age, physical disability, and cognitive impairment. As such, all healthcare professionals should be aware of the risks of dehydration and encourage adequate consumption of liquids within the recommended consistency.

All efforts should be made to maximize nutrient density of foods consumed. Using vegetables and fruits in appropriate consistencies are necessary to assure vitamin and mineral intake is adequate. The national dysphagia diet (NDD) provides clinical guidelines for diet management [97]. However, determination of the choice of diet and stage should be made by the dietitian in consultation with the speech and language pathologist. In management of patients with dysphagia, health professionals must consult across disciplines and determine the most appropriate plan to meet physiologic, anatomic, systemic, and nutritional health needs. There are three levels to the NDD diet: puree, mechanically altered, and advanced. The puree level is designed for patients with severe dysphagia; poor oral phase abilities and limited ability to protect airway. The diet composition does not require chewing or bolus formation. The mechanically altered level is designed for patients with oropharyngeal dysphagia (mild-moderate) who are able to chew. The advanced diet is for patients with mild oropharyngeal diet. For more information, the reader is referred to the American Speech-Language Hearing Association website (http://www.asha.org/SLP/clinical/dysphagia/Dysphagia-Diets/).

Summary

This chapter highlights bidirectional associations and relationships between oral, nutritional, and systemic health and oral infectious diseases. Several themes of interaction that the clinician should be aware of: inflammation, infection, oral function, and salivation that have emerged. Oral diseases with an inflammatory component (primarily although not exclusively periodontal disease) can affect systemic immune and hormonal status, possibly impacting risk for pregnancy complications and CVD. Likewise, systemic inflammatory diseases (autoimmune and immune mediated) can have significant oral manifestations, including chronic mucosal ulceration and salivary gland hypofunction which are addressed in Chapters 8 (inflammation) and 14 (autoimmune diseases). Oral infection is common (caries and periodontal disease) and can be life threatening in patients with other systemic risk factors such as cardiac valve disorders (infective endocarditis) and immunosuppression or myelosuppression caused by disease or medical therapy; oral infection is also the initiating event in the aforementioned inflammatory disorders. Oral function can be impaired whenever there is a painful, sensory, or motor condition (mucosal, periodontal, dental, musculoskeletal, or neuropathic) that affects oral intake of nutrients. Saliva is essential for normal oral immune surveillance, mastication, swallowing, and digestion. Hyposalivation is a common complication of medical management of a wide variety of systemic diseases as well as radiation and chemotherapy for malignancy. Clinicians should explore potential side effects of medications used to determine risk of hyposalivation and guide patients accordingly regarding risk reduction strategies.

Oral healthcare professionals along with registered dietitians and all health professionals need expanded interprofessional training in oral–systemic–nutrition relationships in order to competently address these expanding associations and relationships between oral, systemic, and nutritional health and diseases [98]. Greater awareness of the signs, symptoms, and management strategies for oral–systemic disease must be translated into clinical practice and include clinical pathways for referral and/or consultation for patients with high-risk findings or illnesses.

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Chapter 6
Impacts and Interrelationships Between Medications, Nutrition, Dietary Supplements, and Oral Health

Mark Donaldson

Keypoints

- Adverse health outcomes including diet-, dietary supplement-, and drug–drug interactions are likely to increase as people live longer, have greater numbers of chronic conditions, and take more medications and dietary supplements
- Drug and/or supplement-induced changes to overall nutritional status or to the status of a specific nutrient can be multifactorial
- Many of the drugs used commonly by oral health care professionals have associated pharmacodynamic and pharmacokinetic interactions with nutrients and dietary supplements
- Select drugs can cause primary or secondary malabsorption
- Many prescription and over-the-counter (OTC) medications have the potential to cause adverse oral conditions including oral lesions, stomatitis, hyposalivation, and decreased taste and smell sensations

Keywords Dietary supplements · Oral health · Nutrition · Nutritional status · Secondary malabsorption · Nutrient metabolism · Nutrient absorption · Drug-dietary substance interactions

Introduction

During the decade between 1998 and 2008, the percentage of Americans who took at least one prescription drug in the previous month increased from 44 to 48% [1]. The use of two or more drugs increased from 25 to 31% and the use of five or more drugs increased from 6 to 11%. In the United States, spending for prescription drugs was $234.1 billion in 2008, more than double what was spent in 1999 [2].

As many as 52–74% of prescription drug users also take dietary supplements [3–5]. According to the National Institutes of Health (NIH), more than one-third of all Americans take dietary supplements [6, 7]. The United States Food and Drug Administration (FDA) defines a dietary supplement

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as, “a product intended to supplement the diet” that includes, “a vitamin, a mineral, an herb, or other botanical” in the form of, “a pill, capsule, tablet or liquid” [8]. In 2009, sales of multivitamins and minerals accounted for $4.8 billion of the estimated $26.9 billion spent in the USA on dietary supplements [9].

Given the prevalence of medications and dietary supplement use among consumers, potential dietary supplement-drug interactions warrant consideration in dental practice [10]. Furthermore, since nearly 70% of these people do not discuss their supplement use with their primary care providers, oral health care professionals (OHCPs) should ask all patients about their use, particularly when prescribing medications and when considering the patients overall oral healthcare plan [9].

Since obesity is an increasing public health concern, these statistics are particularly staggering when you consider that over 50 million people in the United States seek weight loss products and services at a cost of more than $50 billion annually [11]. Currently, 32.9% of adults (ages 20–74 years old) and more than 17% of teenagers (ages 12–19 years old) are considered to be obese [12]. Weight loss practices reported in the 2007–2008 National Health and Nutrition Examination Survey (NHANES) included use of weight loss supplements, liquid diet formulas, prescription diet pills and/or laxatives, in addition to diet and activity approaches [13]. Regardless of the methodology, diets that include the unusual and possibly restrictive approaches to eating can lead to potential harm and negative dental and overall health consequences, yet many patients still prefer to try weight loss supplements and drugs [14].

Adverse health outcomes including diet-, dietary supplement-, and drug–drug interactions are likely to increase as Americans live longer, have greater numbers of chronic conditions, and take more medications [15]. Among adults 65 years of age or older, 40% take 5–9 medications regularly and 18% take 10 or more [16]. Age-related physiological changes, a greater degree of frailty, a larger number of coexisting conditions, and polypharmacy have been associated with an increased risk of adverse events [17, 18]. Older adults are nearly seven times more likely than younger persons to have adverse drug events that require hospitalization [19].

This chapter explores the impacts and selected interrelationships between medications, nutrition, dietary supplements, and oral health. Drug-induced nutrient deficits and their mechanisms will be discussed, including drug-induced adverse oral conditions. We also explore the increasing number of dietary supplement interactions with commonly prescribed medications in dentistry.

Drugs and Overall Nutritional Status

Drug-induced changes to overall nutritional status or to the status of a specific nutrient can be multifactorial [20]. Drugs can influence our overall food intake, digestion, and absorption of *macronutrients* such as proteins, carbohydrates and fats; and they can also cause *micronutrient* depletion of our vitamins, minerals and organic acids either by preventing nutrient absorption (*primary malabsorption*), enhancing nutrient elimination, or both. Drugs can interfere with the synthesis of nutrients and alter the body’s ability to transport, store, or metabolize nutrients, thus impairing a patients’ ability to maintain or improve their nutritional status (*secondary malabsorption*). Some drugs also have the potential to cause disturbances in gastrointestinal (GI) function that can impair a patients’ ability to maintain or improve their nutritional status. The inhibition of GI absorption of vitamins by cholestyramine (a cholesterol-lowering drug) is just one example of this interaction. Other examples include: the enhancement of potassium, magnesium, and zinc excretion by thiazide diuretics; and the acceleration of vitamin D metabolism and calcium depletion by anticonvulsants such as phenytoin and phenobarbital [21].

Some drugs may also be associated with altered metabolic function or macronutrient status (e.g., hyperglycemia, pancreatitis, osteoporosis, hyperlipidemia, and weight gain) [22–26]. Furthermore, drugs may alter food intake by effects not involving the gastrointestinal tract (e.g., visual changes, cognitive disturbances, and gait abnormalities). These types of drug-induced nutritional deficiencies and drug-nutrient reactions are more likely to occur among elderly patients taking multiple drugs for chronic illness who may also have other risk factors for inadequate nutritional intake (i.e., economic, masticatory efficiency, access to health care) [27]. This topic is covered in greater depth in Chapter 3.

Although micronutrients are needed only in small amounts for the human body to function properly, their deficiency leads to critical health problems. Micronutrient status can be influenced by drugs, as in the case of altered vitamin, mineral, or electrolyte status [20]. Many drug-induced oral lesions can be the direct effect of a drug or a result of drug-induced vitamin deficiencies [28–30]. Head and neck conditions and painful oral lesions may further impair the patient's ability to maintain adequate nutritional intake and can have a negative impact on their oral and overall health [31].

Mechanisms of Drug Effects on Nutrients

Most drugs taken orally are absorbed via passive transport across the mucosal membrane of the small intestine into the bloodstream. The phospholipid bilayer that comprises this membrane is very *lipophilic* (fat-loving), so that lipophilic drugs cross this membrane very easily by passive diffusion along the concentration gradient since, "like dissolves like." Once absorbed, these drugs can be distributed in fat, muscle, or water, or bound to proteins, used by the body, metabolized, and ultimately excreted.

Metabolism occurs primarily in the liver where the drug is usually inactivated and converted into a more *hydrophilic* (water soluble) form necessary for renal elimination. Since not all drugs can be synthesized to be lipophilic, some medications are intrinsically more hydrophilic and require an active transport mechanism to be absorbed. Examples of *active transports* are those that require chemical energy, such as from adenosine triphosphate (ATP), and include transmembrane ATPases and sodium–potassium pumps. Bisphosphonates such as alendronate (Fosamax®) are good examples of hydrophilic medications that are difficult to absorb orally and which require these types of active transport mechanisms to be absorbed. For this reason, many of these agents are administered intravenously, or if patients are given oral tablets they are instructed not to take these medicines with anything other than a glass of water and preferably on an empty stomach, sitting or standing, first thing in the morning.

Chronic diseases or drug-induced cellular damage of the intestinal mucosa can reduce drug absorption resulting in lower blood levels of the drug by damaging active transporters that carry drugs and nutrients into the bloodstream, or interfering with the structural integrity of the villi lining the mucosa. Conversely, decreased liver function may increase blood levels of the drug by slowing drug metabolism, especially in older adults, allowing more of the active form of a drug to be available for longer periods of time. In addition, a decline in renal function due to increasing age or caused by chronic diseases such as diabetes, can significantly decrease the elimination of drugs leading to increased blood levels of the drug [32].

Decreased absorption, altered metabolism, or increased elimination of drugs can contribute to drug-induced nutritional deficiencies, mostly in the form of micronutrient deficiencies. Intestinal enzymes such as pepsin, amylase, and lipase (which help to digest food) and bacteria are needed to help absorb vitamins B_1, B_2, B_6, B_{12}, and vitamin K. Malabsorption of these nutrients can be caused by drugs that damage the lining of the intestines or by drugs that kill off these bacteria, such as broad-spectrum antibiotics, thus reducing drug absorption and enzyme action [33].

Table 6.1 The signs and symptoms of malabsorption [34]

Malabsorption of	Clinical features	Laboratory findings
Calories	Weight loss with normal appetite	
Fat	Pale and voluminous stool, diarrhea without flatulence, steatorrhea	Stool fat >6 grams/day
Protein	Edema, muscle atrophy, amenorrhea	Hypoalbuminemia, hypoproteinemia
Carbohydrates	Watery diarrhea, flatulence, acidic stool pH, milk intolerance, stool osmotic gap	Increased breath hydrogen
Vitamin B12	Anemia, subacute combined degeneration of the spinal cord (early symptoms are paresthesias and ataxia associated with loss of vibration and position sense)	Macrocytic anemia, vitamin B12 decreased, abnormal Schilling test, serum methylmalonic acid and homocysteine increased
Folic acid	Anemia	Macrocytic anemia, serum and RBC folate decreased, serum homocysteine increased
B Vitamins, general	Cheilosis, painless glossitis, acrodermatitis, angular stomatitis	
Iron	Microcytic anemia, glossitis, pagophagia	Serum iron and ferritin decreased, total iron binding capacity increased
Calcium and vitamin D	Paresthesia, tetany, pathologic fractures due to osteomalacia, positive Chvostek, and Trousseau signs	Hypocalcemia, serum alkaline phosphatase increased, abnormal bone densitometry
Vitamin A	Follicular hyperkeratosis, night blindness	Serum carotene decreased
Vitamin K	Hematoma, bleeding disorders	Prolonged prothrombin time, vitamin K-dependent coagulation factors decreased

Primary Malabsorption

The signs and symptoms of malabsorption are represented in Table 6.1 [34]. As mentioned earlier, primary malabsorption occurs when drugs depress the uptake of nutrients from the small intestine without interfering with nutrient metabolism. Drugs can alter micronutrient absorption in a number of ways: blocking transport systems, changing the pH of the stomach, inactivating intestinal enzymes, removing bile salts from the sites of absorption of fat-soluble vitamins (A, D, E, and K), or changing the bacterial flora. Commonly used drugs that cause malabsorption include: antacids, certain antibiotics (neomycin and tetracycline), cholestyramine, colchicine (an antigout drug), and laxatives [34].

Overuse or abuse of antacids can lead to phosphate depletion and osteomalacia (vitamin D deficiency). Antacids also affect the absorption of riboflavin (vitamin B_2), copper, zinc, and iron. Tetracycline reduces calcium absorption by binding to calcium and forming an insoluble complex that is excreted rather than being absorbed. Bile acid sequestrant cholesterol-lowering agents such as cholestyramine can decrease the absorption of vitamin B_{12}, folic acid, iron, and the fat-soluble vitamins. Chronic use of medications that decrease gastric acid (i.e., histamine [H_2]-receptor antagonists such as ranitidine, and proton pump inhibitors such as omeprazole), can lead to B_{12} or iron deficiency; iron requires acidic gastric conditions for optimal absorption. Vitamin B_{12} also requires an acidic pH to be freed from its protein-bound state. Only when B_{12} exists in its free state is it able to react with intrinsic factor and be physiologically useful to the body. Iron deficiency can therefore result from reduced gastric acid production and not always a decrease in iron alone. Conversely, a lack of intrinsic factor can lead to vitamin B_{12} deficiency.

Drugs, such as metoclopramide, that increase gastric emptying, can cause rapid passage of food through the entire GI system, which results in reduced nutrient absorption due to inadequate time for gastric digestion or saturation of absorption transport systems in the small intestine. Mineral oil and overuse of other laxatives can lead to fat-soluble vitamin deficiencies by increasing the rate of

Table 6.2 Drugs that can result in nutritional deficits [34]

Drug	Examples	Nutrient deficit	Possible clinical signs
Alcohol		Folic acid, Mg, niacin, thiamine, Vit B_2, Vit B_6, Vit B_{12}, Vit C, Zn	Angular stomatitis, cheilitis, glossitis, peripheral neuropathy
Analgesics and anti-inflammatory agents	Aspirin	Folic acid, Fe, protein, Vit C	Anemia, cheilitis, glossitis
	Colchicine	K, Na, Vit A, Vit B_{12}, Vit K	
	Corticosteroids	Ca, K, Vit D, Zn	Osteopenia, osteoporosis
	NSAIDs*	Folic acid	Anemia, cheilitis, glossitis
	Sulfasalazine	Folic acid	Anemia, cheilitis, glossitis
Antacids	Aluminum hydroxide, sodium bicarbonate	Folic acid, Ca, Cu, Fe, Mg, Phosphate, Zn	Osteomalacia
Antibacterial agents	Trimethoprim	Folic acid	Anemia, cheilitis, glossitis
	Sulfa	Folic acid	Anemia, cheilitis, glossitis
	Tetracyclines	Ca, Vit B_6, Vit B_{12}, Mg, Zn	Angular stomatitis, cheilitis, glossitis, peripheral neuropathy
Anticoagulants	Coumadin	Vit K	Hemorrhage
Anticonvulsants	Phenobarbital, phenytoin, primidone	Folic acid, Vit B_{12}, Vit D, Ca	Osteomalacia
	Carbamazepine	Folic acid	Megaloblastic anemia, cheilitis, glossitis
Anti-parkinson agents	Levadopa	Vit B_6	Angular stomatitis, cheilitis, glossitis, peripheral neuropathy
Antiretroviral agents	Zidovudine, ribavirin	Cu, Zn	
Antituberculosis agents	Isoniazid	Ca, Vit B_6, Vit D, Vit E, niacin	Angular stomatitis, cheilitis, glossitis, pellagra, peripheral neuropathy
	5-ASA	Folic acid, Vit B_{12}	Megaloblastic anemia
Antiulcer agents	H_2-receptor antagonists	Ca, Fe, folic acid, Vit B_{12}, Vit D, Zn	Dyspnea, neuropathy, pernicious anemia, redness and burning of the tongue
	Proton pump inhibitors	Vit B_{12}	Neuropathy, pernicious anemia, redness and burning of the tongue
Cancer chemotherapy targeted agents	EGFR** antagonists	Ca, K, Mg	Asthenia, debilitating skin rashes, dry mouth, mouth ulceration, stomatitis
	mTORI***	K, P	Anemia, mucositis, stomatitis, taste disturbances, lymphopenia, leukopenia, thrombocytopenia, neutropenia
Cardiovascular agents	Digoxin	Ca, Mg	
	Potassium chloride	Vit B_{12}	Neuropathy, pernicious anemia, redness and burning of the tongue
Dihydrofolate reductase inhibitors	Methotrexate	Folic acid	
Diuretics	Thiazides	K, Mg, Na, Zn	
	Potassium-sparing	Ca, folic acid	Anorexia, cheilitis, glossitis, megaloblastic anemia
	Loop diuretics	K, Mg, Vit B_1, Vit B_6, Zn	Angular stomatitis, cheilitis, glossitis, peripheral neuropathy
	Hydralazine	Mg, Vit B_6	Angular cheilitis, peripheral neuropathy
	Triamterene	Folic acid	

(continued)

Table 6.2 (continued)

Drug	Examples	Nutrient deficit	Possible clinical signs
Hormonal agents	Oral contraceptives	Folic acid, Vit B_2, Vit B_6, Vit B_{12}, Vit C, Mg, Zn	Angular stomatitis, cheilitis, glossitis, peripheral neuropathy
Hypercholesterol agents	Statin drugs	Folic acid	Anemia, cheilitis, glossitis
	Bile sequestrants	Fat, Fe, folic acid, Vit A, Vit B_{12}, Vit D, Vit E	Anemia, cheilitis, glossitis
Laxatives	Mineral oil	Vit A, Vit D, Vit E, Vit K	Osteomalacia
Oral hypoglycemic agents	Sulfonylureas	Thiamine	
	Metformin	Vit B_{12}	Megaloblastic anemia
Sedatives	Chlorpromazine	Vit B_{12}	Anemia, cheilitis, glossitis

Vit: vitamin
*NSAIDs: nonsteroidal anti-inflammatory drugs
**EGFR inhibitors (epidermal growth factor receptor antagonists)
***mTORI (mammalian target of rapamycin inhibitors)

intestinal motility, speeding transit time, and again decreasing the amount of time available for nutrient absorption [35]. Increased large intestinal motility can result in inadequate time for potassium reabsorption and can lead to hypokalemia and abnormal heart rhythms. Table 6.2 summarizes the drugs that can result in nutritional deficits [34].

Secondary Malabsorption

Secondary malabsorption is caused by the interference of a drug with the absorption or metabolism of another nutrient. Good examples include drugs that alter the metabolism of vitamin D, which is responsible for stimulating calcium and phosphorus absorption. Vitamin D deficiency leads to inadequate calcium absorption, decreased calcium plasma levels, and reabsorption of calcium: all of which result in decreased plasma calcium levels. Glucocorticosteroids such as prednisone, dexamethasone, and methylprednisolone can lower production of a biologically active vitamin D metabolite, which leads to a consequent decrease in calcium absorption. These medications also decrease bone mineralization by causing mobilization of calcium from the skeleton. Bone demineralization and fractures can result from steroid-induced osteopenia and osteoporosis, especially in postmenopausal women or with prolonged use of these drugs [36]. Vitamin D deficiency in patients on chronic anticonvulsant drugs such as phenobarbital and phenytoin is caused by acceleration of hepatic conversion of the vitamin and its active metabolite (25-hydroxycholecalciferol) into an inactive form, causing decreased serum calcium levels. Osteomalacia may occur within months after the initiation of anticonvulsant therapy, especially in patients with inadequate calcium intake [37, 38]. In both cases, supplemental calcium with vitamin D should be provided routinely to avoid such risks.

Nutrient Metabolism

Once absorbed, a nutrient is metabolized primarily by enzymes in the liver, providing another opportunity for drugs to interact and affect nutrient metabolism. Some medications are designed to function as antivitamins by combining with or inhibiting enzyme systems required for the conversion of vitamins to their coenzyme or active form [21]. For example, folate is necessary for cells and tissues that rapidly divide, such as cancer cells. Methotrexate is an anticancer medication that binds to dihydrofolate reductase enzymes, preventing the conversion of folic acid (from dihydrofolate) to its

Table 6.3 Medications that are typically used to treat malabsorption in adults [40]

Medication/dosage	Comment
Antidiarrheal agents	
Loperamide 2–4 mg as needed, not to exceed 16mg/day	
Diphenoxylate with atropine (Lomotil®) 1–2 tabs after loose stool, not to exceed 8 per day	1 tab = 2.5 mg diphenoxylate component
Deodorized opium tincture 10% (10 mg per mL) 0.3–0.6 mL three times daily	Note: Highly concentrated. Contains 25 times more morphine than paregoric. Abrupt discontinuation may cause withdrawal symptoms
Bile acid binding resins	
Cholestyramine 4 grams three times daily	Administer ≥1 hour before or >4 hours after other drugs to prevent decreased absorption of other drug(s)
Colestipol granules 5–10 grams three times daily	Administer ≥1 hour before or >4 hours after other drugs to prevent decreased absorption of other drug(s)
*Pancreatic enzymes**	
General: Approximately 30,000 units (lipase component) with each meal	
Pancrelipase delayed-release capsules (Creon minimicrospheres)	Enteric-coated micro pellets may be sprinkled on soft acidic foods
Pancrelipase tablets and powder (Viokase, others) 1 gram (equivalent to 20,000 units lipase component) with meals	Effect improved if given with acid-suppressing drugs
*Vitamins and minerals***	
Vitamin A 40,000–50,000 units twice daily during acute repletion	Maintenance: 8,000–20,000 units/day (Dosage ≥15,000 units can be teratogenic)
Vitamin D3 (cholecalciferol) 30,000–50,000 units/day	Monitor serum calcium
Vitamin K 2.5–12.5 mg daily	
Folic acid 5 mg/day during repletion	Maintenance: 1 mg/day
Vitamin B_{12} (cyanocobalamin) 1 mg subcutaneously (should be repeated × three over first week of repletion)	Maintenance: 100 mcg q 1–2 months
Calcium carbonate 500 mg (elemental calcium) twice daily	Monitor serum calcium
Magnesium gluconate 1–4 grams (54–216 mg elemental magnesium) four times daily	Often produces diarrhea
Ferrous sulfate 325 mg (65 mg elemental iron) three times daily***	Reduce does if gastrointestinal symptoms occur

All dosages are adult oral dosages, if not otherwise stated
*Dose titration may be needed
**Maintenance doses for fat-soluble vitamins are highly dependent upon the degree of ongoing malabsorption. Blood levels should be checked every 1–2 years
***Available as a solution. Equivalent dosage mixed in 8 ounces orange juice will greatly enhance absorptive efficiency due to vitamin C content of juice

biologically active form (tetrahydrofolate), thus inhibiting the growth of these cells. Another example of a medication acting as an antivitamin includes coumarin anticoagulants, such as warfarin. Warfarin antagonizes vitamin K activity by causing the retention of the inactive form of vitamin K, thereby inhibiting the coagulation process. These anticoagulants are indicated in orthopedic and cardiac patients to help avoid complications such as deep venous thrombosis (DVT) and pulmonary emboli (PE).

Some drug therapies affect nutrient metabolism inadvertently leading to vitamin or coenzyme deficiencies. Isoniazid (an antituberculosis medication) and levodopa (a medication used to treat Parkinson's patients) both inhibit the normal metabolism of vitamin B_6, often causing neuropathies that can be reversed with vitamin B_6 supplements. Anticonvulsants, especially phenytoin and

phenobarbital, not only cause vitamin D and K deficiencies, but with prolonged use also cause folic acid deficiency by inducing the liver enzymes that metabolize these vitamins [39]. Once again, these side effects are easily treated by supplementing vitamin D, K, and folic acid to treat this altered metabolism. Table 6.3 summarizes medications that are typically used to treat malabsorption in adults [40].

Other medications affect nutrient metabolism by directly affecting specific organs. Excessive alcohol intake, for example, may result in abnormal liver and pancreatic function [41]. Alcohol-induced pancreatitis leads to changes in overall vitamin absorption and utilization. Specifically, alcohol interferes with thiamine (vitamin B_1) metabolism, resulting in thiamine deficiencies which may manifest as peripheral neuropathies, or in extreme cases as *Wernicke-Korsakoff syndrome*, a chronic degenerative neurologic disorder. Alcoholics may also develop vitamin B_6 (pyridoxine) deficiencies and pellagra, secondary to niacin (vitamin B_3) deficiency [42]. Pellagra (niacin deficiency) is classically described by "the four D's": diarrhea, dermatitis, dementia, and death [43]. Folate (vitamin B_9) deficiency is also frequent in chronic alcoholics because of interference with absorption, storage, and conversion of this vitamin into its active form in the liver, as well as altered vitamin A metabolism.

Nutrient Absorption and Metabolism in the Diabetic Patient

The pancreas is the exocrine gland responsible for releasing insulin and pancreatic enzymes essential for the digestion of fat, protein, and starch (glucose). Several drugs may damage this exocrine gland, thereby causing hypo- or hyperglycemia. Drug-induced hypo- or hyperglycemia significantly affects nutrient absorption and metabolism. In patients without diabetes, *hypoglycemia* is a clinical syndrome with diverse causes, in which low plasma glucose concentrations lead to adverse symptoms and signs, which are resolved when the plasma glucose concentration is raised [44]. In patients with diabetes, however, hypoglycemia is defined as all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm. Medical management of diabetes includes antihyperglycemic agents and hypoglycemia is often a consequence of therapy. Table 6.4 lists medications other than antihyperglycemic agents and alcohol that are commonly associated with causing either hypo- or hyperglycemia in both diabetics and nondiabetics [44–46].

The interaction between drugs and food, then, may be classified into five categories with respect to nutrient absorption: those causing reduced, delayed, increased, and accelerated absorption, and those in which food has no effect [47]. Food may reduce drug absorption by acting as a physical barrier, inhibiting drug dissolution, and preventing drug access to the mucosal surface of the GI tract. Alternatively, specific ions or other substances in food may cause reduced drug absorption (e.g., the chelation of tetracycline by calcium ions such as Ca^{++} in milk). For drugs that are absorbed via active transporters, direct competition for active carriers may occur between protein fragments and drug molecules, giving rise to decreased drug levels in the blood. Table 6.5 summarizes these five categories of drug-food absorption interactions [48, 49].

Historically, drug-food interactions were a particular problem for oral controlled-release (CR) or sustained-release (SR) products. These delivery formulations present a greater quantity of drug to the patient per single dose unit than conventional dosage forms and are designed to deliver the drug at a controlled rate over an extended period. With some of these original formulations, food had a marked effect on systemic availability and a serious and prolonged effect on circulating drug levels; essentially, the pharmacokinetics of drugs are affected by the interaction of drugs with food, which changed the drugs physicochemical and physiological properties (food effects). Recently, several pharmaceutical technologies have been used to control these food effects. Since drugs exhibit different patterns of solubilization depending on release formulations, our traditional CR and SR

Table 6.4 Medications other than antihyperglycemic agents and alcohol commonly associated with causing either HYPER- or HYPOglycemia [44–46]

Medications which may induce HYPERglycemia		Medications which may induce HYPOglycemia
Alpha-interferon	Levodopa	6-Mercaptopurine
Aminophylline	Lithium	Angiotensin-converting enzyme inhibitors
Amprenavir	Megestrol	Angiotensin receptor antagonists
Asparaginase	Methyldopa	β-Adrenergic receptor antagonists
Beta-agonists	Morphine	Cibenzoline
Caffeine	Nelfinavir	Disopyramide
Calcitonin	Nicotine	Gatifloxacin
Chlorpromazine	Oral contraceptives	Glucagon
Corticosteroids	Pentamidine	Heparin
Cyclophosphamide	Phenothiazines	Indomethacin
Diazoxide	Phenytoin	Levofloxacin
Didanosine	Ritonavir	Lithium
Diltiazem	Saquinavir	Mifepristone
Estrogens	Sympathomimetics	Pentamidine
Ethacrynic acid	Theophylline	Propoxyphene
Furosemide	Thiazides	Quinine
Haloperidol	Thyroxine	Trimethoprim-sulfamethoxazole
Indinavir	Vacor	
Isoniazid		

Table 6.5 Food and altered drug absorption [48, 49]

Commonly prescribed drugs whose absorption is reduced by food			
Acetaminophen	Cicaprost	Levodopa, Carbidopa	Pravastatin
Alendronate	Ciprofloxacin	Methotrexate	Sotalol
Atenolol	Didanosine	Naproxen	Tacrine
Azithromycin	Doxazosin	Navelbine	Tetracycline
Cefprozil	Flecainide	Norfloxacin	Verapamil
Ceftibuten	Hydralazine	Phenytoin	Zidovudine
Commonly prescribed drugs whose absorption is delayed by food			
Albuterol	Erythromycin	Methotrexate	Topiramate
5-Aminosalicylic acid	Famotidine	Nifedipine	Trazodone
Cefaclor	Flurbiprofen	Ofloxacin	Valproic Acid
Cefdinir	Fluvastatin	Penciclovir	Vigabatrin
Cefprozil	Hydroxychloroquine	Rifabutin	Zalospirone
Diclofenac	Isosorbide-5-mononitrate	Salsalate	Zidovudine
Diltiazem	Lomefloxacin	Terazosin	
Doxycycline	Loracarbef	Theophylline	
Commonly prescribed drugs whose absorption is increased by food			
Alprazolam	Diltiazem	Moclobemide	Theophylline
Amiodarone	Encainide	Nifedipine	Ticlopidine
Atovaquone	Felodipine	Oxcarbazine	Tramadol
Cefuroxime	Fluconazole	Oxybutinin	Vanoxerine
Clarithromycin	Itraconazole	Phenytoin	Vinpocetine
Cyclosporine	Levodopa	Progesterone	Zalospirone
Danazol	5-Methoxypsoralen	Sparfloxacin	
Commonly prescribed drugs whose absorption is not affected by food			
Amlodipine	Cimetidine	Morphine	Tiaprofenic acid
Bisoprolol/hydrochlorothiazide	Diltiazem	Paroxetine	Trimetazidine
Bromocriptine	Fluvoxamine	Procainamide	Verapamil
Brompheniramine	Ibuprofen	Pseudoephedrine	
Carbamazepine	Metoprolol succinate	Ranitidine	

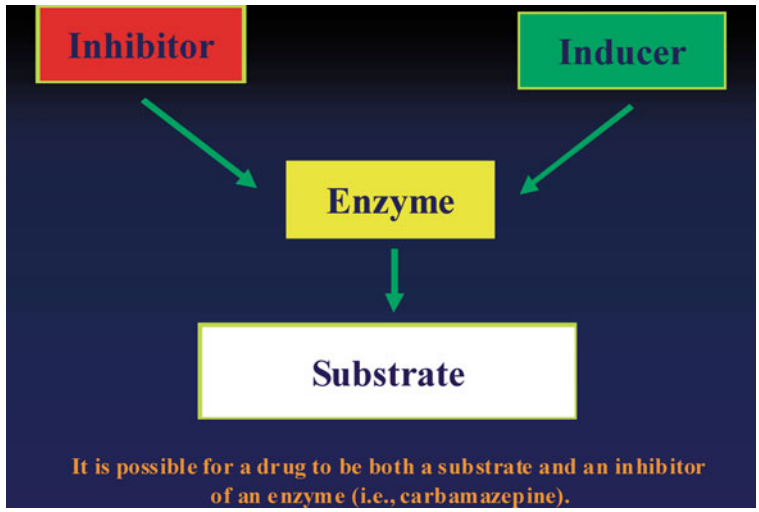

Fig. 6.1 Similar to drugs, dietary substances can also be described by pharmacokinetics and pharmacodynamics. Like drugs, dietary substances can also be *substrates* (substances metabolized by enzymes) or *precipitants* (substances that induce or inhibit enzymes that metabolize drugs). Enzyme induction means that the enzyme has increased activity, leading to faster drug or dietary substance metabolism and clearance, and therefore a decreased systemic drug or dietary substance concentration resulting in a therapeutic failure. Conversely, enzyme inhibition causes decreased metabolism, increased systemic drug, or dietary substance concentrations, and therefore an increased risk of adverse events and toxicity [50, 51]

products have been re-engineered as nanoparticle, solid dispersion, and cyclodextrin systems, which may control the solubility and release of insoluble drugs. Other advances in controlled-release technologies, such as osmotic-controlled release and colon-specific delivery systems have helped control food effects and therefore mitigate this historical problem.

Drug-Dietary Substance Interactions: Pharmacokinetics and Pharmacodynamics

A *drug-dietary substance interaction* is defined as, "the result of a physical, chemical, physiologic, or pathophysiologic relationship between a drug and a nutrient(s) present in a food, nutritional supplement, or food in general [50]." Such interactions manifest clinically as compromised nutritional status due to altered *pharmacokinetics* (PK) and/or *pharmacodynamics* (PD) of a drug or dietary substance. So far we have discussed both pharmacokinetics of certain drugs (what the body does to the drug; absorption, metabolism, distribution, and excretion), and pharmacodynamics (what the drug does to the body).

Similar to drugs, dietary substances can also be described by pharmacokinetics and pharmacodynamics. Like drugs, dietary substances can also be *substrates* (substances metabolized by enzymes) or *precipitants* (substances that induce or inhibit enzymes that metabolize drugs). Enzyme induction means that the enzyme has increased activity, leading to faster drug or dietary substance metabolism and clearance, and therefore a decreased systemic drug or dietary substance concentration resulting in a therapeutic failure. Conversely, enzyme inhibition causes decreased metabolism, increased systemic drug, or dietary substance concentrations, and therefore an increased risk of adverse events and toxicity (Fig. 6.1) [50, 51]. These interactions are challenging to assess because, unlike most drugs, dietary substances are mixtures, composed of multiple, and usually unknown, bioactive ingredients.

Table 6.6 Medications that are most commonly used in dentistry [54]

Analgesics and anti-inflammatory agents	*Local anesthetics*
Acetaminophen	Articaine
Aspirin	Bupivacaine
Codeine	Lidocaine (± epinephrine)
Glucocorticoids (dexamethasone, prednisone)	Mepivacaine (± levonordefrin)
Hydrocodone	Prilocaine
Ibuprofen	Benzocaine Topical
Nonsteroidal anti-inflammatory analgesics	Dyclonine Topical
Oxycodone	Lidocaine Topical
	Tetracaine Topical
Antibiotics/Antifungals	*Sedatives*
Amoxicillin	Benzodiazepines (alprazolam, diazepam, lorazepam, midazolam and triazolam)
Azithromycin	Zaleplon
Cephalexin	Zolpidem
Chlorhexidine (topical)	*Emergency Medications*
Clarithromycin	Albuterol
Clindamycin	Aspirin
Clotrimazole (topical)	Diphenhydramine
Doxycycline	Epinephrine
Erythromycin	Flumazenil
Fluconazole	Glucose
Metronidazole	Naloxone
Nystatin	Nitroglycerine
Penicillin	Oxygen
Tetracycline	

While a drug-dietary substance interaction may occur in anyone, patients with weakened physiologic function, such as the elderly, immunocompromised, and critically ill, are at the highest risk of experiencing untoward effects [51]. Understanding the underlying mechanisms of these interactions and potential causative bioactive compounds helps in making the most appropriate proactive clinical decision, however, prospective and systematic studies on mechanisms and outcomes of many of these interactions are insufficient or lacking altogether. Clinicians are often faced with being reactive, then, to the consequences of these interactions in order to best guide a patient's therapy.

A mechanistic understanding of the varied effects of dietary substances on drug metabolism forms the basis for optimizing pharmacotherapy by minimizing potential adverse effects. To determine the risks associated with particular dietary supplement-drug interactions, clinical databases and clinical decision support tools are available which classify interactions according to the level of risk they pose to the patient. Two clinical databases commonly used to evaluate drug–drug interactions (Lexi-Comp; Hudson, OH) [52] and dietary supplement-drug interactions (The Natural Medicines Comprehensive Database; Stockton, CA) [53] were recently reviewed with respect to the most common drugs that OHCPs utilize and the most common dietary supplements that they are likely to encounter [9]. The authors concluded that medications most commonly prescribed by OHCPs can be given without regard to dietary supplement-drug interactions, although patients currently taking ginkgo, St. John's wort, evening primrose, or valerian should consult with their primary provider before taking these supplements with other prescribed medications [9]. A summary of the medications most commonly used in dentistry can be found in Table 6.6 [54]. The 20 commonly used dietary supplements that were reviewed in this summary can be found in Table 6.7 [55].

Whether drug-dietary substance interaction or drug-induced nutritional deficits translate into frank nutrient deficiencies depends on several factors, including the overall nutritional status of the

Table 6.7 Commonly sold dietary supplements in the United States [55]

Aloe vera
Bilberry
Black cohosh
Cranberry
Echinacea
Elderberry
Evening primrose
Garlic
Ginger
Ginkgo
Ginseng
Grape seed extract
Green tea
Horny goat weed
Milk thistle
St. John's wort
Saw palmetto
Soy
Valerian
Yohimbine

individual. Inadequate diet and subsequent low stores of nutrients can increase the chance of nutrient depletion, causing clinical symptoms of nutrient deficits. For example, patients in long term care facilities on anticonvulsants who get little exposure to sunlight and who may have a marginal dietary intake of vitamin D have a higher incidence of developing osteomalacia and osteoporosis [33]. The length of time that a drug is taken also has a significant impact on the depletion of nutrients. As an example, the incidence of vitamin D deficiency in patients on anticonvulsants increases the longer the drug is taken [33].

Multiple drug regimens may also increase the risk of nutritional deficiencies if the drugs affect the same absorption or metabolic pathways. Individuals with tuberculosis and concurrent malnutrition taking isoniazid and para-amino salicylic acid can develop vitamin B_6, B_{12}, and folic acid deficiency, and subsequently develop pellagra because B_6 is needed to convert tryptophan to niacin. Increased body fat, decreased muscle mass, or dehydration can also effect the distribution of lipophilic drugs such as benzodiazepines, digoxin, and synthetic steroids, [56] or hydrophilic drugs such as warfarin, procainamide, atenolol, quinidine, propranolol, theophylline, digoxin, and cimetidine [57]. These physiological changes result in increased or decreased drug concentrations that can lead to the displacement of nutrients from plasma proteins or tissue-binding sites. Ultimately, this can lead to increased excretion of either the affected free (unbound) nutrient or in drug–nutrient complexes.

Drugs used to treat chronic diseases can also lead to increased nutrient requirements. For example, selected drugs such as sulfasalazine, isoniazid, and methotrexate contribute to folic acid deficiencies in patients with inflammatory bowel disease, tuberculosis, and rheumatoid arthritis, respectively [58]. Individuals with end-stage renal disease may develop deficiencies in riboflavin (vitamin B_2), vitamin C, and folic acid, if they are not given supplemental doses of these nutrients because of the nature of the disease and the use of diuretics and dialysis which can deplete these micronutrients. Patients with chronic renal disease also have impaired absorption of calcium secondary to a decrease in renal production of 1,25-dihydrocholecalciferol. Vitamins are crucial in health and human disease, according to several studies that investigated this relationship. Select vitamins may have an important role in the prevention of certain cancers, with vitamin C being perhaps the most noteworthy [59–62]. However while some case reports have shown that vitamin C

Table 6.8 Drugs associated with xerostomia [63–69]

Drug category	Generic drug name		
Anticholinergic agents	Atropine	Benztropine	Scopolamine
	Belladonna	Oxybutynin	Trihexyphenidyl
Antidepressant and antipsychotic agents	Citalopram	Amitriptyline	Pimozide
Selective serotonin-reuptake inhibitors (SSRIs)	Fluoxetine	Desipramine	Phenelzine
Tricyclic antidepressant (TCAs)	Paroxetine	Imipramine	Bupropion
Heterocyclic antidepressants	Sertraline	Haloperidol	Nefazodone
Monoamine oxidase inhibitors (MAOIs)	Venlafaxine	Mirtazapine	Olanzapine
Atypical antidepressants			
Diuretic agents	Chlorothiazide	Hydrochlorothiazide	
	Furosemide	Triamterene	
Antihypertensive agents	Captopril	Enalapril	
	Clonidine	Guanfacine	Methyldopa
	Clonidine/ chlorthalidone	Lisinopril	
Sedative and anxiolytic agents	Alprazolam	Flurazepam	Triazolam
	Diazepam	Temazepam	
Muscle relaxant agents	Cyclobenzaprine	Orphenadrine	Tizanidine
Analgesic agents	Codeine	Propoxyphene	
Central nervous system/opioids	Meperidine	Tramadol	Naproxen
Nonsteroidal anti-inflammatory agents	Methadone	Diflunisal	Piroxicam
(NSAIDs)	Pentazocine	Ibuprofen	
Antihistamines	Astemizole	Chlorpheniramine	Loratadine
	Brompheniramine	Diphenhydramine	Meclizine

Drugs listed have been reported to have a xerostomia incidence of 10% or more

may have a positive impact in select types of patients with cancer undergoing specific therapies, there is insufficient scientific evidence to support any benefit or recommendations. Concurrent vitamin C supplementation with different chemotherapy regimens cannot be recommended as a standard treatment at this time until further evidence on its safety and efficacy is determined.

Finally, nutritional deficiencies and drug-dietary substance interactions are more likely to occur among elderly patients taking multiple drugs for chronic illnesses who may also have other risks for inadequate nutritional intake (i.e., economic, masticatory efficiency, or healthcare access). Commonly prescribed cases of drugs for chronic illnesses that disproportionately affect the elderly and can lead to significant health problems such as megaloblastic and iron-deficiency anemia, hyperkalemia, hyper- or hypocalcemia, osteomalacia, and osteoporosis, hip fractures, decreased wound healing, organic brain disease, and peripheral neuropathies include: analgesics, anti-inflammatories, anticonvulsants, antidepressants, and other psychotropics, antihypertensives, GI protectors, and hormone replacement therapy [41]. Drug-induced oral lesions, also prevalent among the elderly, can be a direct adverse effect of a drug or a result of drug-induced vitamin deficiencies [42]. Painful oral lesions can further impair the patient's ability to maintain adequate nutritional intake [31].

Drugs and Appetite

Drugs can affect appetite as well as GI function, resulting in alterations in food intake. Drugs affecting appetite may have either a central or peripheral (localized) effect. Some drugs such as antidepressants and prednisone may increase appetite through a central effect and cause weight gain,

Table 6.9 Drugs associated with stomatitis [70]

Drug category	Generic drug name		
Anticholinergic Agents	Atropine	Benztropine	Scopolamine
	Belladonna	Oxybutynin	Trihexyphenidyl
Antidepressant and Antipsychotic Agents	Citalopram	Amitriptyline	Pimozide
Selective serotonin-reuptake inhibitors (SSRIs)	Fluoxetine	Desipramine	Phenelzine
Tricyclic antidepressant (TCAs)	Paroxetine	Imipramine	Bupropion
Heterocyclic antidepressants	Sertraline	Haloperidol	Nefazodone
Monoamine oxidase inhibitors (MAOIs)	Venlafaxine	Mirtazapine	Olanzapine
Atypical antidepressants			
Cancer chemotherapy and targeted agents	6-Mercaptopurine	Epirubicin	Mitoxantrone
	6-Thioguanine	Erlotinib	Paclitaxel
	Bleomycin	Etoposide	Panitumumab
	Busulfan	Everolimus	Pemetrexed
	Cabozantinib	Fludarabine	Pralatrexate
	Capecitabine	Fluorouracil	Procarbazine
	Carboplatin	Gemcitabine	Regorafenib
	Cetuximab	Hydroxyurea	Sorafenib
	Cisplatin	Idarubicin	Sunitinib
	Cyclophosphamide	Ifosfamide	Temsirolimus
	Cytarabine	Irinotecan	Teniposide
	Dactinomycin	Mechlorethamine	Thiotepa
	Daunorubicin	Melphalan	Topotecan
	Docetaxel	Methotrexate	
	Doxorubicin	Mitomycin	
Diuretic agents	Chlorothiazide	Hydrochlorothiazide	
	Furosemide	Triamterene	
Antihypertensive agents	Captopril	Enalapril	
	Clonidine	Guanfacine	Methyldopa
	Clonidine/ chlorthalidone	Lisinopril	
Sedative and anxiolytic agents	Alprazolam	Flurazepam	Triazolam
	Diazepam	Temazepam	
Muscle relaxant agents	Cyclobenzaprine	Orphenadrine	Tizanidine
Analgesic agents	Codeine	Propoxyphene	Naproxen
Central nervous system/opioids	Meperidine	Tramadol	Piroxicam
Nonsteroidal anti-inflammatory agents (NSAIDs)	Methadone	Diflunisal	
	Pentazocine	Ibuprofen	
Antihistamines	Astemizole	Chlorpheniramine	Loratadine
	Brompheniramine	Diphenhydramine	Meclizine

whereas others such as chemotherapeutic agents contribute to weight loss by causing dry mouth, taste changes, anorexia, nausea, and vomiting. Many drugs have oral side effects such as xerostomia (Table 6.8) [63–69] or mucositis also known as, "mouth ulcers" (Table 6.9) [70], or can cause a decreased taste or smell sensation that can affect food intake (Tables 6.10 and 6.11) [71].

Potassium iodide is secreted into the saliva, producing a constant unpleasant taste that is difficult to eradicate; chlorpromazine and metronidazole cause a persistent metallic taste that indirectly decreases food intake; and penicillamine causes zinc depletion, leading to loss of taste and loss of desire for food [71, 72]. Digoxin, especially in patients with decreased renal function, can cause marked nausea and vomiting. Biguanides, such as metformin, used as oral hypoglycemic agents in

Table 6.10 Drugs associated with a decreased taste sensation [52, 71, 93]

Generic Drug Name and Associated Taste Sensation			
Ageusia			
Bleomycin	Etoposide	Lovastatin	Spironolactone
Capecitabine	Flunisolide	Methimazole	Sunitinib
Cetuximab	Glycoprrolate	Nelarabine	Tamoxifen
Chemotherapy (in general)	Hydrochlorothiazide	Nimotuzumab	Temozolomide
Daunorubicin	Hyoscyamine	Ofloxacin	Temsirolimus
DenileukinDiftitox	Imatinib	Oxaliplatin	Terbinafine
Dicyclomine	Interferon	Oxcarbazepine	Testosterone
Docetaxel	Ixabepilone	Paclitaxel	Triazolam
Doxorubicin	Leflunomide	Peginterferon	
Erlotinib	Lenalidomide	Raltitrexed	
Etidronate	Lomefloxacin	Regorafenib	
Dysgeusia (bitter)			
Acetazolamide	Amphetamines		
Dysgeusia (metallic)			
Allopurinol	Ethionamide	Levamisole	Tocainide
Auranofin	Flurazepam	Lithium	Ethambutol
Beta-lactam antibiotics	Interferon-gamma	Metronidazole	Iodine
Tetracycline			
Dysgeusia (salty)			
Amiloride	Bretylium	Chlorhexidine	
Dysgeusia (sweet)			
5-fluorouracil			
Dysgeusia (general)			
Captopril	Everolimus	Nitroglycerin	Vandetanib
Dipyridamole	Lisinopril	Selegiline	Vismodegib
Enalapril			
Hypogeusia			
Amphotericin B	Carbamazepine	Cisplatin	Sulfasalazine
Amrinone	Carboplatin	Levodopa	
Hypogeusia, dysgeusia, ageusia, loss of sour taste			
Diltiazem	Isotretinoin	Nifedipine	

Table 6.11 Drugs associated with a decreased smell sensation [71, 93]

Amlodipine	Cocaine	Felodipine	Silver nitrate
Alpha-interferon	Cytosine	Flunisolide	Terbinafine
Beta-blockers	Diltiazem	Lovastatin	Tobacco products and smoke
Cadmium	Doxycycline	Methotrexate	
Ciprofloxacin	Enalapril	Nifedipine	

the treatment of diabetes mellitus, cause impaired appetite and decreased food intake. Chemotherapy drugs, especially cisplatin, actinomycin D, adriamycin, dacarbazine, streptazocin, nitrosoureas, nitrogen mustard, cyclophosphamide, and folic acid analogs induce nausea, vomiting, affect taste, anorexia, and subsequent weight loss [73]. Oral pain, taste changes, and lesions can even occur with some of our newer, "targeted" chemotherapy, which based on their molecular specificity, were initially believed to have significantly less side effects. Examples of these newer agents include the

monoclonal antibody EGFR inhibitors (epidermal growth factor receptor antagonists such as nimotuzumab), and mTORI (mammalian target of rapamaycin inhibitors such as temsirolimus) [74–76]. In patients who may have marginal intake of required nutrients, drugs causing anorexia can further result in nutritional deficiencies.

Drug Interactions with Food and Alcohol

As discussed earlier, pharmacokinetics can be defined as, "what the body does to a drug." It focuses primarily on how drug-drug and drug-supplement interactions change the way a drug or supplement is absorbed, distributed, metabolized, and excreted (ADME). The absorption of drugs may be increased or decreased by the presence of food, which changes the pH, osmolality, gastrointestinal secretions, and motility of the GI tract (Table 6.5) [48, 49, 77]. Drug *bioavailability* (a measure of the amount of drug that is actually absorbed from a given oral dose) may be affected by direct interactions between the drug and food, such as the formation of drug-protein complexes, chelation with polyvalent metal ions, or nutrients that bind to drugs and make them unavailable. Some examples of these types of interactions include: iron which binds with tetracycline, ciprofloxacin, and ofloxacin, causing reduced absorption and blood levels; and again, tetracycline which forms an insoluble complex with calcium, rendering it ineffective when taken with dairy products [20, 49, 50, 77–79].

Food may act as a mechanical barrier, preventing access to the epithelial surface of the GI tract where medications are absorbed, increasing transit time, binding of drugs or nutrients to nonabsorbed fraction, or indirectly inhibiting drug absorption because of increased digestion by GI secretions. Drugs taken with food may remain in the stomach for extended periods and be broken down before they can be absorbed in the intestines. This is especially significant with drugs that are meant to be rapidly absorbed or have a short half-life [48, 80]. Delayed gastric clearance of drugs such as erythromycin, captopril, penicillin, digoxin, and levodopa would cause more of the drug to be metabolized in the stomach, less of the active drug available for absorption, and a suboptimal clinical response [48–50]. Excessive consumption of foods rich in vitamin K can alter prothrombin times in patients on coumadin. For this reason, patients taking coumadin do not have to avoid foods high in vitamin K, such as liver, broccoli, brussel sprouts, and green leafy vegetables (e.g., spinach, Swiss chard, coriander, collards, cabbage), but it is important that they keep their intake consistent so that the amount of vitamin K eaten remains relatively consistent.

Certain foods can also affect the rate of drug metabolism or elimination. Grapefruit juice, even consumed 24 hours before taking certain drugs, can inhibit the intestinal cytochrome P_{450} 3A4 enzymes necessary for the metabolism of many drugs resulting in higher systemic drug concentrations and an increased clinical effect and adverse drug reactions. Examples of these drugs include aliskiren, amiodarone, amlodipine, atorvastatin, carbamazepine, diazepam, erythromycin, felodipine, lovastatin, midazolam, nifedipine, oxycodone, rivaroxaban, simvastatin, ticagrelor, and triazolam [81, 82]. Foods can also affect the rate of elimination of a drug by changing the pH of the urine. If the pH of the urine is modified, it is possible that there will be prolonged effects of a drug by increasing the unionized form in the urine (favoring reabsorption) or expedited elimination by promoting the excretion of the ionized form. For example, if the urine has a low pH (more acidic), weakly basic drugs such as amitriptyline and chloroquine are more rapidly excreted, because they form water-soluble salts [48, 80]. Foods that can cause acidification of the urine include meat, fish, chicken, seafood, eggs, cheese, peanut butter, and most processed carbohydrates such as breads and pasta. Conversely, the action of some drugs is prolonged if the pH of the urine is high (more basic) because there is decreased ionization and therefore reduced elimination and increased absorption by

the kidneys. Low protein diets, chronic antacid use, citrus fruits, milk products, and most vegetables can raise urine pH [83]. This alkalinizing effect of the diet leads to less of the ionized form of drugs such as gentamicin, quinine, or procainamide being reabsorbed, and therefore these medications are excreted much more rapidly.

Interactions between some foods and drugs can result in systemic reactions, some of which can be life threatening. Tyramine, a chemical that appears in some plant and animal products that have been fermented or aged, is a potent vasopressor that can cause marked elevation in blood pressure and, in severe cases, hypertensive crisis. Monoamine oxide enzymes, found in the liver, GI tract, and adrenergic nerve endings, metabolize tyramine before it can reach the systemic circulation [84]. Monoamine oxidase inhibitors (MAOIs) include drugs used to treat severe depression such as isocarboxazid, phenelzine and tranylcypromine, seligeline used to treat Parkinson's disease, and the antineoplastic drug procarbazine. If a patient taking these drugs eats food containing tyramine, it is not metabolized as efficiently and can cause a rapid increase in blood pressure and an increased incidence of cerebrovascular accidents (CVAs) also known as strokes. Examples of foods and beverages that contain tyramine include beer, red wines, vermouth, homemade breads, cheese, sour cream, bananas, red plums, figs, raisins, avocados, fava beans, Italian broad beans, green bean pods, eggplant, pickled herring, chicken and beef liver, dry sausages, canned meats, salami, yogurt, soup cubes, commercial gravies, chocolate, and soy sauce. All of these foods should be avoided by individuals taking MAOIs [84].

When alcohol is consumed in excess, it causes malabsorption or decreased absorption of many nutrients, in particular the intestinal absorption of fat- and water-soluble vitamins [85]. In addition, there is the malabsorption of folate, thiamine, vitamin B_{12}, calcium, magnesium, fatty acids, and protein as discussed earlier in this chapter [85]. Alcohol can cause hypoglycemic reactions in individuals taking oral hypoglycemic agents, which when combined with these agents can cause mental confusion, weakness, hypotension, and loss of consciousness. Tetraethylthiuram disulfide (Disulfiram® or Antabuse®) produces a "disulfiram" reaction (flushing, headache, nausea, vomiting, and chest and abdominal pain) when even very small amounts of alcohol are consumed [86]. A similar reaction is seen with alcohol and other drugs, including metronidazole, oral hypoglycemic agents such as the sulfonylureas, chloramphenicol, and griseofulvin. In addition, alcohol has an additive or synergistic central nervous system (CNS) depressant effect when combined with sedatives such as barbiturates, benzodiazepines, and opioids. It increases the risk of phenytoin-induced folate deficiency and can cause hypotension when combined with coronary vasodilators, such as nitroglycerin [87].

Alcohol dissolves gelatin capsules and increases the rate of dissolution and absorption of drugs given in capsule form. It potentiates the adverse nutritional effects of other drugs that cause anorexia, malabsorption, vitamin antagonism, and mineral wasting [87]. Healthcare providers should be aware of the possibility of interactions with alcohol, both with the medications they prescribe and with other medications people may take, and advise patients accordingly.

Drugs that Affect Oral Health

Many prescription and over-the-counter (OTC) medications have the potential to cause adverse oral conditions. Drug-induced oral lesions or disorders occur frequently, especially among the elderly who take multiple medications to treat chronic diseases. Additive or synergistic effects between medications can increase the incidence of such adverse events, either directly as an adverse effect of the drug, or indirectly as the result of drug-induced nutrient deficiencies [80]. These effects can present as part of a general systemic effect, a specific oral adverse effect to the systemic use of a

Table 6.12 Medications causing other drug-induced adverse oral conditions [52, 88–93]

Gingival overgrowth	
Antiepileptic drugs	Primarily phenytoin (prevalence ranges from 0 to 84% with an average effect of around 50%) but there are case reports in patients taking other antiepileptic drugs, such as valproic acid, phenobarbital, carbamazepine, although this side effect is seen in less than 5% of patients taking these medications
Calcium channel blockers	The prevalence of calcium channel blockers has been reported to be 15–85% with an average composite of around 42%, in patients taking nifedipine. Verapamil, diltiazem, felodipine, or amlodipine, is significantly less and reported to be around 5%
Immunosuppressant drugs	Primarily cyclosporine with a reported average prevalence of 25–50% in adults and a significantly higher prevalence being reported in children, with more than 70–97%
Esophageal/Mucosal damage	
Tetracyclines	Tablets may lodge and quickly dissolve in esophagus, concentrating acidic drug in a small space leading to injury. Doxycycline is most commonly implicated; tablets appear less injurious than capsules
Bisphosphonates	Alendronate may be inherently caustic; once in the stomach, refluxed alendronate may erode the esophageal mucosa in most documented cases of esophageal injury, patients did not follow manufacturers' administration instructions
NSAIDs	Fast dissolution rates expose esophageal mucosa to drug before swallowing can effectively clear it
Potassium chloride	Chemical erosion, especially if tablet gets lodged in the esophagus. Many cases involve patients with cardiomegaly impinging on the esophageal lumen
Quinidine	Appears to be injurious when lodged in esophagus many cases involve patients with cardiomegaly impinging on the esophageal lumen
Other drug-induced oral reactions	
Fixed drug eruption	Ampicillin, barbiturates, chlorhexidine, captopril, dapsone, gold salts, NSAIDs, Penicillamine, sulfonamides, tetracyclines
Aphthous-like lesions	Alendronate, azathioprine, beta-blockers, captopril, cyclosporine, docetaxel, fluoxetine, gold salts, imiquimod, indinavir, interferons, losartan, NSAIDs, olanzapine, penicillamine, sertraline, sulfonamides, temsirolimus, tiotropium
Burning mouth syndrome	Angiotensin-converting enzyme inhibitors (ACEIs), antiretrovirals, candesartan, cephalosporins, chloramphenicol, eprosartan, estradiol, fluoxetine, penicillin, sertraline, peginterferon, venlafaxine
Motor disorders	Amphetamines, antipsychotics, metoclopramide, prochlorperazine, promethazine, selective serotonin-reuptake inhibitors (SSRIs)

drug, or a local effect secondary to direct contact with the oral mucosa (i.e., chemical erosion). The presence of these adverse oral effects can impair appetite and food intake and adversely affect the nutritional status of the patient. Tables 6.8 through 6.12 summarizes common drug-induced adverse oral conditions [63–71, 88–93].

Xerostomia

Xerostomia is the perception of dry mouth and may or may not be associated with actual hyposalivation. Xerostomia is probably the most frequent, undesirable effect of medications. Common classes of medications such as anticholinergics, centrally-acting antihypertensives, antihistamines, antipsychotics, narcotic analgesics, sedatives, muscle relaxants, anticonvulsants, antineoplastics, antidepressants, and diuretics can all decrease normal salivary secretion (Table 6.8) [63–69]. Drug-induced xerostomia can cause alterations in taste and difficulty in chewing and swallowing, leading to dental disease, decreased food intake, subclinical malnutrition, and reduced resistance to other diseases and stress, especially among the elderly and the immunosuppressed. Lack of lubrication can

further cause mucosal irritation, inflammation, and ulceration, and make it difficult for the patient to wear removable dental prostheses [94].

Hyposalivation increases the development of oral fungal infections that can lead to complaints of oral pain, burning, and altered taste. Decreased salivary flow leads to decreased enzymatic debridement of plaque, decreased buffering and neutralization of acid formed in the tooth decay process, and increased accumulation of food debris, increased cariogenic flora, reduced remineralization of tooth structure, resulting in increased caries and periodontal disease [94].

Changes in Taste and Smell

Many drugs induce abnormalities of taste and smell (Tables 6.10 and 6.11) [71, 93, 95, 96]. The alteration may be a decreased sensitivity in taste perception (*hypogeusia*), a total loss in the ability to taste (*ageusia*), or an unpleasant or altered taste sensation (*dysgeusia*) [71, 93, 95, 96]. Although ageusia is rare, drugs can commonly give rise to dysgeusia or hypogeusia by interfering in the chemical composition and amount of saliva, directly affecting taste-receptor function or signal transduction (either stimulating or desensitizing), or by adversely affecting the renewal process of taste buds [71, 93, 95, 96]. The effect of drugs on taste may also be mediated by their actions on trace metals such as copper, zinc, and nickel [71, 93, 95, 96]. Reduction in salivary flow may concentrate electrolytes in the saliva, resulting in a salty or metallic taste. Alterations in taste can cause anorexia, food aversion, affecting quality of life and leading to weight loss.

Classifications of medications that can alter taste or smell include the anticonvulsants, antidepressants, antihistamines, antihypertensives, anti-inflammatories, antimicrobials, antineoplastics, asthma medication, lipid-lowering drugs, and muscle relaxants [71, 93, 95–98]. Representative medications from these drug classes which are most frequently associated with altered taste and smell are listed in Tables 6.10 and 6.11. Up to 4% of patients treated with angiotensin-converting enzyme inhibitors (ACEIs) may have dysgeusia, although this adverse effect is self-limiting and reversible within a few months, even with continued therapy [97, 98]. Taste disturbances in general tend to be self-limiting and often reversible in 2–3 months following discontinuation of the medication. It may be feasible to contact the patient's physician to see whether there are substitute medications that can be used that have less effect on either salivary flow or taste. Possible approaches to relief from dysgeusia include increased use of flavoring agents during food preparation, substituting alternative protein sources if the patient is unable to tolerate meat, and use of artificial saliva as needed. Optimal oral hygiene is essential. Use of a "swish and spit" strategy with iced lemon water can temporarily decrease dysgeusia and increase patient comfort and satisfaction with subsequent meals [99]. Patients should be reassured that, in most cases, taste will return to baseline. If the patient has persistent taste disturbances, referral to an oral medicine specialist and a registered dietitian for medical nutrition therapy would be appropriate.

Mucositis/Glossitis

While *stomatitis* has been interpreted historically to encompass both mucositis and glossitis, it is now defined more specifically as related to localized lesions such as aphthae (cankers). *Mucositis* describes a more diffuse mucosal reactions with or without ulceration, while *glossitis* refers to inflammation of the tongue. Each of these conditions can be caused by both local effects and systemically-mediated responses of medications (Tables 6.9 and 6.12) [52, 70, 88–93]. Pain from mucosal lesions can be severe and can interfere with oral care, eating, oral medication intake, and

speech. Some cases of drug-induced stomatitis have no clinical presentation other than erythema, whereas other cases can be categorized as allergic stomatitis, lichenoid drug eruptions, lupus erythematous-like eruptions, pemphigus-like drug reactions, and erythema multiforme [70, 88–93, 100]. Mucositis is a common side effect of a wide variety of antineoplastic agents, including radiation therapy and medications such as methotrexate, 5-fluorouracil, doxorubicin, daunorubicin, bleomycin, and melphalan [101–103]. Allergic reactions can occur either locally from contact with the medication or from systemic administrations of the drug. Lichenoid drug eruptions have been linked to several medication classes, including antibiotics (tetracycline, penicillin, sulfonamides, nitrofurantoin, isoniazid, streptomycin, ketoconazole, and griseofulvin), oral hypoglycemics (sulfonylureas), antihypertensives (β-adrenergic blocking agents), ACE inhibitors, nonsteroidal anti-inflammatory agents (NSAIDs), and heavy metals (especially gold compounds) [103]. Secondary oral effects may be seen with drug-induced vitamin deficiencies including the B-complex vitamins, iron, vitamin C, and vitamin A [34]. Thiamine deficiency (often the result of chronic alcoholism) may lead to painful mucosa and small vesicles on the buccal mucosa and tongue. Riboflavin (vitamin B_2) and pyridoxine (vitamin B_6) deficiencies have been associated with angular cheilitis, atrophic glossitis, burning mouth, and mucosal ulcerations. Isoniazid, which inhibits the metabolism of B_6, can be associated with peripheral neuritis affecting the cranial nerves that supply the oral cavity. Acute deficiencies in niacin, folic acid, or vitamin B_{12} can cause the oral mucosa to become red, swollen, and tender to the touch. Pernicious anemia caused by vitamin B_{12} deficiency and folic acid deficiency can cause painful glossitis and gingivitis, as well as atrophy of the papillae of the tongue, resulting in a "bald" tongue. Long-term use of methotrexate, cholestyramine, colchicine, alcohol, metformin, methyldopa, cimetidine, allopurinol, and oral contraceptives have all been implicated in vitamin B_{12} deficiency (Table 6.2) [34]. Niacin deficiency (pellagra) also causes an atrophic glossitis. Vitamin C deficiency causes red, spongy gingiva that bleeds easily and, in severe cases, can cause extensive destruction of the periodontium.

Dysphagia

Drugs that cause xerostomia can also interfere with a patient's ability to swallow. Antipsychotic drugs can cause laryngeal dystonia early in treatment and tardive dyskinesias with chronic treatment that can cause dysphagia. A number of antidepressants may lead to muscle hyperactivity and can be associated with bruxism. Drug-induced esophageal injury can also cause difficulty in swallowing, usually as a result of non-chewable tablets or capsules that get lodged within the esophagus, dissolve, and release their concentrated contents, causing direct mucosal damage (Table 6.12) [52, 87–91, 104]. An important warning sign is a dull, aching pain in the chest or shoulder after taking the drug. Many factors influence the severity of drug-induced injury to the esophagus. Chemical and physical properties of the drug, such as its chemical formula, pH, concentration of medication, drug formulation, and size and shape of the tablet or capsule, play a role. Other factors include delay in transit time of the drug and duration of contact with esophageal mucosa. When gelatin capsules are administered with inadequate liquid, they may become sticky as they dissolve and delay transit time of the drug [105]. When a gelatin capsule becomes lodged in the esophagus, it may be difficult to dislodge with repeated swallows of water. Preexisting swallowing problems (i.e., esophageal dysmotility conditions, stroke) or anatomical abnormalities (e.g., esophageal strictures or tumors) may alter the passage of the drug to the stomach [105].

Aspirin, tetracycline, quinidine, potassium chloride, vitamin C, and iron can all cause esophageal ulcers [105]. Alendronate and other bisphosphonates can cause esophagitis, including severe

ulcerations. Patients should take alendronate with a full glass of water and remain in an upright position for at least 30 minutes before eating to prevent esophageal ulceration.

The best treatment for drug-induced esophageal damage is the discontinuation of the problematic drug. Patients should be instructed to swallow several sips of water to lubricate the throat before taking a tablet or capsule and then take the medication with at least 8 ounces of liquid. Tablets or capsules should be swallowed while in an upright or sitting position, and the patient should not lie down immediately after taking a tablet or capsule to ensure that the solid dosage forms pass through the esophagus and into the stomach [105]. Patients should also avoid irritating foods such as citrus juices and alcohol.

Gingival Hyperplasia

Enlargement and overgrowth of the gingiva was originally recognized in patients using phenytoin and more recently with the calcium channel blocker class of cardiac drugs, cyclosporine (an anti-rejection medication for transplant patients), and the anticonvulsant valproate sodium (Table 6.12) [52, 88–93]. An inverse relationship appears to exist between oral hygiene and the degree of gingival enlargement. In rare cases, the extent of the gingival hyperplasia is such that it impedes the patient's ability to eat, and excess tissue must be surgically removed.

Summary

The interactions between medications, nutrition, dietary supplements, and oral health are becoming more important especially given our aging population who are not only getting older, but are retaining their dentition longer while "collecting" chronic diseases through the increased usage of multiple medications on a chronic basis. Adverse outcomes include a reduced therapeutic response because of drug-drug or drug-dietary supplement interactions resulting in changes to drug absorption, bioavailability, metabolism and excretion. Drug-induced nutritional deficiencies and interactions between medications and food or alcohol further compound this milieu. The risks of drug-drug and drug-nutrient interactions and their outcomes depends on the patient's age, physiologic status, including renal and hepatic function, disease history-the number of drugs and supplements being taken, and overall nutritional status. Predictions of the risk of drug and nutrient interaction may be possible if the characteristics of the prescribed drugs, dietary supplements and patient physiology and nutritional status are known. Diagnosis of a clinical problem as an adverse drug-drug or drug-nutrient interaction depends on recognizing if the problem appeared after a drug had been prescribed and/or a change in diet has occurred.

Laboratory tests may be useful in clarifying the diagnosis, especially with drug-induced vitamin deficiencies. Avoidance of drug-, nutrient- and dietary supplement-drug interactions depends on knowledge of the risk as well as avoidance of combinations that impose a high-risk situation. Careful monitoring of the oral cavity for signs of drug-nutrient vitamin deficiencies can allow for intervention before a patient's nutritional status is compromised. Use of sialagogues, topical fluorides and remineralizaing products can prevent damage of the oral mucosa and teeth as the result of drug-induced xerostomia.

In summary, it is incumbent on all of the members of the healthcare team to have a current knowledge of the interrelationships between medications, nutrition, dietary supplements, and oral health. Review and frequent update of all medications that a patient is taking (i.e., prescription, over-the-counter, supplements, nutriceuticals and even illicit drugs) and appropriate dietary evaluation

considering the patient's underlying medical condition(s) are vital in order to anticipate, prevent, and appropriately treat unwanted interactions.

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Part III
Relationships Between Nutrition and Oral Health

Chapter 7
Oral Consequences of Compromised Nutritional Well-Being

Paula Moynihan, David P. Cappelli and Connie Mobley

Keypoints

- Dental structures are influenced by nutritional status only during the period of tooth formation. Thereafter, deficient nutrition may influence the supporting structures of the teeth and the oral mucosa
- Adequate early feeding programs in developing countries are important to avoid enamel defects and compromised salivary secretion, both of which may increase susceptibility to dental caries, the latter having more widespread oral consequences
- The early signs of nutritional deficiencies are seen in the oral soft tissues and include thinning, inflammation, and ulceration. Malnutrition also impairs immune responses and may predispose to life-threatening diseases of the oral soft tissues such as noma
- An optimal nutritional status is important in reducing the origin and severity of periodontal disease but is likely to be of limited value if the stimuli from dental plaque are not removed. Further research is needed in order to identify to what extent dietary modification will modulate periodontal disease and subsequent tooth loss
- Nutritional status and oral health are reciprocally related, and each one affects the other— a downturn in nutrition impairs oral function

Keywords Oral consequences · Nutritional well-being · Nutritional status · Enamel developmental defects · Dental caries · Vitamin D · Vitamin A · Salivary secretion · Disorders of the oral mucosa · Periodontal disease

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Introduction

Nutrition affects the development of the teeth and the development and maintenance of the oral tissues. Often, the very early signs of suboptimal nutritional status are first seen in the mouth, which has been described as a "mirror of nutritional status." Oral healthcare professionals (OHCPs) are therefore in a position to be the first to notice compromised nutrition, and a sound knowledge of the symptoms and signs will enable them to take the appropriate action. Knowledge of the systemic and oral consequences of compromised nutritional status in the oral cavity will help OHCPs in the provision of comprehensive oral healthcare. The OHCP should recognize when a patient needs to be referred to a dietician, and, likewise, dieticians should recognize the oral symptoms of nutritional deficiencies.

In this chapter, compromised nutritional well-being encompasses general undernutrition such as protein energy malnutrition (PEM), deficiencies of specific nutrients, and diets that fall short of current recommendations for intakes of food types, such as a low intake of fruits and vegetables. This chapter discusses each oral disease or disorder in turn, relating the condition to compromised nutritional well-being. The conditions covered include enamel developmental defects, dental caries, impaired salivary gland function, disorders of the oral mucosa including noma, periodontal disease, and briefly discusses oral cancer, which is addressed in greater detail in Chapters 12 and 13 in this book.

Compromised Nutritional Status and Enamel Developmental Defects

Calcification of enamel of deciduous incisors begins at 14 weeks *inutero* and continues until about 4 months after birth. Lesions to the enamel of the deciduous incisors are therefore most likely to be caused by perinatal or neonatal insults. Simultaneously with calcification of the deciduous dentition, the tooth germs for the permanent teeth develop. Mineralization of the permanent dentition starts with the first molars around birth, and all teeth (with the exception of the third molars) have normally started to mineralize before 3 years of age. The crowns are complete at 5–7 years of age, and root formation is complete between 10 and 15 years of age. For a full description of the development of the dentition see the paper by Nanci [1] listed in the references for this chapter.

Developmental defects may be broadly classified into opacities (fluorosis or white or yellow areas of opaque enamel) that are caused largely by excess fluoride ingestion, or "hypoplasia," a term that describes surface defects of enamel (pits, fissures, or larger areas of missing enamel). There are many causes of enamel developmental defects including congenital defects, effects of drugs, trauma, infection, and metabolic disturbances [2]; compromised nutritional status is just one cause. Most attention has focused on excess ingestion of fluoride as a cause of fluorosis and disturbances of calcium and phosphorus metabolism and deficiencies of vitamins A and D and protein as nutritional causes of hypoplasia. Damage to the teeth during the development is permanent damage that affects the aesthetics of the teeth and the susceptibility to dental diseases.

Protein Energy Malnutrition and Enamel Developmental Defects

The most common enamel abnormality in severely malnourished children is linear enamel hypoplasia (LEH) [3, 4], characterized by a horizontal groove on the labial surface that stains post eruption. In developing countries, hypoplasia is common and linked to malnutrition in children. Both malnutrition in early childhood and impaired maternal nutritional status can result in

hypoplasia. Enwonwu [5] reported the prevalence of hypoplasia to be approximately 21% in 4 years old Nigerian children from low socioeconomic backgrounds compared with 0% in affluent areas. Almost 75% of the defects were caused by prenatal damage. Sweeney [4] reported a prevalence of LEH of 73% in children with third-degree malnutrition compared with 24% in children with lesser malnutrition. The reason why children with malnutrition were more susceptible to hypoplasia was unclear until Nikiforuk and Fraser found, in a study of subjects with disturbances of calcium and/or phosphate metabolism, that hypocalcemia was associated with hypoplasia [6]. In chronic undernutrition, hypocalcemia develops as a result of diarrhea and thus may explain the association between PEM and defective enamel development. Acute diarrheal disease may also lead to low serum levels of vitamin A, which may contribute to the development of hypoplasia. Fluorosis is caused by excessive fluoride ingestion; however, PEM has also been shown to exacerbate the effect of excessive fluoride ingestion, causing more severe enamel fluorosis [7].

Deficiencies of Vitamins A and D and Enamel Hypoplasia

Vitamin A is important in maintaining normal epithelial tissue integrity and histodifferentiation of the tooth. Vitamin A functions in the normal differentiation of the enamel organ, which is an essential prerequisite for tooth development to occur normally. Numerous animal studies have shown that a deficiency of vitamin A impairs histodifferentiation of the tooth [8]. Vitamin D is intricately involved in mineralization processes, and, therefore, a deficiency of this vitamin will impair normal mineralization.

The early half of the twentieth century was an exciting time in the discovery of the vitamins, and during this period Lady May Mellanby conducted extensive studies on the effects of the vitamins on the development of the teeth and their resistance to disease [9–12]. In 1918 [9], she reported that dogs reared on a diet deficient in vitamin D had delayed development of teeth that were poorly aligned with deficient calcification of enamel. Mellanby noticed the high prevalence of hypoplasia in the primary dentition of British children and suggested that this was caused by vitamin deficiencies, especially vitamins A and D [10]. She attributed the improvements in British children's teeth between 1929 and 1943 to the improved diet of the wartime food policy, which provided cheap milk; free cod liver oil to pregnant mothers, infants, and young children; fortification of white flour with calcium carbonate; and the addition of vitamins A and D to margarine [11].

Mellanby examined teeth of children in England and in India and found that gross hypoplasia was slightly more prevalent in India; however, the prevalence of mild hypoplasia was similar in the two countries. She attributed the higher gross hypoplasia in India to the poor diet and greater diarrheal disease and the lower-than-expected mild hypoplasia to the high exposure to sunlight and resulting good status of vitamin D [12]. In support of these observations, Cockburn et al. [13] found that supplementation with vitamin D during pregnancy resulted in raised cord blood vitamin D levels and reduced incidence of enamel defects in deciduous teeth in the offspring.

Associations Between Hypoplasia of Enamel and Dental Caries

In addition to the aesthetic disadvantages of enamel defects, there is evidence that hypoplasia is associated with an increased risk of caries [14–17]. Mellanby [14] studied more than 300 teeth from at least 200 British children aged 2–13 years. Nearly all teeth with hypoplasia were carious, whereas only 25% of teeth without hypoplasia were carious. In Guatemalan children aged 2–6 years, 48% of children without hypoplasia were caries free but only 31% of children with hypoplasia were caries

free [15]. In a study of Chinese children, Li et al. [16] found that almost 25% of children aged 3–5 years had hypoplasia, and only 7% of these children were caries free compared with 21% of children without hypoplasia. Matee et al. [17] found a higher incidence of nursing-bottle caries in young children with hypoplasia.

The Effect of Compromised Nutritional Status on Dental Caries

Protein Energy Malnutrition

The worldwide distribution of severity of dental caries has changed markedly since the late 1970s, with a marked decrease in prevalence in developed countries but an increase in many developing countries that parallels an increase in sugar consumption. Where sugars are available in developing countries, the level of caries observed is higher than expected from observations in industrialized countries, and this has led to the hypothesis that malnutrition enhances the cariogenic effects of sugars [5, 18]. This has been demonstrated in animal experiments, which have shown increased caries in rat pups whose dams received a protein-deficient diet during pregnancy and lactation [19]. However, the milk quantity as well as quality would be affected in such an experiment, making it difficult to separate the effect of deficient calories from deficient protein. Further research showed that addition of protein alone was able to restore the low level of caries observed in the well-fed rats.

There are three potential mechanisms to explain how deficiency of protein, energy, or both increase caries susceptibility. First, malnutrition results in defectively formed enamel that is poorly calcified (see the previous discussion of hypoplasia) and therefore susceptible to dental decay. Second, undernutrition causes delayed eruption and exfoliation of the dentition, and this affects the caries prevalence at any given age [5, 20–22]. Enwonwu found that malnourished children aged 7–24 months had 2.5 fewer erupted teeth compared with well-nourished children of a similar age. Alvarez et al. [20–22] conducted a series of investigations into nutritional status and eruption and exfoliation of dentition in Peruvian children from a poor area of Lima. Occurrence of caries as a function of time was shifted to the right and occurred 15 months later in malnourished children compared with well-nourished children. This suggested that one reason for a higher level of caries in children with malnutrition at age 6 was the delay in exfoliation of the primary dentition. When the study was expanded to look at the permanent dentition [21], eruption of the permanent dentition occurred 2.5 years later, and hence caries prevalence at age 12 was lower because many of the secondary teeth had not erupted. The third mechanism by which PEM increases caries susceptibility is through its effects on salivary gland function and saliva quality. The effects of compromised nutritional status on salivary gland function are considered in a later section.

Vitamin Deficiencies and Dental Caries

Vitamin D

Mellanby postulated that vitamin D deficiency was the cause of dental caries in British school children because deficiency of this vitamin resulted in hypoplasia that rendered the teeth susceptible to dental decay. She tested her vitamin-deficiency theory in intervention studies and found that initiation and spread of caries was lower and hardening of precarious lesions was higher in children receiving dietary supplements [23]. Children supplemented with cod liver oil developed fewer caries lesions in erupting permanent teeth (but not erupted teeth) compared with a control group receiving

olive oil. Many investigators did not accept the vitamin theory and rightly claimed that the effect of dietary sugars was of greater significance. Mellanby modified her view to say that vitamin D was *a* factor during the development of teeth rather than *the* factor responsible for caries.

A resurgence of vitamin D deficiency in children has been noted in many countries including the UK, US, and elsewhere [24–26]. Data from the US indicate that vitamin D deficiency is more common in overweight and obese children as well as children from minority backgrounds [27]. Furthermore, in some religions, females fully veil themselves and receive little vitamin D through the action of sunlight on the skin. This renders them susceptible to deficiency of vitamin D and may result in increased caries susceptibility in their offspring. An intervention study in which full-spectrum lighting was installed into classrooms in Alberta, Canada, found that fewer caries developed in the schoolchildren compared with children from classrooms with conventional lighting [28]. Another intervention study conducted in Scotland, UK, in which pregnant mothers received a vitamin D supplement from the 12th week of pregnancy resulted in fewer caries in the children at age 3 years compared with the children of a control group who did not receive a vitamin D supplement [13]. A 2013 systematic review of 24 clinical trials has indicated that vitamin D helps prevent dental caries [29]. Deficiency of vitamin D during the development of the teeth is likely to cause defects in the enamel that render the tooth more susceptible to dental caries [30].

Vitamin A

Animal experiments have shown that deficiency of vitamin A causes gross structural changes in teeth, and this increases risk of dental caries [31–33]. Vitamin A deficiency is often associated with diarrhea and PEM and may increase susceptibility to dental caries by causing hypoplasia and also by affecting normal salivary function.

In conclusion, PEM and deficiencies of specific nutrients per se will not cause dental caries in the absence of dietary sugars. Even in severely malnourished communities, dental caries is rare when intake of sugar is below 10 kg/person/year. Likewise, optimum nutritional status will not protect against dental caries if the frequency and amount of intake of dietary free sugars is too high.

The Effect of Compromised Nutritional Status on Salivary Secretion and Composition

Saliva is a complex oral fluid that has a key role in the physiological homeostasis of the oral cavity. Composed mostly of water, saliva also contains proteins and electrolytes. Saliva is produced in the major salivary glands (parotid, submandibular, sublingual) and the minor salivary glands which are located in the submucosa of the oral tissues [34]. The three major salivary glands contribute to approximately 90% of the salivary flow, while the minor glands produce the remaining 10% of saliva [35]. Adequate salivary flow is critical to maintain mechanical cleansing of the oral cavity, to buffer against acids produced by the microorganisms that reside in the oral plaque, and to facilitate the host response to pathogenic bacteria that may be harbored in the biofilm [36, p. 3]. Saliva can contribute to the remineralization process especially for persons with access to optimally fluoridated community water. The parotid gland provides the greatest contribution to production of stimulated saliva, while the submandibular glands are responsible for the majority of the production of unstimulated saliva [35].

Salivary flow has a critical role in maintaining oral health. Diminished salivary flow or hypo-salivation, xerostomia, is a known risk factor for an increased incidence in dental caries caused by either a functional or organic disturbance. In addition, diminished salivary flow can impede normal

oral function. Xerostomia is a component of normal aging, but can be exacerbated by certain medical conditions, including Sjogren's syndrome, lupus erythematosus, Rheumatoid arthritis, radiation therapy of the head and neck, and Parkinson's Disease, to name but a few. Xerostomia is also caused by polypharmacy, neurological and psychological disorders, dehydration, and mouth breathing [37]. Adequate hydration, as well as avoiding products containing alcohol or tobacco, should be recommended. An increase in consumption of moist, soft-textured foods, and reduction in the intake of dry, spicy, or salty foods should be included in dietary recommendations for all persons who are experiencing symptoms of xerostomia [38]. Details about xerostomia associated with specific oral health conditions are discussed in Chapters 13 and 14.

Nutritional deficiencies affect both salivary gland formation and function as well as saliva composition. Factors that have an influence on salivary gland formation include the degree of malnutrition, timing of the deficiency, consistency of diet, salivary gland function, and the source of saliva. In relation to gland function, it is particularly important to determine the period when malnutrition takes place—for example, in utero and during lactation, in young age or in older age [38].

Protein Deficiency

Moderate and severe protein malnutrition results in alterations to salivary gland growth and function [39–41]. When protein deficiency takes place at an early stage of development, the submandibular gland has been found to be smaller [42]. Events that take place during these early stages of development may not be completely reversed when a diet adequate in protein is subsequently provided. Protein malnutrition induced in young adult rats resulted in changes in parotid gland weight and a decreased β-adrenoceptor density, whereas submandibular gland weight and β-cell density were both reduced [40]. However, several studies have shown no effect on gland weight when protein malnutrition is induced in aged animals [43].

Johnson et al. [41] evaluated the effect on parotid gland growth and secretory function of animals fed diets with different protein concentrations (20 or 7%) and different consistencies (powdered or solid). A reduced parotid gland weight was found in the rats fed the low protein (7%) diet. This reduced gland weight was observed for the low-protein diet when it was fed as either a solid or powdered form. However, the parotid gland weight observed in the animals fed the low-protein diets was similar to the animals fed a normal protein diet (20%) in a powdered form. The composition of the parotid gland saliva was higher in proline-rich proteins in both groups of animals on the low-protein diets. The flow rate of parotid saliva was significantly reduced by both the diet consistency and the dietary protein concentration. Although protein deficiency has a marked effect on salivary gland growth and function, diet texture, which affects the requirement for mastication, was also found to be a significant factor. This finding is supported by other researchers where a change in saliva volume [44], gland weight [45], and salivary composition [43–45] has been found during protein malnutrition. The majority of their work has been conducted on animals. However, although somewhat difficult to extrapolate the results to humans, one might expect someone with protein malnutrition to have a reduced gland function.

Vitamin and Mineral Deficiencies

Essential vitamins and minerals are necessary for optimal gland function. Wang et al. found that when rats were fed low-calcium diets, they developed a salivary secretion dysfunction [46]. Vitamin

A has also been found to affect the morphology and function of salivary glands in animals [47, 48], and it has been observed that vitamin D deficiency reduces parotid gland secretion [49]. Different explanations have been suggested, but a function disorder in the salivary gland has been postulated to be the most likely explanation. For vitamin D, it has been proposed that the vitamin is necessary for the synthesis of proteins, which in turn is essential for the utilization of extracellular calcium in the secretion process [49]. Other effects of specific nutrient deficiencies on saliva cited in the literature include a reduction in acidic proline-rich proteins in parotid saliva of zinc-deficient rats [50] and reduced saliva secretion rate and impaired peroxidase protection in iron-deprived rats [51]. It is possible that reduced saliva calcium content may reduce the capacity for the hard tissues to remineralize.

Effects of Childhood Malnutrition on Saliva

In 8–12 year-old Indian children with moderate to severe PEM, extensive analyses of their salivary production and composition found the following: (a) a decreased stimulated salivary secretion rate related to the severity of PEM, but no difference in the unstimulated salivary secretion rate; (b) a lower content of calcium and chloride ions and total protein secretion in stimulated saliva; and (c) impaired immunological and agglutinating defense factors noted in unstimulated saliva [52]. The magnitude of decrease in salivary protein concentration and arginase activity increased with increased severity of PEM, suggesting that protein content of saliva and its arginase activity may be used as an index of PEM in the early stages of the disease [53].

Effects of Moderate Malnutrition in Adults on Saliva

In one of the few studies carried out on human adults where a low energy (300 kcal/d) liquid diet was given for 7 days, a reduction in stimulated salivary secretion rate, phosphate, and calcium ion concentrations were found [54]. This observation occurred even when controlled for the absence of chewing. In a previous study by the same investigators, a significant decrease in secretion rate, phosphate, and sialic acid concentration of stimulated whole saliva was observed [55].

Compromised Nutritional Well-Being and Disorders of the Oral Mucosa

Nutritional deficiencies have a profound effect on the integrity of the oral cavity. Malnutrition can contribute to atrophy of the oral mucosa and the thinning, inflammation, and ulceration of the oral mucosa, and the loss of filiform papillae on the lingual mucosa, resulting in glossitis (inflammation of the tongue). Nutritional deficiencies also cause atrophy, inflammation, and fissures to the labial mucosa of the lips, and a common feature of compromised nutritional well-being is angular cheilitis (sores at the corners of the mouth), largely because of the high turnover of cells in the labial commissures. A suboptimum nutritional status will also increase the susceptibility to oral infections, including candidiasis, and secondary staphylococcal infections to damaged, inflamed tissues. The effects of specific nutritional deficiencies on the oral mucosal tissues are summarized in Table 7.1.

A deficiency of vitamin B_{12} causes reversible dysplasic changes to the oral mucosa and recurrent ulcers [56, 57]. A deficiency of vitamin B_{12} also causes atrophy of the lingual papillae, but the condition responds well to vitamin therapy and is reversed within 3 weeks. B_{12} deficiency has been

Table 7.1 Role of some vitamins and minerals in the oral tissues and the oral signs of deficiency

Nutrient	Dietary source	Function	Oral sign of deficiency
Vitamin A	Carotenoids [found in dark green and yellow fruits and vegetables [not citrus], preformed vitamin found only in oily fish, liver, eggs, and fortified margarine	Epithelial differentiation	Mucosal keratinization and leukoplakia; cheilitis; hypoplasia if deficiency occurs during mineralization of the enamel
Thiamin [B1]	Fortified wheat flour and breakfast cereals, milk eggs, yeast extract	Coenzyme thiamine pyrophosphate functions in energy metabolism	Oral sensitivity; burning mouth syndrome, reduced taste perception
Riboflavin [B2]	Dairy products and eggs, fortified breakfast cereals, liver, kidney, and whole grains	Flavoproteins; coenzymes involved in energy metabolism	Angular cheilitis, glossitis, recurrent aphthae
Niacin [B3]	Dairy products, liver, meat, eggs, yeast extract, pulses	Nucleotide coenzyme involved in amino acid metabolism	Mucosal atrophy and stomatitis; glossitis; angular cheilitis
Vitamin B6	Liver, meat, fish, whole grains, and peanuts	Coenzyme involved in amino acid metabolism	Glossitis, cheilitis, burning mouth syndrome; ulceration; lip fissures
Folate	Liver, kidney, green leafy vegetables, oranges, pulses, and fortified breakfast cereals [fortified flour in the United States and Canada]	Purine and pyrimidine synthesis	Glossitis; stomatitis; recurrent aphthae; angular cheilitis; candidosis
Vitamin B12	Meat, fish, eggs, dairy products, fortified breakfast cereals	Purine and pyrimidine synthesis	Atrophic glossitis; stomatitis; recurrent aphthae; dysplasia; angular cheilitis; candidosis
Vitamin C	Citrus fruits, berries, potatoes, green vegetables, bell peppers, parsley	Antioxidant involved in redox reactions	Recurrent aphthae; angular cheilitis; gingivitis/periodontitis
Vitamin D	Oily fish, fortified margarine, eggs, sunlight	Calcium homeostasis	Hypoplasia if deficiency occurs during tooth mineralization
Vitamin E	Vegetable oils, sunflower seeds, whole grains, eggs	An antioxidant	None
Vitamin K	Vegetables, pulses, liver	Formation of clotting factors	Gingival bleeding; post extraction hemorrhage
Iron	Meat, fish, dark green vegetables, pulses, cocoa, fortified breakfast cereals	Hemoglobin and myoglobin formation; enzyme component	Glossitis; angular cheilitis; mucosal atrophy [increases susceptibility to carcinoma]; candidosis
Zinc	Shellfish, fish, meat, poultry, dairy products, pulses	A component of >70 enzymes	Taste disturbances
Selenium	Richest source is animal products	Enzyme component in glutathione peroxidase; protects from oxidative damage	May be protective against oral cancer [high levels promote caries]

associated with stomatitis (inflammation of the oral mucosa), which is common in patients with pernicious anemia. A deficiency of thiamine causes burning-mouth syndrome [58], as do deficiencies of riboflavin and B_6 [59]. PEM is associated with a smooth, red glossitis, affecting in particular, the anterior margins of the tongue. This condition is often referred to as "scarlet tongue." Glossitis is common in patients with iron deficiency anemia. However, glossitis is an early symptom of iron deficiency appearing prior to anemia. The severity of glossitis in iron deficiency is not as severe as that observed in deficiencies of vitamin B_{12} or folate. Cheilosis, or inflammation of the lips is a common sign of deficiency of the B-vitamin complex, being associated with deficiencies of riboflavin, folate, and pyridoxine (See Fig. 7.1).

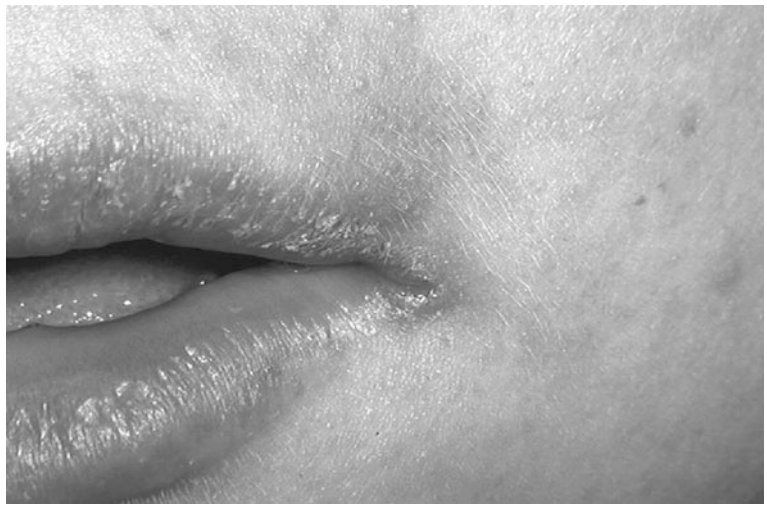

Fig. 7.1 Angular cheilitis: vertical fissuring of lips as a consequence of B-vitamin deficiency

Noma

Noma (also known as cancrum oris) is a gangrenous lesion of early childhood in which the perioral flesh is destroyed. The disease is exclusive to malnourished and poor communities and occurs most commonly in Africa, where the prevalence is 1–7 per 1,000 population. Cases of noma have also been reported in Asian and Pacific countries [60].

Details of the pathogenesis have been reported elsewhere [61]. In brief, compromised nutritional status and/or viral or other infections result in impaired immune function. Next, oral ulcers appear, such as acute ulcerative gingivitis, and these are exacerbated by malnutrition and/or viral infections. The ulcerated tissue provides a site of entry for organisms, including *Fusobacterium necrophorum* and *Prevotella intermedia* that cause the gangrenous lesion [62]. Undernutrition is a key factor in the rapid progression of necrotising ulcerative gingivitis to noma. Mortality from noma is very high (70–90%) [63]; effects are severe esthetic and functional lesions. The prevention of this disfiguring disease relies on prevention of malnutrition in poor countries.

Oral Cancer

Cancers of the mouth and pharynx are the seventh most commonly occurring cancers worldwide and the seventh most common cause of death from cancer. Survival rates average around 50% at 5 years [64]. The epidemiology and prevention strategies for cancers of the head and neck are addressed in Chapters 12 and 3 nutritional management of individuals with head and neck cancer are covered in of this book. There has been much research regarding the associations between diet and oropharyngeal cancers, including individual micronutrients, food types, and dietary supplementation; it is estimated that up to half of oral cancer could be prevented by dietary and associated factors [64].

Nutritional Deficiencies and Periodontal Disease

Periodontal diseases include a group of chronic inflammatory diseases that affect the supporting tissues of the periodontium, including the bone, gingival tissue, and the periodontal ligament. Periodontal diseases are routinely divided into two forms: gingivitis and periodontitis. Gingivitis, usually reversible, is an inflammation of the soft tissue without apical migration of the junctional epithelium. Gingivitis is observed from adolescence through adulthood. Periodontitis presents as a persistent immunoinflammatory response to a complex biofilm that colonize the subgingival niche of the gingival tissues. The most common forms of periodontal disease is found among adults and increases with age; however, periodontitis can also be found in younger individuals [65, 66].

Although convincing scientific evidence supports the fact that the pathogenesis of periodontitis involves infection with Gram-negative, anaerobic oral bacteria and that tissue damage occurs as a result of the complex interaction between pathogenic bacteria and the host's response to infection, several local and systemic factors are known to be associated with the risk or the severity of the periodontal disease [67, 68]. Nutrition is known to be important for maintaining periodontal health, and several dietary aspects may contribute to the disease process. Results of the Health 2000 Survey in Finland demonstrated that both the extent and severity of periodontal disease is associated with obesity [69].

Two potential mechanisms that describe the relationship between diet and periodontal disease have been proposed. The first mechanism is the role that diet plays in the formation of the nutrient rich biofilm. The second mechanism proposes that nutritional deficiencies impact the health of the periodontal tissues. Research into the local effect of diet on plaque has focused largely on the effect of an abrasive diet in reducing plaque formation. Although animal studies demonstrated a relationship between diet and plaque formation [70, 71], the significance to humans is questionable because of differences in tooth morphology. It is also unclear whether, in addition to the influence of diet on amount of plaque present, this relationship extends further to influence the development of gingivitis and periodontitis. A more important influence of diet on periodontal health is the relationship between suboptimal dietary intake and nutritional status, and periodontal disease. Studies discussed in the following sections suggest an association between undernutrition and periodontal disease and the role of specific nutrients such as vitamin C, calcium, vitamin D, antioxidants, and dietary fats in periodontal disease.

Undernutrition and Periodontal Disease

PEM has been linked to periodontal disease. Enwonwu has outlined several mechanism to explain this link including: (1) decreased resistance of mucosa to colonization and invasion by pathogens; (2) impaired salivary flow and antibacterial properties; (3) reduced acute phase protein response in malnutrition; and (4) an increase in the prevalence and potency of pathogenic oral microorganism in PEM [72].

History of Vitamin C and Gingival Diseases

Vitamin C (ascorbic acid) is one of the most well-documented nutrients associated with periodontal health. Severe vitamin C deficiency is known to lead to scorbutic gingivitis (scurvy), characterized by ulcerative gingivitis and rapid periodontal pocket development with tooth exfoliation [73]. Vitamin C promotes a collagen formation and reduces the permeability of endotoxin from the oral

mucosa [74]. Studies show that vitamin C enhances motility of polymorphonuclear leukocytes, and increases host immune responses [75, 76]. A reduction in bleeding on probing after supplementation with vitamin C was noted, suggesting that vitamin C may influence early stages of gingival inflammation [77]. Vitamin C may improve periodontal health by increasing bactericidal activity against *Actinomyces viscosus* [78].

Studies in animals have shown that a diet deficient in vitamin C increases susceptibility of the periodontium to chronic inflammation [79], and acute vitamin C deficiency increases the permeability of the gingival sulcular epithelium. The periodontal effects of vitamin C deficiency in humans are inconclusive. While some epidemiological and experimental evidence has failed to demonstrate significant etiological relationship between vitamin C deficiency and periodontal disease [80, 81], others have reported a direct relationship between gingival inflammation and vitamin C status [79, 82]. In healthy nonsmoking men aged 19–28 years, it was found that vitamin C deficiency contributed to the early stages of inflammation. This finding was noted even when controlling for changes in plaque accumulation or probing depths [77]. Leggott et al. [82] found a significant increase in gingival bleeding after a period with vitamin C depletion, without significant changes in plaque accumulation, probing pocket depth, or when attachment level were observed. Studies that examine vitamin C and its effect on the extracellular matrix and immunologic and inflammatory responses provide a rationale for hypothesizing that vitamin C is a risk factor for periodontal disease.

The role of dietary vitamin C as a contributing risk factor for periodontal disease has been investigated using data from the Third National Health and Nutrition Examination Survey (NHANES III) [73]. The periodontal health of 12,419 adult smokers and nonsmokers ages 20 or older was correlated to their dietary vitamin C intake. The dietary intake of vitamin C showed a statistically significant relationship to periodontal disease in current and former smokers as measured by clinical attachment. Those persons with the lowest intake of vitamin C, and who also smoke, are more likely to experience more severe periodontal disease, indicating a dose–response relationship.

A relationship between vitamin C and wound healing has been documented. In healthy young adult males, classified according to periodontal status, one single intravenous dose of 500 mg of ascorbic acid resulted in statistically significant correlations between gingival status and ascorbic acid concentrations in whole blood and urine [83]. In contrast, Woolfe et al. [84], found that an intake of 1 g vitamin C per day for 6 weeks in normal human subjects did not have an effect on the gingival response to initial therapy, and identical gingival responses to periodontal therapy were found in control and vitamin C—supplemented patients. Final blood vitamin C concentrations appeared to have increased minimally, suggesting that excesses of the vitamin were excreted in the urine. These data suggest that there is little to no value for OHCPs to recommend vitamin C supplementation for periodontal patients when the dietary reference intake (DRI) can be easily met through consumption of a healthy, balanced diet. (See Appendix for U.S. DRI reference).

Dietary Calcium and Periodontal Disease

Dietary calcium deficiency has been associated with changes in collagen synthesis and structure in oral connective tissue, and therefore thought to be a potential modulator for periodontal health [85]. Both animal and human studies suggest a relationship between calcium intake, bone mineral density (BMD), tooth loss [86], and resorption of the alveolar bone [85, 87, 88]*; however, this relationship is not clearly* elucidated.

In a double-blind study, calcium supplementation (1 g) for 180 d without any subsequent periodontal treatment did not influence the periodontal status of patients with moderate to advanced periodontal disease [89]. The periodontal status of patients with a low-calcium intake did not differ

from those receiving adequate calcium. Other studies have reported positive associations between calcium supplementation and periodontal conditions [90, 91]. Periodontal disease has, in humans, been found to be reversed when the patients were given 1 g calcium per day for 180 d [91]. In a study of more than 12,000 adults, Nishida et al. [86] found a statistically significant association between lower dietary calcium intake and periodontal disease in young males and females and for older males. For the females with the lowest level of dietary calcium intake, there was a 54% greater risk of periodontal disease. See Chapter 16, Osteoporosis, for additional information on the role of Calcium and other nutrients in bone health.

Dietary Fats and Periodontal Disease

Dietary omega-3 fatty acids, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) have anti-inflammatory actions that may benefit periodontal health. These long chain fatty acids are found in oily fish and also nuts and seeds, e.g., flaxseed. Though animal studies of the effect of omega 3 fatty acids on the periodontal tissue have shown mixed results, studies in humans are more convincing. Chapple [92] reviewed the literature and noted that shifts in nutritional status are independently associated with periodontal disease. The composition of fatty acids in inflamed gingival tissues is significantly different from that in healthy tissues [93]. Serum concentrations of omega 3 fatty acids have been shown to be lower in patients with alveolar bone loss compared with periodontally healthy subjects [94]. Furthermore, in a cohort study of older Japanese men, a lower intake of omega 3 fatty acids was significantly associated with greater development of periodontitis compared with a higher intake of omega 3 fatty acids. Those in the lowest cohort of DHA intake were at 1.5 times the risk than those in the highest tertile of intake after adjusting for confounders such as smoking, age, and body mass [95]. In the same cohort study, a high intake of saturated fatty acids was also significantly associated with a greater risk of periodontitis in nonsmokers [96]. Naqvi [97] compared periodontal status to the intake of omega-3 fatty acids in a cohort of 9,182 adults participating in NHANES from 1999–2004. He found that a higher dietary intake of DHA and EPA were associated with a lower prevalence of periodontal disease; however, the link with DHA was stronger than that for EPA in this study. These finding support other work that notes that oxidative stress is modulated by diet and infection, which has an impact on the extent and severity of periodontal disease.

Antioxidant Nutrients and Periodontal Disease

Antioxidants, present in all body fluids and tissues, may protect against tissue-destructive effects of reactive oxygen species. In the periodontal environment, these oxygen species can lead to lipid peroxidation, protein degradation, DNA mutation, and bone resorption [98]. Examples of dietary antioxidants include, ascorbic acid (vitamin C), α-tocopherol (vitamin E), and β-carotene and other polyphenolic dietary components as well as uric acid, nonprotein thiols, and glutathione [99]. In periodontal disease, it has been found that *P. gingivalis* triggers the release of cytokines, resulting in increased activity of polymorphonucleocytes (PMN) and that increased oxidative damage to gingival tissue, periodontal ligament, and alveolar bone may occur [100]. A similar increase in PMN cells has been found after only 3 d plaque accumulation during experimental gingivitis [101].

Reduced salivary antioxidant activity in patients suffering from periodontal disease has been reported to result in reduced concentrations of antioxidants in both saliva [100] and gingival crevicular fluid [102, 103]. Iwasaki found that [104] a higher dietary intake of antioxidant vitamins

compared with a lower intake has been shown to significantly reduce the development of periodontal disease, indicating that a diet low in antioxidant nutrients may increase risk of periodontal disease. This evidence may lead to a possible nutritional strategy for the treatment of periodontal disease [100]. At this time, there is insufficient evidence to support supplementation with megadoses of antioxidant vitamins; once again, an adequate intake may be obtained by consumption of a healthy, balanced diet. Chapter 1 of this book addresses dietary guidelines for optimal oral, systemic, and nutritional well-being.

Nutrition and Diet in Relation to Dental Plaque

It is important to bear in mind the overall pathogenesis of periodontal disease and that the changes seen may vary both inter- and intra-individually in relation to the presence of dental plaque. Good dietary practices and optimal nutritional status are important in reducing the severity of inflammatory periodontal lesions but are likely to be of limited value if the stimuli from dental plaque are not removed.

Summary of the Relevance to Current-Day Dentistry

Although severe nutritional deficiencies are rare in industrialized countries, they are commonly found in developing countries. In the latter, oral diseases are not the primary targets of health authorities where general health aspects take priority. However, it is generally believed that malnutrition impairs innate and adaptive defences of the host and that the severity of oral infections can be intensified, leading to their development into life-threatening diseases such as noma [61]. An optimal dietary intake of nutrients as noted throughout this chapter is one tool that is useful in combating oral diseases. Generally optimal oral health, including reduced levels of dental caries and periodontitis, is considered essential in order to retain a maximum number of teeth into older age, thereby increasing ability to consume a healthy, varied diet throughout the life span.

Risk of the primary oral infectious diseases, dental caries and periodontitis, can be kept at a low level by different preventive tools such as adequate exposure to fluoride, restricted free sugars consumption, oral hygiene, and different antimicrobial agents (with respect to periodontal disease). Unfortunately, there is still a lack of knowledge as to the extent different nutrients interfere with the initiation and progression of certain oral diseases. Little is known about how this differs among individuals and in relation to variation as regards a person's general health perspective, which is influenced by dietary and nutrient intake.

Dental patients may not always be aware of the effects of diet and/or nutritional status on the development and maintenance of a healthy mouth, including teeth free from caries and signs of periodontal disease. It is important that all oral healthcare providers look for potential signs of nutritional deficiencies or nutrition-related problems in all patients, but particularly for those with chronic diseases. The link between nutrition and oral health may vary from subtle to overt.

Summary and Recommendations

The oral consequences of compromised nutritional status discussed in this chapter may directly or indirectly result in an aggravation associated with malnutrition. As noted in the squirrel-wheel in

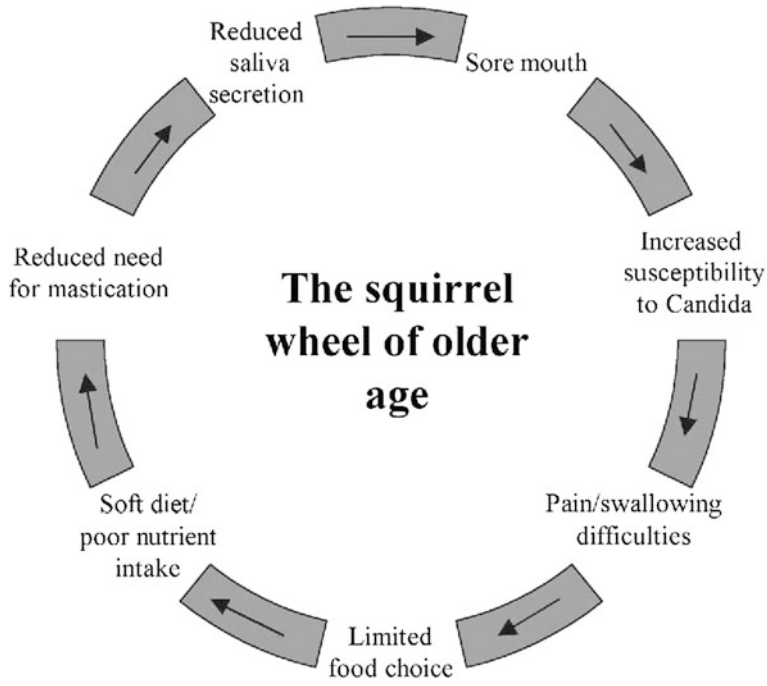

Fig. 7.2 The squirrel-wheel of poor nutrition and oral health

Fig. 7.2, reduced salivary secretions that result in sore gingiva and tongue can increase the susceptibility to infections such as candida. Dental and oral pain can further exacerbate the discomfort and this subsequently can result in difficulties masticating and swallowing, thereby limiting dietary intake, further compounding poor nutrition. A reduced food intake limited to a soft diet, that is often nutritionally inadequate will result in less active salivary glands and a further decrease in saliva flow—the result is a downward spiral, a squirrel-wheel from which it is hard to escape. Basically, any of the variables listed in the figure can begin the cycle that leads to poor dietary choices associated with compromised nutritional status.

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Chapter 8
Nutrition and Inflammation

Victoria L. Woo

Keypoints

- There are multifaceted relationships between nutrition, inflammation, and oral health
- Nutrient deficits and malnutrition can modulate immune function which in turn impacts oral and systemic health
- Dietary fat and fatty acid composition can affect metabolism and inflammation; their impact on systemic inflammatory conditions with oral manifestations and oral diseases merits consideration
- Obesity may be the common denominator that links periodontal disease to systemic inflammatory conditions
- The basis of the links between malnutrition and periodontal disease may be the impact on the inflammatory response

Keywords Nutrition · Inflammation · Inflammatory response · Periodontal disease · Dietary fat · Fatty acid composition · Metabolism · Nutrient deficits · Malnutrition · Oral health

Introduction

The associations between nutrition, inflammation, and oral health have harnessed considerable interest amongst the dental, medical, and related health sciences communities. While each of these relationships has been explored to a variable extent independently, little is known regarding the interaction between all three. In Fig. 8.1, we present the proposed interrelationship between nutrition, inflammation, and oral health. We suggest that the relationships within this triangle are best viewed as dynamic interactions, with deviations in any one factor influencing the other two and likely the entire triangle in a reciprocated manner.

There is general agreement that a broader understanding of the nutrition, inflammation, and oral heath triangle is indicated due to potential implications for clinical practice and patient care. In this chapter, we present the current research and theories pertaining to the relationships between nutrition, inflammation, and oral health. In addition, we aim to highlight those areas that are supported by strong data while drawing attention to areas that merit further study.

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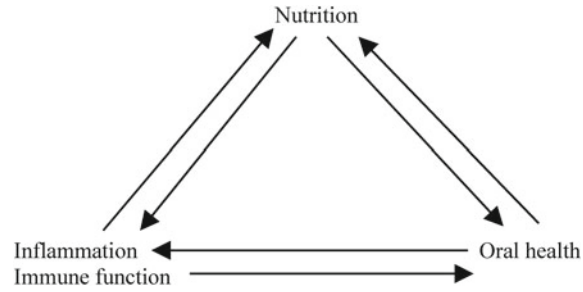

Fig. 8.1 Relationships between nutrition, inflammation and immunity, and oral health

Definitions of Terms

Nutrition

According to Navia [1], nutrition is "a complex science that involves not only food and diets, but also makes use of principles from biochemistry, genetics, immunology, physiology, and molecular biology to deal with the process of incorporating into the body essential compounds from the trophic environment that cannot be synthesized by the human tissues." Malnutrition represents the "pathophysiological consequences of the ingestion of inadequate, excessive, or unbalanced amounts of nutrients or impaired use of ingested nutrients" [2]. It results in an imbalance between the supply of nutrients and energy and the physiologic demands of the body to ensure growth and function [3].

Inflammation

Inflammation is broadly defined as a host reaction elicited in response to tissue injury [4]. This reaction is characterized by a release of substances from neighboring cells that defend the host against further injury and facilitate tissue healing and repair [5]. Inflammation can assume two forms—acute and chronic—that differ by onset, duration, and cellular composition. Acute inflammation is generally rapid in onset, short in duration, and characterized microscopically by emigration of leukocytes (most notably neutrophils) accompanied by an exudate of fluid and plasma proteins [5]. In contrast, chronic inflammation is typified by slow onset and long duration. The inflammatory infiltrate is predominated by lymphocytes and plasma cells [5] though with prolonged inflammation, other cell types such as fibroblasts are recruited to the site of injury, which contribute to fibrosis and tissue necrosis [5, 6]. The classical hallmarks of inflammation include *dolor* (pain), *calor* (heat), *rubor* (redness), *tumor* (swelling), and *functio laesa* (loss of function). Though inflammation is primarily a protective function of the host, the same mechanisms involved in defense and tissue repair can produce harmful and pathologic changes in the body in a true dualistic manner [7]. Inflammation is closely intertwined with immunity, immune function, and infection. As such, these interrelated processes are discussed in tandem in this chapter.

The Immune System and the Immune Response

The immune system represents a specialized collection of proteins, cells, tissues, and organs that is responsible for defending the host against infection and executing the immune response. The immune response is broadly divided into the two major arms—innate and adaptive. Innate immunity represents the body's immediate defense against infection and first-line barrier to microbial assault. The major components of the innate immune response include the epithelial cells, phagocytic leukocytes such as neutrophils and macrophages, the natural killer (NK) cell, and a variety of plasma proteins such as the complement system proteins [7]. Adaptive immunity is a more specific response that "adapts" to the presence of an infection. In addition to aiding in the elimination pathogens, it also allows for recognition and protection against future challenges by the microbe [7]. The adaptive

immune response is further subdivided into two types—humoral immunity, which is mediated primarily by the antibodies produced by B lymphocytes, and cell-mediated immunity, which is mediated by T lymphocytes and their subsets [7]. The cellular reactions that result from innate and adaptive immunity culminate in inflammation [7].

The immune response is initiated and propagated by an integrated series of pro- and anti-inflammatory cascades that require participation of key inflammatory cells and chemical mediators. Biologically active chemical mediators play an integral role in directing and coordinating the inflammatory response. These signaling molecules are produced in response to inflammatory stimuli [8] and have diverse roles in growth, differentiation, host defenses, and tissue damage. The molecules bind to target cells via receptors and orchestrate a sequence of events, including but not limited to altering vascular permeability, increasing neutrophil chemotaxis, stimulating smooth muscle contraction, and mediating oxidative activity [5]. Their effects may be beneficial or detrimental depending on the clinical setting in which they are elicited [9]. Production of the mediators is tightly regulated by an array of control systems that require the participation of various organs, including the liver, brain, adrenal cortex, and immune system [9]. Precise control of mediator production and activity is crucial as disruptions and imbalances can lead to ineffective or exaggerated immune responses and may result in tissue damage and overall harm to the body. Examples of chemical mediators include the vasoactive amines such as histamine, arachidonic acids such as leukotrienes, and cytokines such as tumor necrosis factor (TNF) and interleukins [5]. We will herein focus on selected mediators of relevance to the nutrition, inflammation, and oral health relationship. A more comprehensive review of chemical mediators and their actions can be found in several excellent immunology texts [10, 11].

Infection, Inflammation, and Immune Function

Infection represents the invasion of a host by a pathogenic organism, resulting in cellular injury due to competitive metabolism, production of toxins, intracellular replication, or the effects of antigen–antibody responses. Though the relationship between infection, inflammation, and immunity is complex, it may be helpful from an explanatory standpoint to view inflammation as the link between infection and the immune response. A clearer relationship exists between infection and immune function whereby impaired immunity intensifies infectious processes [8] and optimal immune function protects against infection. Nutritional imbalances can influence this relationship by affecting the availability of nutrients, which in turn impacts the production and activity of the inflammatory mediators that coordinate the immune response [8].

Relationship Between Nutrition, Inflammation, and Immune Function

The relationship between nutrition and inflammation has been examined extensively over the past five decades. The result is an impressive body of the literature that supports a strong and dynamic link between the two, characterized by common pathways of activation and regulation. Historically, research efforts have centered on the influence of undernutrition on inflammation and immune function and specifically, on the promotion of immune incompetence and infection in the setting of nutritional deficiencies [12]. However, the growing epidemic of obesity and obesity-related complications has prompted a shift in focus toward the effects of overnutrition on systemic health, inflammation, and immunity.

Impact of Nutrition on Inflammation and Immune Function

The role of nutrition in inflammation has been recognized for decades and continues to be an active area of nutrition- and immunology-based research. The reader is referred to the authoritative text "Nutrition and Immunology" [13] and to the "Diet and Human Immune Function" [14] and "Dietary Components and Immune Function" [15] editions of this *Nutrition and Health* series which provide excellent and comprehensive reviews on this topic.

The capacity for nutrients to modulate immune function bears significant clinical and public health implications [12, 16]. One of the earliest proposals that nutritional status was linked to the immune system was put forth by Scrimshaw et al. [3] in their 1968 World Health Organization monograph. This publication followed seminal work performed by the same investigators nearly a decade earlier that documented primarily synergistic, occasionally antagonistic, interactions among malnutrition, infection, and host immune responses [17]. As knowledge of immunology was relatively rudimentary prior to the 1970s, this group's observations were considered truly groundbreaking and remain relevant today [18]. Better characterization of the interrelationships between nutrition, immunity, and infection has since been enabled by refinement of immunologic and molecular techniques [18]. It is increasingly apparent that nutrition can affect host immunity on many different levels, including initial development and subsequent function. As such, nutrition may be best viewed as exerting a constant influence on immune-regulated processes.

Undernutrition, Inflammation, and Immune Function

It is important to note that the relationship between malnutrition and immune function is not strictly unidirectional. Rather, there appears to be a cyclical interaction that exists among nutrition, immunity, and infection whereby undernutrition provokes immune dysfunction, compromised immunity predisposes to infectious diseases, and infection further promotes nutrient deficiencies [8]. The global effects of this vicious cycle are seen most lucidly—though not exclusively—in the lower socio-economic classes, where the spiral of malnutrition, infection, disease, and debilitation reduces productivity and exacerbates already impoverished conditions [19].

Adequate nutrition in childhood is essential for proper development and maturation of the immune system [20]. Keusch [21] observed early involution of the thymus gland in children suffering from undernutrition. Chandra [22] demonstrated both a numerical and functional deficiency of CD4+ T-helper cells and moderate decreases in CD8+ T cells [12] in protein energy deficient children, postulating that this was likely due to reduced thymic factor activity. In concordance with these findings, Savino [23] observed diminished thymic development and reductions in peripheral lymphocyte counts in children with severe nutritional deficiencies. Malnutrition-induced reductions in mature T lymphocytes have then been associated with long-term compromises in cell-mediated immunity and diminished T-cell-dependent antibody responses [21] leading to the so-called "nutritionally acquired immunodeficiency syndrome."

In addition to influencing the initial development of the immune system, nutrition also plays a vital role in ensuring the proper function of subsequent immune and inflammatory responses. Nutritional imbalances may interfere with immune function through a variety of mechanisms, including alterations in antibody production; cell-mediated immunity; phagocyte, complement, and T-cell activity; and nonspecific host defenses [18]. Table 8.1 summarizes the effects of select macro- and micronutrients on immune function [18, 24]. Regrettably, a complete description of all nutrients and their roles in immune function is beyond the scope of this text. The reader is referred to excellent reviews by Enwonwu [25], Grimble [26], and Scrimshaw and SanGiovanni [18] for more detailed information. We will herein focus on the immunomodulatory effects of protein deficiency.

Table 8.1 Effects of macronutrients and micronutrients on immune function

Macronutrients	
Nutrient	*Cell/function affected*
Protein (deficiency)	All components of immune system
	Depression of cell-mediated immunity
	Dysfunction of B cells, macrophages, neutrophils, complement
	Effects on cytokine production
Amino acids (deficiency)	Functional changes in humoral immunity
	Depletion of cells of lymphoid tissues (sulfur-containing amino acids deficiencies)
Lipids	Impaired wound healing (linoleic acid deficiency)
	Stimulation of suppressor T cells (linoleic acid excess)
	Improvement of cell-mediated immunity (omega-3 fatty acid excess)
Micronutrients	
Nutrient	*Cell/function affected (animals and humans)*
Vitamin A (deficiency)	Reduced NK activity
	Lower production of interferon
	Impairment of delayed cutaneous hypersensitivity
	Reduction in lymphocyte count; atrophy of lymphoid tissues (thymus, spleen)
	Reduced mobility of peripheral macrophages
Vitamin B6 (deficiency)	Depression of cell-mediated immunity functions
	Depression of antibody production after immunization
	Reduction in lymphocyte count; atrophy of lymphoid tissues
	Diminishment of inflammatory response
Vitamin C (deficiency)	Impairment of neutrophil and macrophage function
	Reduction in thymic humoral factors
	Depression in T-lymphocyte response, complement function
	Impairment of delayed cutaneous hypersensitivity
	Compromised epithelial integrity
Vitamin E (deficiency)	Depression in humoral response, B cell function
	Reduced lymphocyte and leukocyte killing power
	Depression in T-lymphocyte response, phagocyte function
	Impairment of delayed cutaneous hypersensitivity
	Depression of cell-mediated immunity functions
Zinc (deficiency)	Marked atrophy of thymus
	Reduction in leukocytes
	Depression of cell-mediated immunity functions
	Depression in T-lymphocyte response, phagocyte function
	Impairment of delayed cutaneous hypersensitivity
	Impairment of cytokine or lymphokine function or production
Selenium (deficiency)	Impairment of antibody production
	Reduction in bactericidal activity of neutrophils
	Impaired synthesis of antioxidants
Iron (deficiency)	Depression of humoral response, B cell function
	Depression of T-lymphocyte response
	Impairment of delayed cutaneous hypersensitivity
Magnesium (deficiency)	Depression of humoral response, B cell function
(primarily animal)	Depression of cell-mediated immunity functions
	Depression of T-lymphocyte response, phagocytic function
	Impairment of cytokine or lymphokine function or production

Adapted from Scrimshaw and SanGiovanni [18] and Raiten [24]

Protein Energy Malnutrition

Protein energy malnutrition (PEM) is defined as a state of nutrition in which a deficiency or imbalance of energy, protein, and other nutrients causes measurable adverse effects on the body, function, and clinical outcomes [3]. Traditionally, the term PEM was used to describe a spectrum of conditions that were broadly subcategorized into three clinical forms: kwashiorkor (protein-predominant deficiencies), marasmus (protein deficiency and caloric insufficiency), and marasmic kwashiorkor (marked protein and calorie deficiencies) [27]. The effects of PEM on the immune system are profound and involve changes in both innate and adaptive immunity [8]. In PEM, the defense mechanisms primarily targeted are cell-mediated immune function, phagocyte function, T-cell responsiveness, NK cell lytic activity, delayed hypersensitivity, complement system activation, antibody formation and secretion, and cytokine production [8, 12, 18, 22, 28, 29]. These findings have been supported in both experimental models of PEM and clinical studies of protein-deficient individuals [28]. Moreover, malnutrition has been shown to affect the closely intertwined endocrine system by eliciting increased production and secretion of stress hormones and decreased secretion of insulin [8]. Fluctuations in these hormones can further compromise immune competence. For example, elevated glucocorticoid levels can induce macrophage dysfunction and inhibit transcription, expression, and secretion of various cytokines and proteins critical in regulating inflammation [8, 30].

Historically, it was presumed that patients suffering from PEM were susceptible to immune dysfunction because of a lack of endogenous nutrient stores necessary for sustaining host resistance processes [28]. However, it has become increasingly evident that modulation of cytokine biology is largely responsible for nutrition-induced effects on immune function. Malnutrition and in particular, protein deficiency has been associated with altered levels of key inflammatory cytokines such as interleukins (IL), tissue necrosis factors (TNF), and interferons [8, 18, 31]. These cytokines perform their functions in a highly integrated manner and are capable of producing a wide range of metabolic and immune effects [26]. Proposed mechanisms through which PEM may alter cytokine levels include modulation of antioxidant defenses and attenuation of the acute-phase response [32].

PEM and Antioxidants

Antioxidants are substances that neutralize a variety of reactive intermediates such as oxidants and free radicals. Oxidants (also known as oxidizing agents and oxidizers) are agents with oxidizing capabilities that include a large class of molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). The role of oxidants in inflammation and immune stimulation overlaps significantly with free radicals and cytokines [9, 16]. Collectively, these highly potent molecules destroy pathogens and eradicate damaged and/or aberrant cells, thereby facilitating restoration of normal tissue function [16]. Furthermore, these substances share a complex, synergistic relationship through which each can stimulate and enhance the other's production and activity [16]. A crucial mediator in this crosstalk appears to be nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [16], a family of inducible transcription factors that modulate expression of over 180 mammalian target genes [33]. NF-κB activation can occur in response to a variety of stimuli, including the actions of inflammatory cytokines, immune-related stress induced by conditions like bacterial infections, oxidative stress, and many others [33]. It is believed that activation of these factors represents an important pathway for cellular adaptation to these stresses [33]. Well-known inducers of NF-κB include TNF and its associated inflammatory kinases [33].

While the actions of oxidants, free radicals, and certain cytokines are primarily beneficial in the body's defense mechanism, the relationship can rapidly shift to a deleterious one if there is overproduction of either or control systems become deregulated [9]. Antioxidants contribute to minimizing oxidative stress by inhibiting oxidation and maintaining oxidant and cytokine levels within healthy confines [9]. Insufficient levels of antioxidants can alter the antioxidant–oxidant balance in favor of oxidant excess and indirectly modify cytokine-mediated responses to inflammation and

infection. This can lead to disturbances in the normal redox state of cells and cellular damage known as oxidative stress.

PEM diminishes the substrate stores necessary for the production of antioxidants [16]. Amino acids with sulfur moieties like methionine and cysteine are of particular importance because they form the building blocks of a key antioxidant known as glutathione [16]. Deficiencies in the sulfur-containing amino acids and other essential nutrients such as selenium [16], zinc, and vitamins E, A, and D, can impair glutathione synthesis. Glutathione is an essential, endogenous antioxidant that participates in a wide array of metabolic and biochemical reactions [34]. In addition to neutralizing free radicals through glutathione peroxidase and catalase [16], glutathione influences the immune response on several levels, including cytokine production, leukotriene synthesis, lymphocyte proliferation, cytotoxic T cell and NK cell function, and maintenance of other antioxidants in their active form. The importance of glutathione in homeostatic control of various systems becomes apparent when examining patients who suffer from deficiencies in glutathione synthetase and the glutathione S-transferases (GST), the enzymes involved in the synthesis and conjugation of glutathione, respectively. Patients affected with glutathione synthetase deficiency (GSD) exhibit hematologic, metabolic, neurologic, and immune abnormalities [35]. Decreased cellular levels of glutathione have also been documented in diabetes mellitus, cancer, and HIV infection [36]. Deficiencies in GST can also be associated with a variety of clinical complications. The GSTs are a family of enzymes that catalyze conjugation of reduced glutathione, thereby aiding in the detoxification of reactive electrophiles, products of oxidative stress, and carcinogens [37, 38]. The pathologic manifestations attributed to deficiencies in both enzymes are presumably related to increased oxidative stress compounded by a diminished capability to cope with oxidative stress, resulting in accumulation of ROS and noxious substances in target cells [37].

PEM and Acute-Phase Proteins

The acute-phase response (APR) is an essential component of a host's immune reaction to tissue injury [25]. In addition to generating nonspecific responses like fever and elevations in peripheral leukocyte counts [25], the APR is also characterized by increased secretion of various hormones such as corticotropin-releasing factor and hepatic synthesis of vital proteins known as acute-phase proteins [25, 26, 39, 40]. The magnitude of the APR varies depending on the severity of inflammation and extent of tissue injury [25].

Activation of the APR is characterized by increased hepatic synthesis of the acute-phase proteins (APPs) [8, 25],which include c-reactive protein (CRP), serum amyloid A (SAA), α_1-acid glycoprotein, α_2-macroglobulin, ceruloplasmin, metallothionein, and the complement proteins, among others [25, 26]. Collectively, the APPs modulate the immune response by enhancing antioxidant defenses, activating complement pathways [41], and interacting with and modifying the properties of various cytokines [42].

Production of APPs requires adequate dietary intake of proteins and amino acids, trace elements and vitamins, and energy [8]. As with antioxidants, APP synthesis is highly dependent on the availability of essential amino acids like glycine, serine, and the sulfur-containing amino acids methionine and cysteine [8]. These amino acids are typically limited in the setting of PEM [8]. APP production may be further impaired by PEM-induced reductions of certain cytokines such as IL-1 and IL-6 as cytokine levels are believed to be the primary stimulus for APP synthesis [25]. Overall reduction in APPs in conjunction with diminished cytokine levels culminate in APR attenuation. This has been observed in children suffering from even mild malnutrition who are challenged with infection [43]. Ultimately, severe blunting of APR may be associated with grave consequences given its crucial role in tissue healing after injury [25, 43].

Overnutrition, Inflammation, and Immune Function

There is also convincing evidence to show that excessive ingestion of nutrients and energy can have negative implications on inflammation and the immune response. Excess fat—both dietary and stored—can give rise to a plethora of complications. This emphasizes the importance of maintaining an optimal balance between nutrition, inflammation, and immune function [44].

Exogenous Fat: Dietary Fat and Fatty Acids

Dietary fat and fatty acids can exert potent effects on metabolism and inflammation through influence on cytokine production, production of other lipid-derived mediators, and alteration of tissue responses to these mediators [9, 32]. The immunomodulatory effects of fatty acids have been discussed elsewhere in several excellent references [15, 45]. To summarize, there are four types of fatty acids of significance in immune function—(1) Saturated fatty acids such as steric and palmitic acid, (2) ω-9 monounsaturated fatty acids such as oleic acid, (3) omega-3 polyunsaturated fatty acids (ω-3 PUFAs) such as α-linolenic acid and eicosapentaenoic (EPA), and (4) omega-6 polyunsaturated fatty acids (ω-6 PUFAs) such as linoleic acid and γ-linolenic acid [9].

Studies have shown that diets rich in ω-3 PUFAs and poor in ω-6 PUFAs reduce proinflammatory cytokine production and responsiveness [9], resulting in an overall immunosuppressive or anti-inflammatory effect; likewise, diets rich in ω-6 PUFAs are associated with increased proinflammatory cytokine production and responsiveness [9] and generate an overall proinflammatory state. It has been postulated that these changes in cytokine biology are related to shifts in fatty acid composition of membrane phospholipids, a process that is primarily regulated by dietary fat intake [32]. Compounds then formed from the hydrolysis of the membrane phospholipids harbor the innate ability to modulate cytokine production and activity [46]. The anti-inflammatory actions of the ω-3 PUFAs have been ascribed to a decrease in the production of inflammatory cytokines as well as classic inflammatory mediators such as arachidonic acid-derived eicosanoids (prostaglandin E_2) and [47, 48]. ω-3 PUFAs also serve as key substrates capable of being converted to a group of lipid mediators with potent anti-inflammatory properties known as the resolvins and protectins [49–52]. The actions of these mediators, particularly resolvins, appear to be diverse but at least partially involve a reduction of upstream proinflammatory cytokines [51]. In recognizing the anti-inflammatory potential of these lipid mediators, researchers have begun to explore the ω-3 PUFA supplementation as a therapeutic option in various inflammatory diseases. The beneficial effects of administering the ω-3 PUFAs in conjunction with aspirin, which enhances the activity of the lipid mediators through its actions on cyclooxygenase-2 (COX-2), has been demonstrated in vitro and in vivo via inflammatory-disease-animal models [53–56]. Meydani et al. [57] found that fish oil capsules containing ω-3 fatty acids given to both younger and older females diminished the ability leukocytes to produce IL-1, IL-6, and TNF-α. Supplementation with ω-3 PUFAs in the form of fish oil have also been shown to mitigate inflammatory symptoms in rheumatoid arthritis, psoriasis, asthma, atherosclerosis, Crohn's disease (CD), and ulcerative colitis [26, 51].

Endogenous Fat: Excess Body Fat and Obesity

Excessive intake of dietary fat and calories also contributes to accumulation of excess stored fat within the body. The multifaceted role of adipocytes in homeostatic processes and metabolism has become a subject of extensive study over the past two decades. The complex actions of these cells are primarily coordinated by the synthesis and release adipose-derived peptide hormones (so-called "adipokines"), making adipose tissue akin to an endocrine organ rather than a simple energy storage depot as previously believed [58]. These fat-derived substances function in both metabolism and immunity [44] by influencing the immune response, energy balance and glucose regulation, and other cellular processes. Individuals who suffer from adipocyte imbalances are therefore predisposed to the wide array of conditions. These include obesity-related inflammatory disorders, atherosclerosis, and diabetes mellitus [59].

Endogenous fat may influence inflammation and immune function through two main pathways—generation of endoplasmic reticulum (ER) stress and production of ROS. ER stress is a fundamental route through which intracellular inflammatory pathways can be engaged [44]. Increased adiposity imparts higher demands on the ER that leads to generation of ER stress [60–62]. ER stress has been shown to activate key inflammatory kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of NF-$\kappa\beta$ (IKK) [44, 63]. These kinases perform the critical function of integrating signals from multiple inflammatory mediators [44, 63] and acting as cross-communicators between the metabolic and immune arms [44]. The ER is therefore considered a crucial site for detecting metabolic stress and translation to an inflammatory response [62]. In addition, the ER is a major source of ROS [62, 64].

The second and related pathway through which excess fat modulates inflammation is generation of ROS. It has been shown that increased adiposity and prolonged hyperglycemia trigger production of ROS [63, 65], including the redox-sensitive gene transcription factors nuclear factor-$\kappa\beta$ (NF-$\kappa\beta$) and activating protein-1 (AP-1) [65]. High levels of ROS lead to increased oxidative stress [66] which is associated with proinflammatory sequelae [65]. Moreover, long-term derangements in oxidative stress have been shown to contribute to insulin resistance and chronic hyperglycemia, leading to formation of advanced glycation end products (AGEs) and further generation of ROS and oxidative stress in a feed-forward mechanism [67]. Thus, the mechanistically linked pathways of ER stress and ROS operate in a concerted manner toward a common endpoint—a state of hyperinflammation. This supports the increasingly accepted concept that metabolic signals are the likely triggers of inflammatory responses in the setting of metabolic excess [62].

There are significant commonalities between adipocytes and immune cells, from phagocytic potential to complement activation. Both fat and immune cells are capable of secreting mediators such as TNF-α, IL-6, and others, which are involved in both immunity and metabolism [44, 62, 63]. Adipocytes can also produce chemotactic signals that lead to recruitment of inflammatory cells [63]. Hence, adipose tissue can be viewed as a site of inflammatory cell recruitment and accumulation, production of cytokines (so-called "adipokines"), and interaction of fat cells with other effectors of inflammation [62]. Additionally, it appears that the inflammatory response that occurs in the presence of excess adipose tissue is triggered by and resides in the adipocytes themselves [62]. This highly integrated relationship between adipocytes and immune cells is the likely mechanism through which excess adipose tissue is linked to its inflammatory sequelae [63].

Obesity is broadly defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that may compromise health [68]. Early rodent models provided the first molecular evidence of a link between obesity, obesity-related insulin resistance, and inflammation [44]. Investigations utilizing these models revealed overexpression of TNF-α in adipose tissue [69, 70], a finding that was later verified in humans [71]. In addition, study of loss and gain of function models demonstrated that upregulated TNF-α impaired insulin action while absence of TNF-α improved insulin sensitivity, respectively [69, 72]. Subsequent studies have confirmed similar roles for other inflammatory mediators that are overexpressed in the setting of excessive adipose tissue, including IL-6, leptin, monocyte chemotactic protein (MCP)-1, and others [44]. Table 8.2 [44] summarizes the immunomodulatory effects of factors expressed or reduced in obesity. The reader is referred to a review of obesity-related factors involved in metabolism and immunity by Wellen and Hotamisligil [44] for more detail on this topic. Beyond individual cytokines and mediators, obesity has also been associated with activation of key inflammatory kinases like JNK and IKK [44]. These kinases can be further stimulated by lipid-induced elevations in proinflammatory cytokines, effecting a self-perpetuating cycle of increased adiposity and inflammation [63]. These investigational findings were pivotal in establishing a relationship among inflammation, metabolism, and obesity and suggest that inflammation may be the common denominator that links obesity to its pathologic and immunologically related consequences [63]. In recognizing this relationship, researchers have now begun to explore the possibility of manipulating adipocyte biology to selectively activate or inhibit

Table 8.2 Immunomodulatory factors in obesity

Factor	Metabolic regulation	Effects
TNF-α	Increased in obesity	Proinflammatory Promotes insulin resistance
IL-6	Increased in obesity	Multiple effects on inflammation Promotes insulin resistance
Leptin	Increased in obesity	Multiple effects on immune function Promotes fatty acid oxidation
Adiponectin sensitivity	Decreased in obesity	Anti-inflammatory; promotes insulin sensitivity
Visfatin	Increased in obesity	Early B cell growth factor
IL-1	Increased by hyperglycemia	Proinflammatory; regulates insulin secretion
IL-10	Increased in obesity	Anti-inflammatory
C-reactive protein	Increased in obesity	Proinflammatory; atherogenic

Adapted from Wellen and Hotamisligil [44]

immunologic factors such as the cytokines, inflammatory kinases, and more central processes like ROS and ER stress. This may represent a powerful approach to managing and perhaps even preventing obesity-related inflammatory conditions.

Impact of Inflammation and Immune Function on Nutrition

Inflammatory processes can impact nutrient intake and utilization starting with local effects in the oral cavity. The impact of localized inflammatory processes on nutrition is best seen in immune-mediated oral disorders like recurrent aphthous stomatitis and the vesiculo-erosive conditions lichen planus, pemphigus vulgaris, mucous membrane pemphigoid (MMP), and systemic lupus erythematosus. Individuals affected by these conditions may limit their dietary intake and consequently develop nutrient deficiencies secondary to their inability to eat an adequate diet (also covered in Chapters 5, 12 and 15). An additional group of inflammatory diseases that have significant impacts on nutrition are the inflammatory bowel diseases (IBD). The IBDs represent a family of clinically diverse conditions that are characterized by chronic, primarily cell-mediated inflammation that leads to damage of the gastrointestinal (GI) tract [73]. The two principal forms of IBD are ulcerative colitis and Crohns Disease (CD). We will herein focus on CD.

The pathogenesis of the underlying inflammatory changes seen in CD is complex and involves a synchronized interplay of bacterial provocation, genetic susceptibility, immune dysregulation, and environmental triggers [73]. Pivotal events that lead to the initiation of inflammatory changes include upregulation of various inflammatory pathways and persistent activation of mitogen-activation protein kinase (MAPK) and NF-κB signaling [73]. The subsequent release of proinflammatory cytokines such as TNF-α, interferon (IFN)-γ and chemokines, lead to activation of T cells and other immune cells. This is followed by secretion of enzymes that degrade the extracellular matrix and facilitate an influx of inflammatory cells and proinflammatory mediators [73]. These events correlate closely with the pathognomonic transmural (full-thickness) inflammation seen on microscopic examination of CD-affected intestinal mucosa.

Malnutrition affects 20–75% of individuals with IBD and is particularly prevalent in patients with CD [73]. Oral and perioral lesions associated CD are well-documented and can cause difficulty in eating and drinking, ultimately leading to nutritional compromise. Moreover, patients may intentionally restrict dietary intake due to fear of abdominal pain and diarrhea after eating [73] or show

aversion to food because of altered taste sensations (dysgeusia) related to mineral deficiencies. Any existing nutritional deficits may then be exacerbated by impaired intestinal absorption and transport of nutrients due to inflammation and/or a previous history of intestinal resection, enteropathies leading to protein loss, and medication-induced metabolic disturbances [73]. Consequently, patients become subject to a relentless cycle of inadequate dietary intake and nutrient deficiency which may ultimately culminate in PEM [73]. Crohn's disease in children is especially problematic because of the consequences of malnutrition during a critical time of growth. Children with CD are predisposed to constellation of developmental problems including anemia, growth delays, and short stature, and require early and timely nutritional support. Single nutrients and other compounds including ω-3 PUFA-rich fish oils and TGF-β2, which purportedly decrease mucosal inflammation through their anti-inflammatory properties and modulation of key immune cells [73, 74], have been trialed in individuals with CD. Probiotics have also been explored although there is currently no consensus regarding their efficacy in preventing, delaying, and treating the symptoms of CD [73].

Impact of Infection on Nutrition

In most situations, infection has a detrimental effect on nutrition and further propagates the spiral of malnutrition and immune dysfunction. Local infections of the oral mucosa can cause restrictions in dietary intake due to pain and discomfort. Systemic infection and fever can increase demands on energy, micronutrients, and substrates on a more generalized level [19, 65]. In a state of infection, nutrients are diverted to support critical responses of the immune system such as tissue preservation and repair, activation and propagation of immune cells, and cytokine synthesis and regulation [8, 18, 19, 65]. Infection and fever may promote malabsorption and encourage nutrient depletion through diarrhea and urinary excretion [18, 65]. Proteins, vitamin A, vitamin C, and iron are among the many nutrients affected by a state of infection [18]. Lastly, dietary intake may be reduced because of loss of appetite and general malaise associated with infection, placing additional stresses on an already nutritionally compromised host [65]. Ultimately, the short- and long-term impact of infection on an individual's nutritional status is dependent on a variety of factors, including his/her nutritional history, the nature and duration of the infection, and the diet maintained during the recovery period [18].

A two-way reciprocal relationship exists between infection and nutrition. Nutrient deficiencies, if sufficiently severe, can impair resistance to infection [18]. There is also experimental evidence to suggest that nutritional deficiencies can potentially confer a heightened pathogenicity to certain infectious agents [8]. For example, several investigators have found that antioxidant and selenium deficits may induce nucleotide changes at virulence positions in previously avirulent viruses [75, 76]. A clinical example of this phenomenon is Keshan disease. This is a form of cardiomyopathy caused by Coxsackie B virus infections in patients suffering from selenium-deficiency [21]. Malnutrition has also been associated with accelerated viral replication, possibly through activation of NF-κB [8]. Therefore, nutritional status plays an equally critical role in determining the host's response to infection and in some cases, the behavior of the pathogen itself [8, 19] as illustrated in Fig. 8.2 [8].

Acknowledging the interdependent connections between nutrition and inflammation, immunity, and infection highlight the need for both optimal nutrition and intact immune function in the maintenance of overall health (see Fig. 8.3) [44]. Translation of this knowledge in a clinical venue has lead to an exciting field of study known as dietary immunonutrition or dietary immunotherapy [16]. The working definition of immunonutrition is "the modulation of activities of the immune system, and the consequences on the patient of immune activation, by nutrients or specific food items fed in amounts above those normally encountered in the diet" [32]. The target endpoints of immunonutrition are: (1) to enhance the cell-mediated response, (2) to alter the pro- and anti-

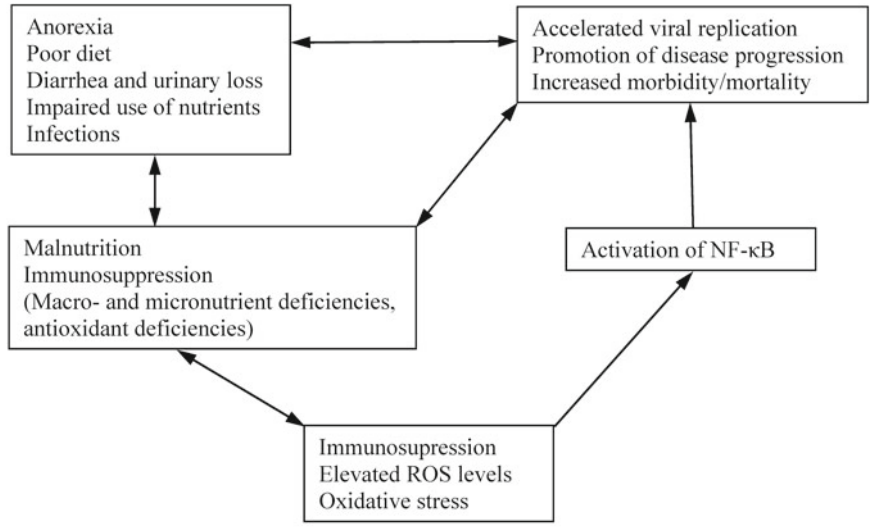

Fig. 8.2 Relationships and interactions between infection, nutrition, and immune function. Adapted from Enwonwu et al. [8]

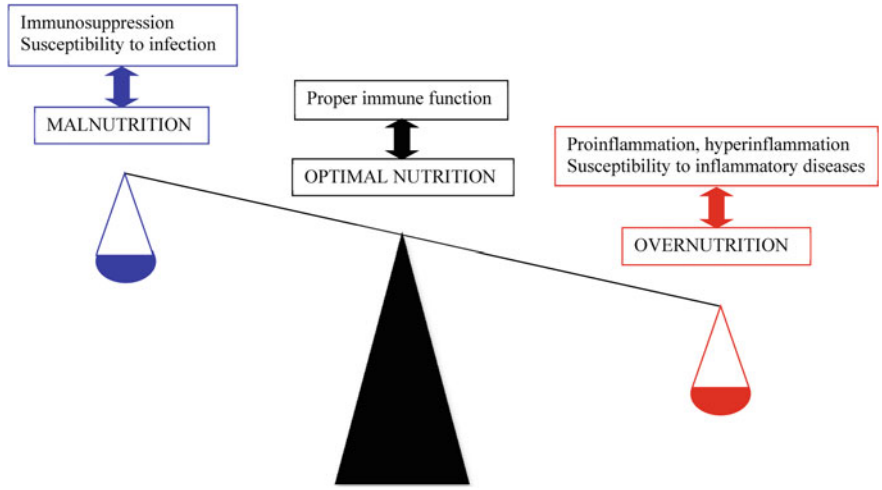

Fig. 8.3 The balance of nutrition and immune function. Adapted from Wellen and Hotamisligil [44]

inflammatory cytokine balance, (3) to prevent overactivation of key transcription factors such as NF-κB [77], and (4) to moderate tissue nutrient depletion [32]. Potential immunomodulatory nutrients that have been identified include the ω-3 PUFAs, the sulfur-containing amino acids, and selenium. With the support of well-designed clinical trials, supplementation with these nutrients is a promising avenue through which immune function can be modulated in both the healthy and compromised patient.

Relationship between Inflammation, Immune Function, and Oral Health

The relationship between inflammation and oral health is perhaps the least understood in the nutrition-inflammation-oral health triangle. While certain aspects of this relationship have been researched extensively, others remain elusive with scarce supporting data. The roles of inflammation and immune function on the initiation and progression of oral diseases are addressed in this section along with the impact of oral health on inflammation, particularly systemic inflammation and its consequences.

Impact of Inflammation and Immune Function on Oral Health

Inflammation may be viewed as both an initiator and potential promoter of various oral mucosal disorders. There is little doubt that inflammation and immune function have significant impacts on oral health. This is clear when one considers the myriad of oral diseases that result from derangements in either process. In Table 8.3, we present a summary of oral conditions associated with an inflammatory and/or immunologic etiology. This vast group includes the vesiculoerosive diseases and oral manifestations of infections, hematological abnormalities, and immune incompetence.

The role of inflammation on the progression of pre-existing oral conditions is also of interest but more challenging to substantiate. It has been previously reported that inflammation can complicate the course of oral diseases such as the immunobullous diseases [78], a family of immune-mediated disorders that are characterized by blistering and sloughing of the mucosa and/or skin with or without formation of frank ulcerations. The gingiva is commonly involved and lesions may be confined to this site or exhibit a more generalized mucocutaneous distribution [79]. The immunobullous diseases seen most frequently in the oral cavity include erosive lichen planus, MMP and pemphigus vulgaris.

The effect of gingival inflammation and periodontal disease on the severity of the immunobullous disorders has been investigated in a limited number of studies [78–82]. Prior investigations have demonstrated that gingival inflammation secondary to dental plaque and calculus deposits can increase both the frequency and severity of lesions in patients suffering from MMP and LP [80–82]. Ramon-Fluixa et al. found a significantly greater percentage oral mucosa affected by lesions in patients with heavier plaque and calculus deposits in their study of 90 LP patients [81]. They also noted a higher incidence of atrophic-erosive gingival lesions as compared to the typically asymptomatic reticular lesions in LP patients with elevated plaque and periodontal indices [81]. Likewise, several authors have documented increased disease activity in patients with MMP and LP who have concomitant periodontal disease and regression of lesions following nonsurgical and surgical periodontal therapy [78–83]. It is also common to observe variation in lesion severity that appears to correlate with the periodontal status of individual teeth. In particular, patients with MMP tend to exhibit more severe disease adjacent to teeth with advanced periodontal involvement and quiescent, sometimes complete absence of disease in edentulous sites or in areas where teeth have been extracted. These studies and clinical observations support a role for gingival and periodontal inflammation in the exacerbation of certain oral diseases. Additional investigations are necessary to confirm the pathophysiologic basis of these findings such as the cellular and molecular events and biological mediators involved. Better understanding of the impact of oral inflammation in the progression of these mucosal disorders is likely to have significant implications on management and treatment protocols.

Table 8.3 Oral disorders associated with inflammatory/immune-mediated etiology

Oral and mucocutaneous disorders
Immune-mediated, autoimmune
Mucous membrane pemphigoid
Bullous pemphigoid
Pemphigus vulgaris
Epidermolysis bullosa acquisita
Linear IgA disease
Immune-mediated, contact
Allergic contact stomatitis
Allergic mucosal reaction to systemic medications
Lichenoid contact stomatitis to dental materials
Cinnamon stomatitis, plasma cell gingivitis
Immune-mediated, not otherwise specified
Aphthous stomatitis
Lichen planus
Chronic ulcerative stomatitis
Orofacial granulomatosis
Infections
Herpes simplex infection (acute herpetic gingivostomatitis, intraoral recurrent herpes)
Herpes zoster infection
Hand-foot-mouth disease, herpangina
Streptococcal infections
Actinomycosis
Candidiasis
Zygomycosis
Aspergillosis
Systemic disorders with oral manifestations
Infections
Mycobacterial infections (tuberculosis, leprosy)
Syphilis
Deep fungal infections (e.g., histoplasmosis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis, cryptococcosis)
Immune compromise
Human immunodeficiency virus (HIV) disease
AIDS
Necrotizing ulcerative gingivitis (NUG)/necrotizing ulcerative periodontitis (NUP)
Noma
Immune-mediated
Erythema multiforme
Behçet's syndrome
Paraneoplastic pemphigus
Oral manifestations of lupus erythematosus
Oral manifestations of graft versus host disease
Oral manifestations of psoriasis
Oral manifestations of inflammatory bowel disorders
Oral manifestations of diabetes mellitus
Oral manifestations of sarcoidosis
Oral manifestations of Wegener's granulomatosis

Impact of Oral Health on Inflammation

For the past two decades, there has been tremendous interest in characterizing the association between oral health and systemic diseases. Many of the systemic disorders that have been linked to gingival and periodontal inflammation also share a component of inflammation in their underlying pathoetiology. The relationship between periodontal disease and arthrosclerosis, respiratory disorders, and diabetes has attracted most attention. However, more conditions are expected to be recognized as investigators continue to explore the oral and systemic health link. We provide a brief overview of the impact of oral health, particularly gingival and periodontal diseases, on systemic diseases in the following subchapter.

While the emphasis thus far has been focused on the impact of oral disease on systemic health, it is also of interest to consider how systemic disease may influence oral health. Several case-controlled studies published in the early 1990s suggested that patients with a history of myocardial infarction exhibited poorer oral health compared to controls [84]. However, subsequent investigations analyzing the association between cardiovascular health and incidence and severity of periodontal disease have produced inconsistent results [6], due in part to variable diagnostic criteria and importantly, confounding factors such as overlapping risk factors between the diseases being investigated. Conflicts aside, these studies raise the intriguing possibility that the oral-systemic disease relationship is indeed bidirectional in nature. A better understanding is likely to emerge as ongoing scientific efforts uncover the pathophysiological mechanisms that underlie the oral and systemic health link.

Interrelationship Among Nutrition, Inflammation and Immune Function, and Oral Health

We have thus far discussed the reciprocal relationships that comprise the nutrition, inflammation, and oral health triangle. A greater understanding of these relationships and how they impact one another is desirable because of potential implications on the provision of clinical care. The interrelationship between nutrition, inflammation and immune function, and oral health as it pertains to a globally prevalent oral infection—periodontal disease—is addressed in this section.

Periodontal Disease: The Intersection of Inflammation, Malnutrition, and Oral Disease

Periodontal disease is a chronic inflammatory condition characterized by variable destruction of the periodontium, including the gingiva, periodontal ligament, and surrounding alveolar bone. The broadest definition encompasses a spectrum of clinical disorders from the gingivitis to the most severe forms of periodontitis [85]. Both periodontal pathogens and the host immune response are fundamental components of this disorder, playing key roles in the evolution and consequences of periodontal inflammation. This is supported by the four-stage paradigm of pathogenesis proposed by Enwonwu [25], which include (1) colonization, (2) invasion, (3) destruction, and (4) healing. While there is little doubt that bacteria, inflammation, and host defense mechanisms are integral to the development of periodontal disease, evidence supporting the contribution of nutrition has only emerged in the last few decades. In fact, it was historically believed that nutrition had minimal influence on the development of periodontal inflammation, with the exception of vitamin C

deficiency in the setting of scorbutic gingivitis [86]. This new knowledge now permits us to explore the inflammation-nutrition-oral disease triangle in the context of periodontal disease.

Inflammation, Immune Function, and Periodontal Disease

The relationship between periodontal disease, inflammation, and immunity is well established and supported through decades of the scientific literature [87]. A complete review of the often complex literature is beyond the scope of this text and the reader is referred to excellent reviews by Lamster and Novak [88], Gemmell et al. [87, 89] and Graves [90] for more detailed information. What follows is a brief overview of the key elements and theories in periodontal disease immunology, with an emphasis on the contributions of inflammatory cells and the host immune response.

The initiation and progression of periodontal disease is contingent on exposure to a periodontal pathogen and the elicitation of an immune response by the host [87]. Per Enwonwu's four stages of evolution, the periodontal lesion likely begins with bacterial colonization of the periodontium and probable differential overgrowth of potential periodontal pathogens [25]. However, local destruction of the structures does not occur until the second stage—invasion—during which host defense mechanisms provoked by microbial infiltration effect tissue injury [25, 86, 87]. A critical event in the host's response is detection of periodontal pathogens by toll-like receptors (TLRs) [90]. Binding of bacterial components to TLRs leads to activation of transcription factors and importantly, elaboration of various cytokines [90, 91]. Production of cytokines is the likely intermediate mechanism that links bacterial stimulation to tissue destruction [90]. There is purported variation in a patient's ability to mount a response and the efficacy of this response, and it appears that much of this variation may be rooted in genetics [92]. This observation lead to the development of the patient susceptibility theory, which proposes that an individual may be more or less susceptible to developing periodontal disease based on their inherent immune response to an inciting pathogen [92]. This theory has been criticized for being too simplistic as it does not account for contributions of local and environmental factors such as viral infections, smoking, physical and mental stress. It is now favored, however, that these latter factors are likely more important in the progression rather than initiation of periodontal disease. Nevertheless, the concept of susceptibility was novel in its recognition that variability in host immune response may influence the evolution of periodontal disease and inflammation, both in a destructive and protective manner [90].

Upon introduction to a periodontal pathogen, components of the innate immune system are activated and orchestrate the initial events of the host response [86]. During phagocytosis and phagocytic degranulation, respectively, polymorphonuclear leukocytes (PMNs) produce singlet oxygen (O_2^-), a ROS, and myeloperoxidase release hypochlorous acid (HOCl), another ROS [93]. As detailed previously, ROS produces a number of direct and indirect effects, including destruction of DNA and proteins, oxidation and lipid peroxidation of enzymes, stimulation of cytokine release via NF-$\kappa\beta$ activation [94], and activation of osteoclasts [95]. Excessive levels of ROS can be damaging to tissues and is counteracted in part of the actions of antioxidants. The significance ROS in periodontal disease is substantiated by studies that demonstrate a positive association between ROS levels and severity of periodontal disease [96, 97] and higher levels of ROS in adult patients with periodontitis compared to controls [98]. As a corollary, researchers have also shown depletion of antioxidants levels within the periodontium [99] and decreased concentration of plasma total antioxidants [100] in patients with periodontal disease. More recently, a study conducted by Jenzsch et al. [101] provided early evidence that antioxidant intervention may be beneficial in reducing periodontal inflammation in affected patients, as measured by clinical and biochemical parameters.

The third stage of destruction is heralded by a shift in the inflammatory milieu [8]. Macrophages continue to be present and release a variety of factors such as monokines, collagenases, and ROS that promote periodontal decomposition. However, the predominant cell types in this stage are

lymphocytes and plasma cells [92, 102]. In addition to damage mediated by macrophages, destruction of the periodontium may occur by lymphocyte-mediated direct cytotoxic activity or through the elaboration of chemical mediators such as cytokines [8] and chemokines, chemotactic cytokines that stimulate recruitment of inflammatory cells [90]. It has been suggested that the different cytokine patterns secreted by the Th1 and Th2 CD4+ T-cell subsets contribute to the development of periodontal inflammation [8, 87, 103]. Though the Th1-and-Th2 paradigm remains somewhat controversial due to conflicting results in the literature and lack of longitudinal studies [90], it supports an ever growing body of knowledge that links cytokine biology to the immunopathogenesis of periodontal disease. Cytokines of key significance in periodontal infections include, but are not limited to, IL-1, IL-6, IL-8, TNF-α, and IFN-γ [8, 103, 104]. Investigations using gain or loss of function animal models have established a cause-and-effect relationship between numerous cytokines and periodontal tissue loss [90]. Unfortunately, most studies to date examining cytokine levels in human subjects with periodontal disease have yielded somewhat inconsistent results [87]. This may be partially attributed to variation in patient selection as well as disparities in laboratory detection techniques [87]. Furthermore, the measurable effects of individual cytokines are difficult to evaluate because of their involvement in complex feedback mechanisms and pathways [62]. It is also uncertain how variations in blood cytokine levels are reflected at the level of the periodontium [8]. A broader understanding of roles of ROS and cytokines in the pathogenesis and progression of periodontal disease holds the promise of designing targeted therapies. This may include use of vitamin C, vitamin E, carotenoids, and reduction of glutathione to mitigate ROS damage and anti-inflammatory drugs to suppress key cytokines and/or cascades [87]. More intriguing still is the concept of providing tailored therapy as a prophylactic approach to periodontal disease based on a patient's susceptibility profile. Interestingly, there has been a recent resurgence of interest in cytokine therapy, which was historically plagued by challenges in achieving sustained therapeutic levels and undesirable side effects [87, 105]. Many of these limitations have since been overcome with bioengineering advances that improve the bioactivity and directed delivery of cytokines [105].

Nutrition and Periodontal Disease

Enwonwu et al. [8] and Genco [106] have suggested that nutritional deficits contribute to the pathogenesis of periodontal disease by altering the oral microbial ecology and modulating the host inflammatory response and reparative processes. Purported mechanisms through which this occurs include malnutrition-induced changes in cytokine expression, phagocyte action, and T-cell function [8, 25]. Malnutrition may also promote continued destruction of the periodontium by limiting substrates, factors, and nutrients critical for host defense and repair mechanisms [25, 107]. It is therefore logical to hypothesize that nutritional intervention may halt progression or even prevent onset of periodontal destruction. Unfortunately, there are few studies examining the efficacy of nutritional intervention in periodontal disease. Kesavalu et al. [54] showed that rats infected with *Porphyromonas gingivalis*—a key periodontal pathogen—exhibited reduced bone loss when given a ω-3 PUFA-rich diet compared to controls. Gene analysis of the ω-3 PUFA-fed rats confirmed decreased levels of IL-1β and TNF-α and increased intracellular antioxidant enzymes [54]. El-Sharkawy [47] corroborated these findings in a double-blinded clinical study of 80 patients, in which they documented significantly improved clinical and biochemical outcomes in patients receiving ω-3 PUFAs and a daily aspirin over a 6-month period. Among the improved parameters in their test group were significantly reduced probing depths, significant gains in attachment, and significant reduction of periodontal disease biomarkers such as Receptor Activator of Nuclear factor Kappa B Ligand (RANKL), a marker of bone resorption, and matrix metalloproteinase-8 (MMP-8), a marker of tissue destruction. Miley [108] demonstrated modest improvements in periodontal and gingival disease parameters in patients taking long-term vitamin D and calcium supplementation compared to

nontakers. A follow-up study confirmed persistence of these changes at the 6 and 12 months mark in the same patient population [109]. These authors postulated that the improvements were likely attributed to the ability of vitamin D to modulate cytokine production and stimulate monocytes and macrophages to secrete peptides with antimicrobial activity [110–112]. Meisel et al. [113] reported reduced probing depths and attachment loss in patients exhibiting higher serum magnesium levels related to use of magnesium-containing medications compared to controls. Lastly, in a double-blinded, randomized clinical trial, Chapple [114] showed an improvement in probing pocket depths compared to controls in patients given dietary supplementation with encapsulated fruit, vegetable, and berry juice powder concentrates. Similar investigations evaluating vitamin, micronutrient, and probiotic administration in periodontal patients have been undertaken but remain scarce in number. It noteworthy that some have questioned the validity of these studies due to methodological deficiencies, particularly the probiotic studies [115]. Hence, there is an overall agreement that more rigorous scientific researches must be undertaken before nutrient supplementation can be recommended as an adjunctive therapeutic option for periodontal disease.

The effects of obesity on oral health and specifically periodontal health has been explored for decades in animal models. In 1977, Perlstein and Bissada [116] examined histopathologic changes in the periodontium of obese and nonobese rats stimulated with local irritation. These investigators found that obese rats exhibited more severe histologic parameters of periodontitis compared to the controls in response to gingival irritation [116]. Reynolds et al. [117] found that rhesus monkeys subjected to a 30% reduction in caloric intake demonstrated less periodontal pocketing, lower IgG antibody response, and lower IL-8 levels compared to control fed monkeys [117]. These in vivo findings have been explored only to a limited extent in a small number of human studies. Saito [118] found a positive correlation between increased body mass index (BMI) and risk of periodontitis. Similarly, Ritchie [119] demonstrated that increased body mass and weight gain were associated with increased gingival bleeding and more severe periodontal disease, respectively. Han et al. [120] further confirmed significant associations between indices of obesity—including BMI and visceral fat area—and periodontitis in their study population. As a corollary, a study conducted by Shimazaki et al. [121] showed patients in the lowest quintile in BMI had significantly lower risk of developing severe periodontitis compared to subjects in the higher BMI quintiles. Proposed mechanisms for the pervasive role of obesity in inflammatory disorders include hyperinflammation through generation of cellular stresses and modulation of the host immune and cytokine responses as mentioned previously. Poor diet choices in individuals prone to excess adiposity may also be a contributing factor [86]. Additional research that examines the relationship between obesity and periodontal disease from both a pathomechanistic and clinical perspective has been recommended [86]. Such studies may also provide the foundational knowledge necessary to recommend dietary caloric restriction in high-risk patients.

Periodontal Disease and the Systemic Link

The expanding body of evidence that links periodontal disease to various systemic disorders has strengthened the support for an oral-systemic health link. As part of the Baltimore Longitudinal Study of Aging, Nesbitt [122] examined the association between periodontal disease and metabolic syndrome (MetS)—a constellation of central obesity, insulin resistance, hypertension, and other metabolic risk factors for diabetes and cardiovascular disease. These investigators found that individuals with higher levels of alveolar bone loss were significantly more likely to have MetS and suggested that periodontitis may contribute to development of MetS and elevations in systemic inflammation [122]. The manner in which periodontal inflammation effects change at the systemic level remains an area of active research. The cellular events postulated to be responsible for this oral-systemic interplay likely involve participation of mediators such as proinflammatory cytokines

that are produced locally within the periodontium and peripherally in the blood or distant organs. Systemic dissemination of these inflammatory mediators and cytokine-mediated activation of the APR with generation of acute-phase proteins are believed to be key events [6, 123, 124]. Subsequent trigger of the immune response and secretion of mediators from distant sites [6] may then influence both the initiation and progression of certain disorders like atherosclerosis [125, 126]. Another mechanism through which local inflammation may produce systemic effects is via cross-reactivity or molecular mimicry with immune components generated by periodontal pathogens such as heat shock proteins (HSPs) [127]. Other possibilities include periodontitis-induced bacteremia that causes bacterial invasion of target organs, direct colonization of the gastrointestinal or respiratory tracts due to aspiration or ingestion of oral microbes [6, 127], and common susceptibility whereby individuals susceptible to periodontal disease are also genetically predisposed to other inflammatory conditions like cardiovascular disease.

Summary

In summary, this chapter highlights the proposed relationships and interrelationship between nutrition, inflammation—including infection and immunity—and oral health. Through exploration of the various components of this triangle, we see that certain relationships are well understood while others require further study. In particular, there has been research dedicated to the bidirectional associations and interactions between nutrition and inflammation but little application of this knowledge to the oral system. Likewise, the three-way interaction between nutrition, inflammation and immunity, and oral health have not been explored extensively. The triangle is best viewed as a multidirectional cycle in which the integrity of each element—nutrition, host immunity, and oral health—is at least partially influenced by the other two (see Fig. 8.4). Optimal function of each element is critical as shown by the plethora of complications that arise with disturbance of any one. This includes both the local and systemic consequences of malnutrition, immune dysfunction, infection, and oral diseases.

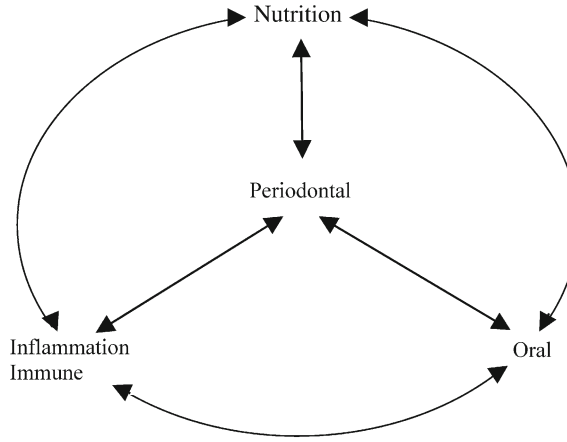

Fig. 8.4 Interrelationship between nutrition, inflammation and immunity, and oral health

It is of great interest to better define the role of nutrition in the nutrition-inflammation-oral health paradigm, recognizing that nutrition represents a potential means to achieve systemic and oral health. Nutrition-related areas identified as meriting further investigation include immunonutrition and cytokine therapy, dietary requirements of patients with oral mucosal disorders, use of

micronutrient supplementation to mitigate oxidative stress, and use of nutrient supplementation to prevent progression of inflammatory disease [8].

Lastly, it is of interest to note that the study of periodontal disease and its systemic health consequences has greatly advanced our understanding of the relationships among inflammation, infection and immunity, nutrition, and oral disease. It has also provided the framework to explore other inflammatory and infectious oral conditions that harbor the potential for systemic consequences, such as the necrotizing ulcerative gingivitis and noma. It is fascinating that the perception of the oral-systemic link has truly become bidirectional over time—shifting from focus on the oral manifestations of systemic disorders to the systemic effects of oral disorders. As with the study of periodontal disease, it is with great hope that research dedicated to exploring these oral and systemic conditions may serve as a platform for cultivating collaborative efforts between and within the various disciplines of medicine, dentistry, and nutritional sciences. This was a unified goal put forth in 2000 by a workshop on nutrition and oral infectious diseases at the Forsyth Institute and again in 2009 by a symposium dedicated to advancing nutrition and oral health research at the International Association for Dental Research (IADR). It also remains an ongoing objective of the International Association of Dental Research Nutritional Research Group. These inter- and multidisciplinary efforts will undoubtedly advance our understanding of the complex relationships between inflammation, nutrition, and oral disease and the oral-systemic health link.

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Chapter 9
Complementary and Alternative Medicine Practices and Oral and Nutritional Health

Diane Rigassio Radler

Keypoints

- Many Complementary and Alternative Medicine (CAM) therapies lack strong scientific evidence
- Dietary supplements are the most widely used CAM therapy among consumers; however, they are not subject to the regulations that apply to foods and drugs
- Health professionals have professional responsibilities to dialogue with their patients about safety, efficacy, indications, and effectiveness of CAM treatments
- Approaches to safe use of dietary supplements and evaluating CAM practitioners are addressed

Keywords Complementary and alternative medicine · CAM · Dietary supplements · CAM practitioners · Oral health

Introduction

Complementary and alternative medical practices (CAM practices) refer to those preventative and therapeutic choices that are outside of conventional, mainstream options within the United States (U.S.) and cover a broad range of approaches to healing. Many CAM practices are indigenous to other cultures worldwide and are considered to be traditional healthcare practices. The increasing use of CAM practices within the U.S. has been documented since the early 1990s [1–4], but little is known about their efficacy or long-term safety. The ongoing challenge for the U.S. healthcare system has been to assess the appropriateness of a variety of CAM modalities using an evidence-based approach. Several of these modalities have implications for the oral healthcare provider (OHCP) and is the focus of this chapter.

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Table 9.1 Types of complementary and alternative medicine practices[a]

Type	Characteristics
Mind–body interventions	Mind–body interventions focus on the mind's ability to influence the body's function and symptoms and include such approaches as hypnosis; meditation; guided imagery
Natural products	Natural products include herbal and other dietary supplements and probiotics
Manipulative and body-based methods	The manipulative and body-based category includes methods involved in the manipulation or movement of the body, such as chiropractic, osteopathy, and massage
Other	Other CAM practices may include Alternative medical systems (homeopathy, naturopathy, traditional oriental medicine); Energy therapy (magnet, qi gong); and movement therapy

[a] *Source* National Center for Complementary and Alternative medicine (www.nccam.nih.gov)

What is Complementary and Alternative Medicine?

The authoritative body for CAM in the U.S. is the National Center for Complementary and Alternative Medicine (NCCAM) within the National Institutes of Health. NCCAM describes CAM as "a group of diverse medical and healthcare systems, and products, that are not generally considered as part of conventional medicine" [5]. NCCAM notes that the term "conventional medicine" refers to medicine as practiced by those with MD (medical doctor) or DO (doctor of osteopathy) degrees and may be called allopathy, Western, regular, or mainstream medicine [5]. "Complementary" refers to practices that are adjunctive to conventional practice. "Alternative" refers to practices that are used instead of conventional practices. Over time, however, as more CAM therapies establish evidence-based outcomes, there may be some introduction of CAM into conventional medicine [6, 7]. Hence "Integrative," a more inclusive term, refers to the practice of combining allopathic, complementary, and alternative approaches to deliver health care that is superior to any one modality alone [5]. NCCAM groups CAM practices in broad categories such as mind–body interventions, use of natural products, and manipulative and body-based methods [5]. These are explained in Table 9.1.

Trends in CAM Usage in the United States

CAM increased in popularity in the United States for the past few decades, and continues to be used [1–3, 8]. A survey conducted in 1990 by Eisenberg and colleagues is widely considered to have served as a wake-up call for healthcare professionals concerning the growing popularity of CAM in the U.S. [1]. In this landmark survey of 1,539 respondents, the researchers disclosed that one in three Americans who participated in the survey had used at least one CAM therapy during the past year and that visits to CAM providers totaled 425 million, which exceeded the number of visits to all U.S. primary care physicians that year. The majority of those who used CAM therapies for serious medical conditions also sought care from their conventional physicians, but approximately 72% did not disclose their CAM activities to these physicians. Further, most (estimated at 75%) of the expenditures associated with the use of CAM therapy were paid out-of-pocket.

When consumers were surveyed in 1997, an even greater number of participants had used a CAM modality (42% vs. 34% in 1990), out-of-pocket expenditures were similar, and the same percentage of users did not share their CAM activities with their conventional physicians [2]. A 2001 survey examined lifetime use and age at onset and found 67.6% of 2,055 respondents had used at least one CAM therapy in their lifetimes [3]. For the population as a whole, lifetime use increased with age. This study concluded that the trend for CAM therapies was strong and that there would be a continuing demand for CAM therapies for the foreseeable future. National survey results report similar findings with 38% of adults disclosing CAM use [4, 9], and 49% specifying use of a dietary supplement product [8] for reasons that include boosting energy and a general sense of well-being.

Given the prevalence of CAM use, OHCPs should be prepared to communicate with patients on their patterns of use and whether or not the CAM is intended for a systemic effect or to treat an oral health condition. In rural communities and low income or minority populations, access to dental care may be challenging and patients may turn to alternative remedies for oral conditions such as pain, bleeding gums, and xerostomia [10, 11].

Concerns About Efficacy and Safety of CAM Therapies

Among the key issues regarding CAM use that concern healthcare providers is the uncertainty over efficacy and safety of CAM practices. Many of these modalities have been used in other cultures for centuries. In the U.S., however, consumers are quick to adapt therapies that have not been validated through research. Concerns regarding natural products that may differ from those of other countries due to species, soil, water, growing conditions, or the circumstances regarding product manufacturing further complicate assurance of consistent health outcomes associated with CAM practices. The creation of NCCAM in 1998 was a major step forward in establishing the groundwork for investigating efficacy and safety of various CAM modalities in the US. The mission of NCCAM is to subject CAM practices to rigorous scientific scrutiny to identify usefulness, safety, and efficacy of CAM in health care [12]. NCCAM's research approach includes basic and translational research as well as observational and clinical trials. Areas of interest include chronic pain, inflammation, and modalities to support health and wellness [13]. For those CAM modalities that are found to be health-promoting, the expectation is that they can be safely integrated into mainstream medicine. However, given the paucity of clinical trials of CAM on dental and oral health outcomes, clinicians should individually evaluate the risk/benefit profile and make a determination to use or not to use the CAM approach within patient care modalities. Rakel [14] describes a system of evaluating the benefit in light of the potential harm. In weighing the evidence with the harm to make an informed choice, the clinician can assess if there is evidence with no or minimal harm, then there is potential for use; conversely if there is little evidence and potential harm, the indication for use would be unfavorable. However to weigh the evidence against possible harm, the OHCP must be well versed in the CAM modality or should consult with or refer to a CAM practitioner.

Dietary Supplement Health and Education Act of 1994

Dietary supplements are considered natural products [5]. The large number of dietary supplement products available and the use of supplements by consumers may be attributed to the passage of the Dietary Supplement Health and Education Act of 1994 (DSHEA, pronounced "De-shay"). Congress

passed DSHEA as an amendment to the Federal Food, Drug, and Cosmetic Act [15]. DSHEA included several provisions that set dietary supplements and dietary supplement ingredients apart from the usual regulations that apply to food and drugs. It defined "dietary supplement," established a new framework for assuring safety, provided guidelines for the use of claims that could be made about dietary supplements and for the literature that was displayed where supplements were sold, established labeling requirements for dietary supplements, and granted the Food and Drug Administration (FDA) the authority to establish Good Manufacturing Practices (GMPs) for the production of dietary supplements.

DSHEA defined a dietary supplement as a product intended to supplement the diet that contains a vitamin, a mineral, a herb or other botanical, an amino acid, or a combination of these. Additionally, a dietary supplement is intended for ingestion in pill, capsule, tablet, or liquid form; is not represented for use as a conventional food or as the sole item of a meal or diet; and is labeled as a "dietary supplement" [15]. All dietary supplements must be labeled as such and must carry the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" [15]. This disclaimer is mandatory for all supplements, whether or not they are effective in improving health. It conveys no judgment on the part of the FDA as to whether or not the supplement is effective for its intended purpose.

To help consumers decipher how much is known about the intended purpose of a dietary supplement, DSHEA further established regulations for product claims. There are two types of claims that are of particular help to supplement users: health claims and structure/function claims. Health claims are the "gold standard," must make a direct linkage between a dietary ingredient and a health benefit, and have significant scientific agreement to support the claim [16]. Dietary supplements cannot claim to decrease risk of a disease unless the claim has been cleared by the FDA as a health claim [16]. An example of an approved health claim may be applied to dietary carbohydrates and dental caries; noncariogenic carbohydrate sweeteners such as sugar alcohols may claim "sucralose, the sweetener in this food, does not promote tooth decay."

The second type of claim, the structure/function claim, and is more general, stating that a particular supplement may promote a healthier condition but the claim cannot make a direct link between the supplement and a disease [17]. These may be more commonly used as they do not require preapproval from the FDA for a manufacturer to make the claim. Structure/function claims cannot state that a supplement will prevent, treat, or cure a disease. An example of an allowable structure/function claim would be: "Soy isoflavones promote bone health" since it makes no reference to a disease state.

In contrast to drugs, dietary supplements are not subjected to premarket approval for safety and efficacy. However, DSHEA did establish current Good Manufacturing Practices (GMPs), which were phased in by 2010, and manufacturers of dietary supplements in the U.S. are required to abide by these stated practices [18]. GMPs apply to manufacturers of dietary supplements and stipulate conditions under which supplements are manufactured, packaged, and tested. Manufacturers are required to follow the regulations for clean and safe manufacturing, quality control, and accuracy in labeling. The GMPs are welcome to healthcare practitioners and consumers to add confidence in buying dietary supplements.

The main difference between how dietary supplements and drugs (both prescription and over-the-counter) are brought to market is associated with the degree of scrutiny that products are subjected to prior to being released to the market. Drugs undergo extensive safety and efficacy testing that involves numerous stages of review that eventually involves human clinical trials. This forms the basis for FDA approval of a drug's entry into the marketplace, whereas dietary supplements do not have to undergo this level of premarket testing and approval, and hence some impure or ineffective products have been documented [19, 20].

Information on dietary supplements with adverse effects can be found on the FDA website at www.fda.gov. Adverse events such as increased blood pressure, heart rate, and dizziness have been associated with supplements that stimulate the central nervous system such as sources of caffeine (guarana) or ma huang (ephedra). In fact, ephedra is banned for sale in the US due to associated adverse effects of dietary supplements containing the substance [21]. In addition to safety concerns, there is often limited evidence that a particular supplement is effective for its intended purpose. However, high quality manufacturers can elect to have their products evaluated by independent testing labs. Among the more rigorous certification programs are those offered by the U.S. Pharmacopeia (www.usp.org) and NSF International (www.nsf.org).

Complementary and Alternative Medicine: Implications for Oral Health

Good oral health is an essential foundation for optimal overall health. The recognition that oral health is integral to general health is reinforced in a position of the Academy of Nutrition and Dietetics and in Healthy People 2020 [22, 23]. Additionally, the Surgeon General's Report on Oral Health [24] underscores the fact that diseases and limitations of the oral cavity may impact general health and wellness. OHCPs are concerned with preventing disorders that affect the health of the oral cavity and preventing and alleviating symptomatic manifestations of systemic diseases. This chapter will review CAM modalities that patients may use for systemic or oral health so that the OHCP may be able to openly communicate on CAM therapies and evaluate the impact the CAM therapy may or may not have on the oral health or procedure provided to the patient.

Whole Medical Systems

Whole medical systems refer to practices or theories in healing that evolved apart from conventional Western medicine. Among the more common whole medical systems are homeopathy, natural medicine, and traditional oriental medicine, which includes acupuncture [5].

Homeopathy

The word "homeopathy" derives from the Greek *homeos*, meaning similar, and *pathos*, meaning suffering. Homeopathy is a medical system developed in the late eighteenth century by the German physician Samuel Hahnemann and is based on the "law of similars," which refers to the concept of "like curing like." When a homeopathic medication ("remedy") is administered to a healthy person, the individual will develop signs and symptoms. If an ill person with similar signs and symptoms is given the same remedy, the ill person often becomes well. The administration of a homeopathic remedy to a well person and the careful noting of all signs and symptoms is called a "proving." One of the fundamental principles of homeopathy is that only a single remedy is administered at a time [25–27].

A second principle of homeopathy is that the minimum dose is given, so that side effects are rare. The original solution is serially diluted until not even a single molecule of the original solute remains. At each dilution, the solution is shaken vigorously, a process called "dynamizing" or "succussion." Since theoretically no solute is present in the final dilution, which is the form used as the homeopathic medication, there is concern among Western scientists that any effect represents simply a placebo effect [28]. Some scientists have suggested that the process of preparing the remedy could alter the molecular structure of water, which may be an important factor in the efficacy

of the remedy. In a critical review of homeopathy, Jonas et al. reported that conclusive evidence for the effectiveness of homeopathy is lacking. While they suggest homeopathy may have value, it should not be used as an alternative when evidence-based therapies are available [29].

Oral Health Implications

Homeopathic remedies are generally considered nontoxic; to the best knowledge of this author there are no published reports on its use causing complications with dental procedures or surgery. While homeopathy cannot replace oral surgery or medication to treat oral diseases or lesions, homeopathic preparations may be adjunct treatments for dental pain or lesions [26, 27]. Oral healthcare professionals (OHCPs) should be concerned that patients may try to relieve symptoms themselves without consulting a homeopathic provider or in lieu of other conventional treatments. If a patient wished to use a homeopathic remedy, it would be prudent for the OHCP to discuss conventional treatment options and provide a referral to a qualified homeopath. In the US, www.homeopathy.org is a source for referrals to a credentialed homeopath.

Traditional Chinese Medicine and Acupuncture

Traditional Chinese medicine (TCM) is a holistic practice in which the body is viewed as being in a state of harmony and balance, both within itself and with the environment in which it lives [30, 31]. Disharmony signals disease, and the therapeutic goal is to bring the individual back into balance. The body and mind are unified, and a universal life force of *chi* (pronounced "chee") is believed to flow throughout the individual along specific channels or "meridians." Maintaining the free flow of *chi* is essential for health. TCM practitioners use a combination of acupressure and acupuncture, herbal remedies, and meditative exercise to achieve balance. Acupressure uses the pressure of the fingers, palm, or elbow to stimulate specific sites along the meridians, whereas acupuncture uses hair-thin needles to stimulate these sites. Acupuncture may be helpful in the treatment of chronic pain conditions by stimulating the release of natural endorphins that mitigate pain. TCM practitioners restore *chi* with the use of Chinese herbal medicines and acupuncture [31].

TCM practitioners are keen observers and include parameters in their examinations not typically used in the Western world. Practitioners ask many questions and observe the voice, emotions, and general demeanor of the patient. They conduct a visual examination that includes body movement, facial colors, and the tongue. TCM practitioners believe they can tell much about the health of the inner organs by observing the health of the tongue: its color, moisture, coating, fit within the oral cavity, and presence of abnormalities. They are careful listeners and also rely on smell to detect disharmony within the body. Finally, they use a touching examination to determine the person's sensitivity to touch and to evaluate pulses, which provides insight into the state of the individual's *chi*.

Oral Health Implications

Acupuncture may be used in some populations for managing periodontal disease, caries, and pain [32]. Individuals may seek acupressure or acupuncture for temporomandibular joint disorders (TMD) and myofascial pain, and to reduce the gag reflex during dental procedures [33]. Treatments provided by a licensed acupuncturist may provide pain relief without adverse effects to the patient. As an analgesic, acupuncture may be an alternative for patients with severe allergic reactions to conventional medications. The results of a systematic review and meta-analysis indicate that efficacy of acupuncture for managing TMD may be limited but that more research is needed [34]. The results of a pilot study demonstrated that trigger point acupuncture may be effective for chronic TMD myofascial pain when compared with sham acupuncture placebo [35].

Acupuncture [36, 37] and acupuncture-like nerve stimulation [38] have been used in patients with head and neck carcinoma to prevent and treat xerostomia. Meng and colleagues [36, 37] reported on the use of acupuncture to prevent xerostomia in patients undergoing radiation therapy. The researchers compared the use of acupuncture to standard care and also to sham acupuncture. In both

instances, the use of acupuncture resulted in reduced xerostomia symptoms and improved quality of life among patients, compared to patients who received standard care or sham acupuncture. Similarly, Wong and colleagues [38] compared an acupuncture-like nerve stimulation to oral pilocarpine for the treatment of xerostomia. In acupuncture-like nerve stimulation, electrical stimulation is applied transcutaneously on the relevant acupuncture points, thus providing therapy to patients without the use of needles or a licensed acupuncturist. The aims of the study were to evaluate the feasibility of delivering the acupuncture-like nerve stimulation and to identify the treatment on xerostomia among patients. The results of the study suggest that acupuncture-like nerve stimulation can have positive impacts on xerostomia symptoms and that the treatment is feasible to further study in a larger population and for a longer duration of time to evaluate sustained benefits.

The use of Chinese herbs may potentially interfere with dental therapy or medications. Since these remedies are typically complex mixtures of several herbs, it can be difficult to determine which active constituents are present and how these might interact with anesthetics and other medications [39]. The Natural Medicines Comprehensive Database (www.naturaldatabase.com) may provide information on individual herbs, botanicals, and natural products.

Mind–Body Interventions

Mind–body medicine recognizes that the mind plays a key role in health and views the mind and the body as a unified whole that should not be treated as separate entities [48]. Psychosocial approaches using the brain, body, and behavioral strategies can influence physical function, pain control, and anxiety [41, 42, 44]. Several mind–body interventions are used to promote a state of relaxation in the body. Meditation and hypnosis may have applications to dental therapy. Meditation involves deep breathing exercises and focused attention to effect muscle relaxation. Dr. Herbert Benson introduced the concept of the "relaxation response" in the early 1970s [40]. In this approach, he brought together a number of different types of relaxation and meditation techniques, with a common outcome of a state of consciousness that reduced heart rate, blood pressure, breathing rate, brain-wave patterns, and often, pain. Mindfulness meditation derives from the Buddhist tradition and is the concept of staying in the present moment. It underlies all of the mind–body interventions and promotes a state of enhanced relaxation and insightfulness. Hypnosis is a state between sleep and wakefulness that allows for relaxation and deep concentration [40–48].

Oral Health Applications

Patients may use mind–body interventions to manage fear of dental therapy or to minimize pain. Published research [45, 46, 49, 50] suggests that some individuals are helped by a combination of one or more of these approaches to control dental anxiety and pain. Nonpharmacologic approaches may be advantageous to patients; OHCPs may consider training and use of mind–body approaches as applicable.

Biologically Based Treatments

Natural Products (Dietary Supplements)

Dietary supplements can be conveniently divided into botanicals, which include herbs and other plant materials with potential health benefits, and nutritionals, which are essentially all other dietary supplements such as vitamins, minerals, amino acids, fatty acids, and metabolites [5, 15]. Dietary

supplements of primary interest to OHCPs fall mainly into the categories of anticoagulants, anti-inflammatory agents, antimicrobial agents, immune stimulants, and analgesics. While some interactions may be based on theoretical cumulative or opposing actions of drugs and dietary supplements, a 2013 review of drugs commonly used in dentistry and dietary supplements suggests that interactions may occur with ginkgo, St. John's wort, valerian, or evening primrose; patients using any of the medications commonly used in dentistry and taking these supplements should be advised to discontinue the use of the supplements 1–4 days prior to visits to OHCPs [51].

Botanicals (Phytotherapy)

Patients presenting for dental care may be using botanicals for the treatment of dental symptoms or for an unrelated chronic disease or for health promotion. If the dietary supplement is used for an oral problem, the OHCP should be aware and ascertain if it is in lieu of a conventional treatment. Whether for treatment of a systemic disease or for disease prevention, the practitioner should evaluate it for safety, efficacy, and potential interactions with planned procedures. Botanicals that may be of interest and concern to the OHCP are listed in Table 9.2 [52].

Nutrition Supplements

Table 9.3 includes various supplements with consumer uses and relevance to the OHCP. Patients should be encouraged to consume a variety of foods for nutrient adequacy and to be advised that it is the position of the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) that supplemental vitamins and minerals or both may be beneficial in the circumstance that a well-balanced diet cannot be maintained [53–55]. No scientific evidence has been found in the published literature that a select combination of vitamins and minerals in supplement form will enhance oral health or prevent oral disease.

Manipulative and Body-Based Methods

Chiropractic

Chiropractic, like natural medicine, embraces the belief that the body has the inherent ability to heal itself and that the practitioner's role is to facilitate this natural propensity. Developed in the late 1800s by Daniel David Palmer, chiropractic is rooted in the belief that proper alignment of the spine impacts the health of the body [56]. Wellness and prevention are the guiding principles in chiropractic. Treatment is noninvasive, and practitioners do not employ drugs or surgery. Instead, chiropractors focus on keeping the nervous system healthy and removing any musculoskeletal problems (called "subluxations") that may interfere with optimal functioning of the nervous system [56, 57].

The term "chiropractic" derives from the Greek *chiropraktikos*, which means "effective treatment by hand." Chiropractors manually manipulate the body to promote optimal functioning of the nervous system by aligning the spine properly and relieving muscle tension. The chiropractic philosophy is based on two fundamental precepts: the importance of the influence that the structure and condition of the body has on its physiological functioning and the importance of the mind–body connection in promoting healing and maintaining health.

Chiropractic is a popular modality, particularly for those seeking relief from chronic pain, such as low back pain or temporomandibular or fibromyalgia pain. Although popular with consumers,

Table 9.2 Use and considerations regarding botanical supplements [39]

Supplement	General use(s)	Oral use(s)	Considerations
Aloe vera	Anti-inflammatory	Mouth rinse	May cause diarrhea, malabsorption, electrolyte imbalance when ingested
Bilberry	Relieve diabetic neuropathy Antioxidant Improve eyesight	As an astringent rinse to treat mildly inflamed mucous membranes of mouth and throat	
Calendula	Anti-inflammatory, reduce swelling, improve wound healing	Applied topically to treat inflammation of oral mucosa	May cause allergic reactions in individuals sensitive to members of the Asteraceae (daisy) family
Cayenne	Used topically for pain relief	Topical application for pain relief for toothache, trigeminal neuralgia	Capsaicin is active compound in chili/cayenne peppers—Irritant to skin and eyes. Topical use only
Chitosan	Weight loss, improved strength, reduce cholesterol	Applied topically to gums may decrease risk of periodontal disease	Derived from exoskeleton of crustaceans, so should be avoided in people with shellfish allergy
Echinacea	Upper respiratory infections, wound healing	Locally applied as antimicrobial for oral health, inflammation of mouth	Research has not demonstrated efficacy in oral health. Do not use with immunosupressants or hepatotoxic drugs, or with AIDS, tuberculosis, or autoimmune diseases
Ephedra	Central nervous system stimulant		Tachycardia, hypertension, arrhythmias; reduces effectiveness of prednisone
Evening primrose oil	Premenstrual syndrome, menopause symptoms, Sjogren's syndrome		Source of gamalinolenic and linoleic acids that may interfere with anticoagulation/antiplatelet activity
Feverfew	Migraine headaches, menstrual symptoms Inflammation		If leaves are chewed, may cause mouth ulcers, sore tongue, swollen lips, and taste changes; may interfere with blood clotting; avoid with use of aspirin, NSAIDS; may cause allergic reactions in individuals sensitive to members of the Asteraceae (daisy) family
Garlic	Cardiovascular disease (decrease blood pressure and LDL cholesterol)	Inflammation of oral mucosa, or aqueous extract for the treatment and prevention of oral candidiasis	Additive effects with anticoagulant agents. Halitosis unless using "odorless" preparations
German chamomile	Oral mucositis	Oral rinse may prevent or treat oral mucositis associated with some forms of chemotherapy	
Ginger	Nausea/Vomiting	Antiemetic; stimulates saliva and gastric juices	Inhibits platelet aggregation
Ginkgo biloba	Increases peripheral and cerebral circulation		Inhibits platelet aggregation; discontinue at least 36 hours prior to surgery

(continued)

Table 9.2 (continued)

Supplement	General use(s)	Oral use(s)	Considerations
Ginseng, Panax	General tonic, stimulant, improve stress resistance		Interferes with platelet aggregation and possibly with other stimulants. May decrease blood glucose levels in type 2 diabetes. Avoid use with estrogens or corticosteroids
Goldenseal	Anti-inflammatory		May increase saliva production; mouth and throat irritations in high doses
Green tea	Cancer prevention	Oral and esophageal cancer prevention; reduce risk of dental caries	Additional research needed
Guarana	Contains caffeine—used in weight loss aid, reduce fatigue		Avoid use with caffeine, ephedra, or other CNS stimulants; possible additive effect with epinephrine
Kava	Anti-anxiety		Additive effect with sedatives; implicated in liver failure
Maté	Stimulant to relieve mental and physical pain; headache		Additive effect with other CNS stimulants, may increase blood pressure, contains caffeine; possible additive effect with epinephrine
Mexican sanguinaria (*Polygonum aviculare L.*)	Supportive treatment for coughs when taken systemically	Astringent properties may be useful adjunct with usual oral hygiene to reduce gingivitis when applied topically or used as rinse	
Neem	Dental plaque	Topically applied leaf extract gel to gingiva may reduce plaque	More research needed
Pomegranate fruit extract + gotu kola	Periodontal disease	Topically applied to gingiva may reduce risk of periodontal disease	More research needed
Stevia	Sweetener	Use in place of sugar in food/beverages	May help reduce caries risk
St John's wort (*Hypericum perforatum)*	Mild depression Viral infections	Topical application may relieve TMJ pain	Interaction with medications including digoxin, cyclosporin, indinavir, statins, oral contraceptives, nonsteroidal anti-inflammatory agents, and some preoperative drugs such as midazolam and diazepam; may also cause xerostomia
Tea tree oil (*Melaleuca alternifolia*)	Topical use for bacterial and fungal infections of the skin	Topically for bacterial and fungal infections of mucosa, including candidiasis	Oil should not be ingested; contact dermatitis has been reported
Valerian	Antianxiety		Additive effect with barbiturates and other CNS depressants
Yohimbe	Impotence, exhaustion, diabetic neuropathy	To increase saliva flow in those with xerostomia	May elevate blood pressure; do not use in kidney or liver disease, anxiety or panic disorders, or with psychoactive drugs

Table 9.3 Use and considerations regarding nutritional supplements [39]

Supplement	General use(s)	Oral use(s)	Concerns
Calcium	Bone density	Integrity of maxilla and mandible	Inadequate calcium may be implicated in tooth loss and periodontal disease
Coenzyme Q10	Cardiovascular health, adjunctive therapy for symptoms of congestive heart failure	Periodontal disease treatment	Research has not demonstrated efficacy in treating periodontal disease topically. Oral ingestion may reduce systemic inflammation
Glutamine	Abundant amino acid in humans used in immune function and major organs	Mucositis	Oral ingestion may decrease incidence, severity, and duration of chemotherapy mucositis
Lysine	An essential amino acid in human metabolism	Aphthous and herpes ulcers	Additional research is needed to determine effective dose
Omega-3 fatty acids	Decrease inflammation	TMJ	
Vitamin C	Collagen formation, among others	Integrity of gingival and improved healing	Research has not demonstrated benefit of vitamin C supplementation for periodontal disease or oral mucosa healing
Vitamin D	Bone health	Periodontal disease	Higher vitamin D levels have been associated with reduced risk of periodontal disease in adults over 50 years
Vitamin E	Lipid-soluble antioxidant	General antioxidant	Possible additive effect with anticoagulants
Zinc	Immune stimulant		Avoid use with immunosuppressive drugs

conventional medical practitioners remain skeptical that spinal manipulation is connected with the body's ability to heal. NCCAM has established the Palmer Center for Chiropractic Research in an effort to promote clinical research on the use of chiropractic therapies and which diseases or symptoms might be best suited for chiropractic treatment.

All 50 states require chiropractors to be licensed, which involves completing a 4-year program at a nationally accredited college of chiropractic and successfully passing a national certifying examination [57].

Oral Health Implications

Chiropractic is noninvasive and does not involve pharmaceutical drugs. Chiropractic clinicians may adjust the head and neck region to relieve chronic temporomandibular pain. They may also recommend dietary supplements that could have implications for dental care, particularly for those supplements that impair coagulation or alter the action of anesthetics (refer to the Dietary Supplements section of this chapter). OHCPs should discuss with the patient the dietary supplements being taken, identify potential interactions, and guide patients accordingly prior to initiating dental care.

Osteopathy

Osteopathy is a holistic healing system first practiced by Andrew Taylor Still in the late 1800s [58]. Similar to chiropractic, osteopathy includes a form of therapeutic manipulation that seeks to restore optimal flexibility and mobility to the body to relieve pain and promote well-being. Originally osteopaths used long-lever manipulation, which involves the arms and legs as fulcrums for bending and twisting the body. Chiropractic, in contrast, used short-lever manipulation that focused on the protruding parts of the spinal vertebrae. Today, however, osteopathic medicine training is essentially the same as that of medical doctors except that osteopaths receive additional training in the

musculoskeletal system [58]. Osteopathic doctors (DOs) are trained and licensed physicians who may prescribe drugs, perform surgery, and utilize all accepted modalities to maintain and restore health. Many osteopaths serve as primary care physicians because of their commitment to treating the whole person. Rather than being an alternative therapy per se, osteopathy is a conventional medical system that includes the alternative practice of therapeutic manipulation [58, 59].

Oral Health Applications
A patient with chronic orofacial pain or fibromyalgia may use osteopathic manipulation to minimize pain. Osteopathy would not be expected to interfere with dental treatment.

Massage

Massage is an ancient practice commonly used in Chinese, Greek, and Roman cultures. Using their fingers and palms, massage therapists knead or otherwise manipulate soft tissues to relax sore, tired muscles, dispel tension from the body, and improve lymphatic circulation. The benefits of massage are emerging but it is not clear how much of the perceived benefits are due to the bodywork itself and how much to the attention and touch that are an integral part of massage therapy [60, 61].

In the U.S., three types of massage are commonly available: European massage, deep tissue massage, and pressure-point techniques. Swedish massage, a type of European massage, is perhaps the best known in the U.S. This type of massage involves long gliding strokes, kneading, and friction. Rolfing is a popular type of deep tissue massage and involves working with the fascia to loosen the sheaths that cover the muscles, which is thought to allow the body to be held erect with less muscular effort. Acupressure is an example of pressure-point massage and involves pressing with the fingers on the acupressure points throughout the body (see traditional oriental medicine, above). Shiatsu massage is a popular Japanese form of this pressure-point technique.

Oral Health Implications
Individuals may use massage therapy to ease chronic myofascial pain, fibromyalgia, or TMD [62, 63]. Massage is not known to cause harm and may actually provide relief to those with chronic pain and allow for relaxation prior to dental treatment.

Practical Applications

Working with Patients who are Using CAM Modalities

The health practitioner has a professional responsibility to the patient to protect, permit, promote, and partner, described as follows: “First do no harm” [68] and protect the patient from toxic, ineffective, or costly therapies that would be used in place of efficacious treatments. The practitioner should, however, also permit the patient to choose safe treatments and adjunctive treatments with no demonstrated side effects, as long as the therapy is accessible, not prohibitive in cost, and does not displace proven remedies. Health practitioners can promote dialog for safe and effective treatments and help consumers discern good information and reputable therapies and therapists. “Time to Talk” is an educational campaign launched by NCCAM to promote communication between patients and providers regarding CAM use [69]. Strategies, tips, and downloadable posters are available at http://nccam.nih.gov/timetotalk. Ultimately, practitioners should partner with their patients to comanage health and illness, provide direction to resources and evidence, and provide professional input into the decision process. Partnership is also advisable for monitoring progress and response to treatment if a patient makes an informed decision to engage in CAM [64–67].

An open dialog with all patients is essential and should be discussed as part of routine care. Pertinent questions to ask are "what, why, when, where, and how," outlined as follows. The first question to ask is "What are you taking?" Alternatively, the OHCP could ask "Are you taking any supplements?" but that may put the patient on the defense. Assuming that patients are taking supplements may let the patients know that the practitioner is receptive to a discussion. This discussion should include use of any vitamins, minerals, botanicals, or other dietary supplements. It may be followed by a question about any other treatments or therapies used that may be considered complementary or alternative. A patient may not think to inform her OHCP about the acupuncture treatments she is having for headaches, but may in fact lead you to discover other symptoms and therapies not previously disclosed. Also included in the "what" question is "What dosage do you take?" This should include how much per tablet or capsule or how much of a herb is brewed in tea, and should also include the frequency with which the patient consumes the supplement or participates in treatment. For example, oral health implications will differ in the patient who drinks ginger tea occasionally for nausea versus another patient who takes concentrated ginger in capsules twice each day.

The second question is "Why are you taking it?" Is it to remedy a symptom, to treat a disease, or is it for disease prevention? A practitioner may discover a patient who is taking garlic and would question whether he is taking it to treat oral candidiasis or for the prevention of cardiovascular disease, both of which would have very different implications to the practitioner.

The next question is "When did you start taking it?" (or, in the case of a treatment, how long ago did the patient start using the CAM modality) to find out how long the patient has been on the regimen. Often in the case of dietary supplements, symptom relief or treatment may not appear noticeable for several months. If, however, the patient indicates that he has taken the supplement for 4 months without any relief, it may be advisable to discontinue the regimen and try another approach. Another important consideration to ask is "When in the day do you take it?" to discern whether there are potential pharmacokinetic interactions with food or medications or whether the patient takes a remedy at a particular time when symptoms seem most severe.

During the interview, the practitioner should ask, "Where did you obtain your information and where do you buy the product or therapy?" These are important questions to determine if the patient regularly sees a CAM provider or if the information was obtained from advertising or testimonials. The origin of purchase will disclose if the patient is buying directly from the person making recommendations or selecting independently without guidance.

Finally the practitioner should ask, "How is it working?" Is the patient receiving the results that he thought he would? Have the symptoms been completely alleviated or just diminished? Are there any side effects attributable to the treatment?

These questions may at first seem daunting to a practitioner who is not fully knowledgeable about various dietary supplements or CAM modalities. It is intimidating to consider starting a dialog about CAM therapies because of a limited knowledge base. Familiarity with terminology may ease any tension in the discussion. Inquiry to the patient can also be educational to understand their rationale for using a treatment. Additionally, and perhaps most importantly, in order to increase the likelihood of honest responses, patients should understand why an OHCP inquires about CAM.

Choosing Quality CAM

Choosing Quality Dietary Supplements

In evaluating the potential for a dietary supplement, consider the following five factors—mechanism of action, available research, adverse effects, legality of use, and professional ethics. If patients make an informed decision to take supplements, advise them to buy from well-known, reputable

companies to reduce the risk of supplement contamination and adulteration. Consumers should be educated to look for quality control standards. One example is the Dietary Supplement Verification Program (DSVP) set up in 2000 by the United States Pharmacopoeial Convention (USP), an independent, nongovernmental organization, to respond to the need to assure consumers that dietary supplements contain the type and amount of ingredients listed on the label [70]. Manufacturers of dietary supplements voluntarily participate in this program. The rigorous program subjects products to scientific testing for purity, accuracy of ingredient labeling, and quality manufacturing practices. A product that passes the USP standards may bear the DSVP certification mark.

Another similar voluntary certification program for dietary supplements is offered by NSF International [71]. The certification process includes product testing, Good Manufacturing Practices (GMP) inspections, and ongoing monitoring in exchange for the NSF mark.

The USP and NSF International certifications are rigorous and ensure quality at all levels of the manufacturing process. Another potentially useful source of information is ConsumerLabs.com [72]. This company evaluates supplements for labeling accuracy and consistency of product units. ConsumerLabs.com is an independent testing laboratory that investigates whether the label accurately reflects what is in the product container, whether the product is free of contaminates, whether the product disintegrates in a reasonable amount of time so that it can be absorbed by the body, and whether there is consistency among each unit (such as a tablet or capsule) within the product. If a product successfully meets these criteria, ConsumerLabs.com awards its CL Seal of Approval to that product. Test results are available at www.consumerlabs.com. Summaries of the findings are available for free; full reports are available by subscription for a modest fee.

These types of certifications in addition to established GMPs are useful to consumers and healthcare practitioners. They help to identify quality products and increase confidence in the product selected. Consumer and practitioner collaboration will be critical for safe and rational use of supplements.

Evaluating a Practitioner

The web address, http://nccam.nih.gov/health/decisions/index.htm, within the NCCAM website has tips for consumers who wish to explore CAM therapies. Topics include selecting complementary and alternative therapies, examining the practitioner's expertise, considering the cost, partnering with all healthcare providers, and finding credible sources of information about complementary and alternative therapies. Additionally, therapies requiring licenses for practice, such as natural medicine, will have a credentialing organization that may include a referral system or a process to check the qualifications of a particular therapist. OHCPs should familiarize themselves with local CAM practitioners to get to know the resources likely used by patients and to establish a rapport for future consultation with these practitioners.

Legal Issues for OHCPs

All health practitioners must advise patients of potential harm or risk involved with any therapy, whether it is considered conventional or CAM. In order for OHCPs to continue to practice comprehensively and ethically, they must maintain competency through lifelong learning and self-reflection [73]. Malpractice refers to treatment that deviates from the accepted standards of care, which in dentistry, are based on scientific knowledge and proven practice. CAM may eventually prove to be scientifically valid and accepted into mainstream practice, but many of the therapies are not thoroughly supported with scientific evidence.

Table 9.4 Electronic resources

Agency/Resource	Web address
American Botanical Council	http://www.herbalgram.org
CAM on PubMed (a subset of the National Library of Medicine's PubMed free literature search service limited to CAM literature	http://nccam.nih.gov/research/camonpubmed
FDA-authorized health claims for food and dietary supplements	http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm064919.htm#upd
NCCAM	http://nccam.nih.gov
Natural Medicines Comprehensive Database	http://www.naturaldatabase.com
Office of Dietary Supplements	http://ods.od.nih.gov/

Informed consent is always obtained in medical or dental practice for conventional treatments and should be considered for CAM therapy. The practitioner is faced with keeping abreast with contemporary evidence-based findings in CAM research and use, communicating the risks and benefits of the therapy or of the lack of standard care if the patient should choose only the alternative therapy, and obtaining and documenting informed consent from a competent patient [74]. Working together for the optimal solution should provide the patient with the best options from which to choose and the best outcomes in patient care.

Summary

Complementary and alternative healthcare practices are popular in the U.S. Categories of CAM include whole medical systems (homeopathy, natural medicine, traditional oriental medicine), mind–body interventions (meditation, prayer and spirituality), natural products (dietary supplements), and manipulative and body-based methods (chiropractic, massage, osteopathy). Consumers typically use these approaches to augment rather than to substitute for conventional care. Among the CAM modalities likely to be encountered by OHCPs are the use of homeopathic remedies for pain, infection, or swelling [26, 27]; acupuncture for pain [33–35]; mind–body therapies to reduce anxiety and pain [45, 46, 49, 50]; dietary supplements for general health promotion and to treat specific disorders [8]; and manipulative techniques to decrease pain [62, 63].

Homeopathic remedies are readily available to consumers and are considered to be nontoxic. However, to maximize effectiveness, they should be used under the guidance of a qualified homeopathic provider rather than self-medicating. Acupuncture may be beneficial for postoperative dental pain and chronic orofacial pain and xerostomia, and should be administered by a qualified provider [33–35]. Osteopathic, chiropractic, and massage manipulation are also used to minimize pain. None of these modalities are invasive or known to interfere with dental treatments and may provide relief from chronic orofacial pain or fibromyalgia for many patients. Mind–body interventions used by patients to minimize pain or decrease fear of dental therapy may include hypnosis or meditation. The most popular use of natural products is the use of dietary supplements. It is important for the OHCP to ask the patient what they are taking and to know how their supplements may potentially interact with sedatives and other medications used to treat oral conditions. Natural Medicines Comprehensive Database (www.naturaldatabase.com) may be a useful tool for clinicians in evaluating supplements (Table 9.4).

Clearly, it is important for the OHCP to be aware of the CAM modalities being used by patients and to review whether they might interfere with dental treatments. An important finding in surveying CAM users is that they often do not volunteer information to their healthcare providers concerning their use of CAM therapies. A nonjudgmental approach to the patient's choices fosters a comfortable environment and provides an opportunity to educate patients about efficacy and safety of the various modalities and to provide credible resources for further self-education.

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Chapter 10
Genomics and Oral Health: An Overview

Ruth M. DeBusk

Keypoints

- Alterations to DNA that may occur include changes in chromosomal number or structure, changes in DNA sequence, and changes in the epigenome
- In oral health and disease, detection of genetic alterations can be used for a wide spectrum of applications, from distinguishing pathologically similar disorders to predicting susceptibility to various oral diseases, such as caries, periodontal disease, and oral cancers
- Pharmacogenomics and nutritional genomics are new approaches to diagnosing oral diseases, profiling patients' gene-directed drug-metabolizing capabilities, determining dietary requirements based on genotype, and making gene-directed food choices
- Nutritional genomics is a specialized application of genomics to diet- and lifestyle-related disease, which includes the majority of the chronic disorders of modern societies

Keywords Genomics · Oral health · Oral health and disease · Genetic alterations · Nutritional genomics · Pharmacogenomics

Introduction

The Human Genome Project is credited with the arrival of the genomics era. The project was initiated in 1990 and achieved its primary goals by 2003. A multinational collaboration, the project's initial goal was to identify each of the 3 billion DNA nucleotides of the human genetic material and to estimate the number of genes. Although this project has been completed, the core exploration has continued with an expanded focus that includes identifying the function of each gene and its protein product, dissecting the complexity of gene expression and its regulation, and defining the genomes of other organisms used as model systems to help decipher the workings of the human genome. Further, several other important "-omics" disciplines have emerged from the Human Genome Project, such as transcriptomics, proteomics, and metabolomics. Each is focused on understanding key aspects of how the information stored within an organism's genome is converted into the complicated cellular machinery that sustains life.

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Additional "-omics" disciplines, such as epigenomics, pharmacogenomics, nutritional genomics, and microbiomics, focus on how factors from the environment that an organism inhabits communicate with the genetic material to impact the ultimate biological outcome. The weblike complexity of higher organism functioning can be daunting to dissect but, fortunately, the blueprint for life is fundamentally the same among organisms so that many of the findings from research with less complex organisms can be extrapolated to human implications. An overview of the Human Genome Project can be found at the websites for the National Human Genome Research Institute (www.genome.gov) and the U.S. Department of Energy (genomics.energy.gov), which co-administered this global project.

The Human Genome Project brought to the forefront of healthcare an important fundamental biological principle: genes underlie function. There is a direct connection between the information in our genes and our ability to carry out the myriad activities that support life. This awareness alters our thinking about dysfunction ("disease") because it's now clear that there is a logical underpinning to disease, one that can be systematically dissected and targeted with appropriate therapeutic interventions. We do not "get" a disease; disease develops because our individual genetic makeup includes gene variants (also called "genetic variations") that make us susceptible to disease through their ultimate influence on physiological function. The susceptibility may be strong or it may be too weak in itself to lead to significant dysfunction unless one or more environmental factors interacts with those variants. The chronic diseases that challenge healthcare today are the result of interactions between our genes and our environment. Each of us has all the genes that characterize the human species but with slight variations that convey genetic uniqueness to each of us. It's these variations that determine an individual's disease susceptibility and how s/he responds to particular environmental factors, such as food, medications, or environmental toxins. Defining the various factors involved and their interactions is expected to provide clinicians with the potential for more effectively managing existing disease and to be well positioned to prevent disease before it manifests.

Another important accomplishment of the Human Genome Project has been in the area of genetic technology. New technological advances have been developed, but even the original technologies have advanced to the point where analyzing the composition of the genetic material is considerably faster and cheaper than even a few years ago [1]. Ongoing development in genetic technologies is essential for genomics to achieve clinical utility. In order to predict a patient's drug response or disease susceptibility, clinicians will need to know which gene variants are present within an individual's genome. Significant progress is being made in developing fast, accurate, and inexpensive genetic testing and can be expected to continue so that test panels with clinical validity and utility will be readily available for widespread application in the near future. Expect testing to become increasingly simplified in administration but increasingly complex in clinical implications as knowledge expands and multiple gene–gene and gene-environmental factor interactions are discovered and associated with clinical outcomes. Systems biology and bioinformatics will be important behind-the-scenes fields supporting clinical application of the -omic technologies. Recent reviews address emerging technologies and disciplines and their importance to the development of genomics as clinically useful [2–4].

Oral health is of no exception when it comes to the important role of genes in function and is expected to benefit from the scientific foundation and resultant clinical applications of genomics [5–8]. Although the exploration of gene-based mechanisms in dental medicine is in its early stages, gene variants are being investigated for association with caries development, [9, 10] enamel formation, [11] and gingivitis and periodontitis [12–21]. A recent study in twins by Rintakoski and colleagues [22] includes a summary of the key research linking genes and oral disease. Among the clinical applications of genomics to oral health are pharmacogenomics and the prediction of patient response to medication; determining whether a patient is susceptible to being in a pro-inflammatory state, which promotes periodontal disease among other chronic diseases; predicting risk of caries formation; and nutritional genomics and its promise of matching diet and lifestyle choices to the

underlying genotype of the individual in order to better manage existing chronic disease and prevent future disease.

Over the past decade, leaders in dental education have realized that genomics and molecular biology would need to be incorporated into dental practice and began to assess the preparation of dental professionals in these areas [23–26]. Behnke and Hassell [26] evaluated the genetics education requirements for admission into and graduation from dental schools and dental hygiene programs during 2003–2004. They found that none of the dental hygiene schools required a course in genetics for entry nor included one within the curriculum. Of the 54 dental schools, only one required a genetics course prior to entry and six had a formal, required course in genetics within the curriculum. In 2008, one of the three reports from the "New Models of Dental Education" study, funded by the Josiah Macy, Jr. Foundation, addressed genetics and its implications for clinical practice [5]. In this report, the panel considered the anticipated changes in dental practice and the knowledge, skills, and attitudes that would be required by dental professionals in an era of genetics and molecular biology. The report acknowledged the challenges of integrating these disciplines into the typically dense dental education curriculum and offered educational strategies for consideration. Despite the challenges, the fundamental role of genes in health and disease mandates the development of new knowledge and skills for dental professionals who can look forward to an expanded role in caring for the whole patient.

This chapter will provide the fundamentals of genomics, pharmacogenomics, and nutritional genomics and their anticipated applications to oral health and dental medicine.

Genomics

Because the information encoded within our genes is directly linked to our functional outcomes, we now realize that it's important to understand gene-protein-function connections at the molecular level. This section provides a brief overview of the key aspects of how the genes direct the operation of an organism and how information from the environment communicates with the genes. This overview provides the background for understanding the utility of genomic applications, particularly pharmacogenomics and nutritional genomics, to dental medicine.

The Role of DNA

Deoxyriboncleic acid (DNA) encodes the genetic information of all living organisms. That such a chemically simple molecule can contain sufficient information for operating a living organism and that its expression is both carefully controlled and exquisitely responsive to environmental signals is a topic that has fascinated scientists for over 60 years. The molecule itself consists of two strands of nucleotide building blocks consisting of only three components: phosphorus, the 5-carbon sugar deoxyribose, and one of four nitrogen-containing bases: adenine (A), cytosine (C), guanine (G), or thymine (T). This foundational unit of DNA is called a "nucleotide." To form each strand, nucleotides are covalently attached end-to-end in a linear arrangement, with the two strands being held together by complementary base pairing to form a double helix resembling a spiral staircase that winds upward in a right-handed direction. The sugar-phosphate moiety forms the railings of the staircase, with the bases on the inside forming the steps. The bases are held together by weak hydrogen bonds between complementary bases, with A pairing with T and G with C.

It is this linear sequence of bases that encodes the information that directs the synthesis of each of the proteins that does the work of the cells, thereby providing the organism with its functional

abilities. This information is decoded in a complex but stepwise manner. It's first transcribed from the DNA into messenger RNA (mRNA), a single-stranded molecule similar to DNA with ribose as the sugar and the base uracil (U) replacing thymine (T). DNA serves as a template for RNA polymerase to transcribe the DNA into mRNA. As with DNA, complementary base pairing directs the order of the bases of the growing mRNA strand, with the adenine (A) of DNA pairing with the uracil (U) of the mRNA. In humans and other higher organisms, the base sequence of DNA does not translate directly into the amino acid sequence of the protein and must first be processed to remove nucleotides not required for protein synthesis. Once processed, the mRNA is ready for translation into protein. Each set of three nucleotides in the information portion of the mRNA is a "codon" and corresponds to a particular amino acid, which during the translation process will be covalently connected in the correct order to yield the final protein structure. Proteins function in myriad ways: as enzymes, receptors, transporters, regulatory molecules, communicators and, in some instances, hormones. The protein's function is directly related to its amino acid sequence, which determines its molecular folding and, thus, its activity. It's easy to see the implications of an error in any step of this complex process. Introducing even a single alteration in the nucleotide sequence of DNA can potentially alter the amino acid sequence, the protein's conformation and, thus, the function of the protein.

The total DNA contributes to the individual's genotype; the outcome of the expression of the DNA into protein and function defines the phenotype. The genotype is essentially constant throughout one's lifetime due to the stability of the DNA, but the phenotype can vary considerably since the expression of the DNA is subject to influence from a number of environmental factors.

Genes and Their Expression

A gene is a sequence of nucleotides in DNA that contains the information for synthesizing a protein. Data from the Human Genome Project suggest that humans have approximately 20,500 genes [27]. Genes have a characteristic architecture with three major regions: the regulatory region that controls how and when the encoded information is expressed, the promoter region to which the RNA polymerase attaches to begin transcribing the gene into mRNA, and the coding region that generates the amino acid sequence of the protein.

The regulatory region is of particular interest because of its ability to control gene expression and because it's here that environmental factors communicate with the organism at the molecular level. Within the DNA sequence that forms the regulatory region of a gene are specific sequences that serve as "response elements." Specialized proteins called "transcription factors" bind to the response elements and change the conformation of DNA, which allows or prevents RNA polymerase from binding to the promoter region and initiating transcription and, thus, gene expression. Transcription factors can have multiple binding domains. One domain binds to the response element but additional domains can bind small molecular weight ligands, such as nutrients, as well as other transcription factors. Depending upon the particular gene, a multimeric regulatory molecule may be required before the transcription factor complex is "active" and able to influence gene expression. In this way a gene's expression is controlled in response to signals from the environment surrounding the cell. These signals may be transmitted by environmental toxins, xenobiotics ("new-to-nature molecules"), or naturally-occurring components within food, either conventional nutrients, phytonutrients, or other molecules in food that find their way intentionally or unintentionally into the food supply. Such molecules are called "bioactive food components" or, simply, "bioactives."

The processes by which these environmental factors convey their message to the genetic material are complex in execution but elegantly simple in concept. In general, small lipophilic ligands can penetrate the cellular and nuclear membranes and interact directly with transcription factors that in

turn bind to DNA and effect changes in gene expression. For example, omega-3 and omega-6 fatty acids serve as ligands for peroxisome proliferator activated receptors (PPAR), a transcription factor that regulates the expression of the information from a number of genes. Larger, less lipid-soluble ligands bind to cell surface receptors and elicit signal transduction, a cascade of reactions that results in one or more transcription factors binding to DNA and influencing gene expression. An example of this type of communication process occurs with the flavonoid class of phytochemicals, which binds to cell surface receptors, elicits signal transduction, and results in activation of various transcription factors such as nuclear factor kappa beta (NFkB) that in turn controls expression of a number of genes that contribute to the inflammatory and innate immune responses. Thus, by being able to sample the composition of the environment in which they exist and respond accordingly, organisms are able to adapt in beneficial ways that may increase their "goodness of fit" to their environment and improve their survival and reproductive potential.

Alterations to DNA: Changes in Chromosome Number or Structure

Although the focus of this chapter is on molecular genomics, the impact of changes to chromosome structure should be noted because such changes can ultimately impact DNA and its translation into the proteins needed for function. Chromosomes can be thought of as a packaging mechanism by which the large amount of DNA is packed within the microscopic nucleus. A chromosome represents a linear sequence of DNA nucleotides, with each gene and each nucleotide within that gene having a specific "address" on a particular chromosome. Should the normal number of copies of a chromosome or a chromosomal region be increased or decreased, the amount of information available is altered, which can result in more or less of a protein being produced. For the most part, alterations in the amount of genetic material are not well accommodated and these conditions typically lead to serious dysfunction/disease and often death. Similarly, breakage can occur in one or more chromosomes so that material is lost or its location changed (the "sticky" ends of broken chromosomes can append to another chromosome or the broken section can invert and insert "backwards" into the same location). When transcription of this rearranged DNA occurs, the information is often nonsensical, critical proteins are not made, and function is impaired. Such changes in chromosome number or structure are referred to as "chromosomal abnormalities" and will be seen in dental practice because individuals with these aberrations often have oral problems that can range from tooth morphological abnormalities to cleft palate to chewing and swallowing problems. The review by Jafarzadeh on taurodontism may be of interest in that it is often seen with Klinefelter syndrome (more than one X-chromosome in males), the most common chromosomal abnormality in humans [28, 29].

Alterations to DNA: Changes in DNA Sequence

There are two major classes of alterations to DNA at the molecular level, both of which can influence function: changes to the nucleotide sequence of DNA (called "genomic changes") or chemical modification of either the proteins associated with DNA or the DNA molecule itself (called "epigenomics changes"). Epigenomic changes do not alter the nucleotide sequence of DNA and, thus, the information encoded within that sequence is not affected. Instead such changes affect gene expression. Epigenomics will be discussed shortly.

Changes to the DNA nucleotide sequence itself can occur at any point along the DNA. The functional impact of a change will depend upon which region of the gene is affected. In general,

changes within the coding region impact the function of the protein and changes within the regulatory region impact the expression of the gene. Altering expression can impact the amount of protein produced but also affect the timing of production, which can have negative implications for normal development and for disease susceptibility. Thus, the functional impact of a change to the DNA sequence can be quite complex depending upon whether protein structure is affected, protein expression is affected (quantity and timing), and the nature of the environmental milieu bathing the genes.

When the change in nucleotide sequence occurs within the regulatory region, the impact is on the production of the protein rather than on its structure and function. Depending upon the specific nucleotide change, transcription may be increased ("up-regulated") or decreased ("down-regulated"). This change may be negative, neutral or positive, depending upon whether transcription is increased or decreased. For example, it's possible that a nucleotide change could affect the response element in the regulatory region or the transcription factor domain that binds to the response element, thereby changing the dynamics of gene expression. The altered binding may allow the gene to be constitutively expressed (always "on"), to be unable to bind appropriately and thereby unable to be expressed (always "off"), or any level of expression in between these two extremes, depending upon how strong the impact of the alteration is on expression. Changes to the ligand-binding sequence can alter the responses to environmental factors, increasing or decreasing gene expression. These nuances may seem minor but they have major impact when the outcome is whether or not a critical gene is expressed. For example, constitutive expression of the *IL1 or IL6* genes, which are major determinants of susceptibility to chronic inflammation, could have far-reaching effects on an individual's health, including predisposition to gingivitis and other periodontal diseases.

Further, a change in the regulatory sequence may occur in a gene that also contains a change in the coding sequence. In other words, it's possible to have more than one change within the same gene (each nucleotide in the gene presents an opportunity for change).

Alterations to DNA: Changes in the Epigenome

The second type of alteration to DNA is the basis for the developing field of epigenetics/epigenomics, which here will be referred to for simplicity as "epigenomics." First consider that there are approximately 3 billion DNA nucleotides in the human genome that are housed within the microscopic nucleus. A packaging mechanism is needed, similar in concept to the need to condense computer data in order to fit large amounts onto a hard drive. Chromosomes serve as the packaging mechanism for higher organisms. Humans have 23 pairs of distinct chromosomes, one member of each pair contributed by each parent. Important components of the condensation mechanism are histones, positively charged proteins that assemble into sets of eight units called "nucleosomes." Similar to winding thread around a spool, DNA winds around each of the nucleosomes and a highly condensed structure called "chromatin" results, the complex of DNA-histone.

When DNA is condensed, it is not available for transcription. In order to be physically accessible to enzymes that can duplicate or transcribe the DNA, chromatin must be relaxed. Condensation and relaxation are controlled through covalent attachment of chemical groups, such as acetyl groups, to the histone proteins. In the absence of acetylation, chromatin is condensed. Addition of acetyl groups through acetylation relaxes the DNA so that it can be transcribed and the information in the genes expressed. Deacetylation closes the chromatin and impedes transcription.

There is an additional level of modification that further regulates DNA expression and that is the covalent attachment of specific chemical groups, such as methyl groups, directly to the DNA. In general, methylation of DNA silences its expression; demethylation permits expression. This system is superimposed onto the DNA sequence to provide an additional level of control of gene expression

and has been likened to Nature's pen-and-pencil set for its ability to be modified by diet and other environmental influences [30].

Further, epigenetic markings (such as the methyl profile or "signature" of DNA) can be inherited and are influenced by the markings of ancestors at least two generations removed from a current generation. In other words, the diet and lifestyle choices of our grandparents influence our functional abilities [31, 32]. Predictably, nutrition will factor prominently into our understanding of the connection between our genes and our functional abilities and will be a critical determinant of our being able to reach our full genetic potential.

More questions than answers exist concerning epigenomics and its impact on human health. We do know that epigenomics is of major importance in development and differentiation because the turning on and off of genes and the timing of this activity is critical for these processes. Alterations in the developmental program can have profound effects on a fetus. Although it is possible that an alteration may provide an evolutionary advantage to an organism, more examples of detrimental effects are known at this time than beneficial ones. Similarly, in carcinogenesis there are genes (oncogenes) that, when expressed, promote uncontrolled growth and other genes (tumor suppressor genes) that keep such growth under control. Inappropriate methylation of either type of gene could lead to carcinogenesis. For additional information about epigenomics, see recent overviews by Hirst and Marra [33], Villagra et al. [34], Rakyan et al. [35], Park et al. [36], Romagnolo et al. [37] and Stein [38].

Genetic Alterations and Function at the Molecular Level

Clearly changes in DNA or in its epigenomic "markings" are important to our ultimate functioning and to our health and disease susceptibilities. The terminology for such changes is in transition. In this section, the spectrum of biological outcomes resulting from changes in DNA sequence or epigenomics markings is explored. An attempt is made to convey understanding within the present context and to point out limitations to current terminology and how it's likely to change as both knowledge and technology expand. A number of familiar disease states are used to illustrate how understanding of "genetic disease" is undergoing major revision as the molecular basis for disease is now being explored. The important point is that the extent to which function is influenced by changes to genes can that vary from severe to mild depending on the role of the gene and where within the gene the change occurs, which may affect expression of the gene or the structure of the protein if the gene is expressed. Further, for many genes, a change may have no effect on function unless the gene interacts with one or more environmental factors. This latter mechanism seems to occur commonly and to be associated with chronic diseases.

Historically, linking a change in DNA to a change in protein expression or function and ultimately to a disease was a major breakthrough in understanding the critical role of genes in health and disease. Such diseases were originally called "genetic diseases" and thought to be a distinct type of disease that occurred rarely but was typically severe in its impact, which manifested early in life. When such changes were in genes and proteins involved in metabolic reactions, the disease was called an "inborn error of metabolism."

Traditionally the term "mutation" was used to describe a rare change in the DNA sequence, which typically resulted in a detectable disease condition. However, as technology improved, more subtle subclinical effects were detected. In addition to the severe forms of disease, milder forms could be traced to a change in the same gene and, ultimately, technological advances allowed detection of changes that led to increased susceptibility but not necessarily to overt disease. These types of mutations came to be called genetic "variations" and the genetic basis ascribed to "gene variants" in which the DNA nucleotide sequence had been altered. In many cases only when the

variation interacted with specific environmental factors did disease arise. The term "single nucleotide polymorphism" (SNP, pronounced "snip") referred to those variations in which a single nucleotide change occurred and the variation was frequent in the population (initially defined as occurring in >1% of a population). More recently, alterations that change the epigenetic signature of the DNA have expanded the lexicon. The lines between the mutations and genetic variations have begun to blur as technological advances have enabled the discovery that many diseases have a spectrum of symptoms, ranging from severe to mild, regardless of the specific type of change involved or whether it occurs rarely or frequently within a population. The key defining characteristic appears to be the impact of a genetic alteration on functional outcomes.

Cystic fibrosis, sickle cell disease, and the inborn error of metabolism phenylketonuria are classic examples of rare single gene disorders that cause disease and are considered to result from "mutations." Historically, when cystic fibrosis was diagnosed, genetic analysis confirmed the presence of two copies of a mutation in the cystic fibrosis transmembrane conductance receptor gene (*CFTR*). Over 1900 mutations have now been identified in this one gene, some of which lead to severe symptoms and others to a mild condition [39]. The changes have occurred in the same gene in all cases, but the nucleotide involved and the impact on function is the determining factor as to the severity of the outcome. If one of these changes in the *CFTR* gene is found to be common within a population, it might now qualify as a "gene variant" rather than a mutation.

Sickle cell disease also offers a dramatic example of the effect of a change in a single nucleotide on function and health. The substitution of a T for an A in the *HBB* gene sequence that encodes the beta-globin subunit of hemoglobin leads to the neutrally charged amino acid valine replacing the negatively charged glutamic acid. The resultant conformational change to the peptide decreases its ability to bind oxygen. Those with two copies of this alteration exhibit a sickled shape to their red blood cells and the painful symptoms of sickle cell disease under conditions of low oxygen tension. Further, those with a single copy have an intermediate phenotype, sickle cell trait. Not only does the actual change and its impact on function define the phenotype but the number of copies of the change (gene dosage effect) is also an important determinant of the biological outcome. Molecular and clinical details of this disorder can be found in reviews by Frenette and Atweh [40] and, more recently, by Steinberg and Sebastiani [41].

The inborn errors of metabolism (IEM) in which the impact is nutritionally related are similar in concept to cystic fibrosis and sickle cell disease in that they occur rarely but yield a detrimental functional impact. The classic IEM example is phenylketonuria (PKU) in which a single nucleotide change within the *PAH* gene leads to the absence of phenylalanine hydroxylase. This change prevents the conversion of the amino acid phenylalanine to tyrosine and creates a life-threatening deficiency in tyrosine if it is not supplied in the diet. It also leads to an accumulation of phenylalanine and its metabolites, such as phenylpyruvate, which can be detrimental to the developing brain. An overview of *PAH* and its relationship to PKU from an historical and contemporary status is provided by Zurfluh et al. [42].

As knowledge of molecular nutrition and molecular genetics increases, multiple phenotypes for PKU and other IEM have been detected. The review by Gersting et al. [43] of known *PAH* mutations suggests that a variety of types of changes is represented, all impacting the ability to ultimately generate tyrosine from phenylalanine. The spectrum for phenylalanine tolerance varies from PKU, which requires a phenylalanine-restricted diet, to mild hyperphenylalaninemia that does not require dietary restriction. This phenotypic spectrum appears to mirror the impact of the various changes on function and is emerging as a common theme as knowledge of the molecular basis for disease expands.

An example of a mutation that would clearly be labeled a "gene variant" is the 677C > T change in the *MTHFR* gene. This gene codes for the enzyme methylenetetrahydrofolate reductase that converts folate into its 5-methytetrahydrolfolate active form, which in turn is involved in the conversion of homocysteine to methionine as well as supplying other metabolic reactions with methyl groups [44]. Insufficient 5-methyltetrahydrofolate can lead to elevated levels of homocysteine, which

have been linked to increased risk of cardiovascular disease [45]. A cytosine-to-thymine change at nucleotide 677 of the DNA leads to an enzyme that is impaired in its ability to supply adequate levels of active folate. With this particular nucleotide change, the impairment is not sufficient in itself to cause dysfunction and a disease state typically does not manifest unless the individual consumes insufficient folate. Dietary folate insufficiency, however, is suspected by the World Health Organization of being a common global problem [46].

Virtually all of the chronic diseases that plaque modern society, such as heart disease, cancers, diabetes, inflammatory disorders, osteoporosis, and obesity, are caused by changes that can be classified as genetic variations. A change in a single nucleotide may occur along with other single nucleotide changes that alone are minor in functional impact but increase risk in the aggregate or may interact with one or more environmental factors to promote dysfunction and disease. Additionally, changes impact the epigenetic markings of DNA and chromatin and interfere with access to the expression of one or multiple genes. Most likely these changes will also be found to fall at both ends of the mutation versus variation spectrum and points in between.

It should be apparent that the clear distinction between mutation and variation is becoming murkier, not clearer, as knowledge expands. Even the classic disorders such as sickle cell and the IEM are now known to have a spectrum of phenotypes that can be correlated with particular genetic changes and their impact on function. Clarity will not likely be achieved until large numbers of genetic alterations have been studied within multiple genes and the environmental triggers have been identified. The key points here, though, are that a single nucleotide change can have devastating consequences to function or may be silent unless interaction with an environmental trigger occurs. Further, genetic disease appears not to be a type of disease but underlies essentially all disease, with the severity reflecting the impact of the genetic alteration on function. Similarly, the earlier thinking that classified people as "normal" or "abnormal" with respect to a disease is giving way to an understanding that each person is genetically unique. Ultimately clinicians will need to integrate this new shift in thinking into every aspect of patient care, which includes dental medicine. Genomics will be incorporated into diagnosing oral disease, predicting susceptibility to developing cavities, defining a patient's drug-metabolizing capacity, and determining dietary requirements.

Detecting Alterations in the Genome

Genomics and its related -omic disciplines have the potential for fostering the development of personalized healthcare, in which the genetic makeup of each individual can guide health-related decision making. In order to realize this potential, there must be a way to analyze the DNA sequence and its epigenetic markings. The basic technology for genetic testing has been in use for decades and new refinements and enhancements are continually being added. What lags at this point is the research foundation for associating phenotype with genotype. That is, we are in the early stages of associating defined gene changes (mutations or variations or epigenetic markings) with specific disease states and with particular gene-environmental factor interactions that can convert susceptibility into disease or offer effective intervention approaches. The following section provides an overview of the ongoing importance of using family history and genetic analysis to detect disease susceptibility.

Family History

Family history has long been used to predict the potential disease susceptibility of patients by detecting patterns of inherited disease within their extended family. Although there are a number of

limitations to family history as a predictor of disease, this method will continue to be of primary importance until the point at which it becomes economically feasible and clinically relevant to assess the genome of humans directly.

In addition to it being time-consuming to gather genetic history information and many clinicians are not trained in producing and analyzing the resultant pedigrees, there are other important limitations. Family history is most useful for those diseases that result from genes that are inherited by a recognizable mode of inheritance (Mendelian or mitochondrial) and have a sufficiently strong impact on function that when present they are detectable in the phenotype. Additionally, family history is only as accurate as the information that goes into it. Many individuals do not know their family history; many families do not openly discuss topics that are relevant to family history, such as abortions, miscarriages, incest, marriage among close relatives, and family members with mental health conditions. Others are adopted and their biological history may not be known. To the extent possible, the clinician should strive to obtain a family history that covers at least three generations. Numerous forms for collecting family history exist. The U.S. Surgeon General has recently initiated a nationwide drive to help people become more aware of their family history and to document the information to be shared with their various healthcare providers (www.hhs.gov/familyhistory). Family history provides a useful service in raising awareness of inherited disorders that patients may not realize exist within their family but is limited by its inability to detect many of the chronic disorders that providers routinely encounter today.

Genetic Testing

Genetic testing is increasingly being used in healthcare settings. The type of testing may be chromosomal analysis to detect changes in number or structure of the chromosomes or DNA analysis for detecting particular mutations, SNPs, epigenetic modifications, or changes in the number of copies of a gene.

Considerable research attention is being directed toward identifying SNPs associated with a variety of chronic diseases and developing genetic tests. Several tests are presently available for use by providers and consumers. This application of genetic testing is in its infancy but holds considerable promise. The technology used for this type of testing is sound as it is the same as that used for decades in research and clinical labs to test for inborn errors of metabolism and other single gene, rare disorders. The limitation at present is the paucity of research validating the associations between particular SNPs and susceptibility to disease and the associations between particular interventions and improved disease management or prevention. However, genetic testing is expected to be an increasingly fruitful approach as research continues to move forward, providing a much-needed mechanism for identifying disease susceptibility that often cannot be determined through family history. Further, through genetic testing, disease susceptibility can be detected prenatally and can be used to guide diet and lifestyle decisions early in life, with the goal of preventing disease from developing.

Genomic-Related Applications to Oral Health and Disease

The fundamental relationship among genes, gene alterations, protein, and biological function at all levels predicts that gene-related principles will become increasingly integrated into healthcare, including oral healthcare [23–26]. A heightened awareness of the value of including the broad scope of genomics in the dental school curriculum has been apparent during the past decade [5, 26]. This

section provides examples of how genomics, pharmacogenomics, and nutritional genomics are presently being applied clinically.

Genomics

Genetic analysis has long been used clinically to confirm a diagnosis. Once the gene-disease association has been established and the more common mutations identified, it became possible to confirm that an individual has a particular genetic change within a gene known to be responsible for the disease. Clinical applications of genomics also include distinguishing among similar tumor pathologies to arrive at an accurate diagnosis, determining the molecular nature of tumors for diagnostic and treatment purposes, monitoring prognosis and early treatment failure, and identifying microorganisms and viruses that may be causative agents in disease.

A particularly active research area has been the application of genomics to various aspects of cancer therapy. Notable successes include tailoring treatment to the genetic characteristics of the cancer or to the individual's genotype as well as detecting early treatment failure [47]. For example, genomic information has been critical in successful outcomes achieved with the topoisomerase-1 inhibitor irinotecan (Camptosar®) for metastatic colorectal cancer, [48, 49] the tyrosine kinase inhibitor imatinib (Gleevec®) for chronic myelogenous leukemia, [50, 51] and trastuzumab (Herceptin®) for breast cancer [52].

Using genomics to predict future disease is expected to be a major application, with sample collection being noninvasive and as simple as a buccal swab or saliva sampling [53, 54]. Detecting potential susceptibility to disease can help the patient prevent disease as well as alert family members who are at risk and educate them as to their options for disease prevention. Once the specific mutation is known, family members can be tested to see whether they carry that same mutation. This procedure has been used for several decades for the inborn errors of metabolism, cystic fibrosis, sickle cell disease, and numerous other well-characterized single gene disorders. The limitation of this approach is that a negative result can be equivocal. If an individual tests negative for known mutations, it is still possible that the individual has a mutation in that gene but that the specific mutation has not yet been identified (and, thus, would not be detected by current genetic tests).

This scenario is, unfortunately, common at present because genetic technology primarily identifies the more common mutations and tests for their presence. Two enhancements are expected to solve this limitation in the near future. One is the ongoing identification of new mutations by researchers. Another is the increasing use of DNA sequencing to detect genetic changes. In DNA sequencing, the nucleotides within the gene are identified as to composition and order and compared against a DNA sequence that research has shown to be the gene sequence that commonly occurs in healthy individuals. Ultimately the entire genome will be routinely sequenced and analyzed against sequences typical of healthy people in order to detect where an individual differs from the healthy state. The methylation status of the DNA is an additional important characteristic and can also be detected using current technology.

Recent reports of genomic approaches related to dental medicine include a diverse set of applications. Analysis of the amelogenin genes is a useful laboratory procedure in archeology, forensic dentistry, and research [55–57]. The analysis can be used for sex identification as well as for quality control purposes to ensure that sample mix-up has not occurred. DNA sequencing is used to confirm the occurrence of particular diseases within a population, such as the recent identification of Shwachman-Diamond syndrome in a population in which this disorder was not thought to occur [58].

Clinical applications to dental medicine are equally diverse and are best characterized as being in the early stages of development. Detection of genetic alterations can be used for a wide spectrum of applications, from distinguishing pathologically similar disorders to predicting susceptibility to

various oral diseases, such as caries development, [59] periodontal disease, [60–63] and oral cancers [64, 65]. As has been noted for oncology in general, genetic analysis is being applied to oral oncologic disorders for accurate diagnosis, treatment selection, and monitoring treatment failure. For example, in the pathologically similar epithelial odontogenic tumors such as ameloblastomas and clear cell odontogenic carcinomas, DNA analysis is used to aid in accurate diagnosis [66].

Genomics can also be helpful for identifying the underlying molecular basis for noncancerous disorders. Amelogenesis imperfecta (AI) is a group of disorders that involve changes to at least 5 genes involved in enamel formation that give rise to at least 14 subtypes [67–69]. Genomics is helpful in accurately indentifying the underlying molecular basis for AI as well as in predicting the risk to family members [70–79]. The various types of AI are inherited in an autosomal dominant, autosomal recessive, or X-linked recessive manner. Since these traits have different modes of inheritance, they have different predictions of susceptibility for family members, depending on the gene involved and its mode of transmission. In a recent publication, Lindemeyer and colleagues predict that classification of AI will shift from pathology-based to gene-based before long [80].

Amelogenesis imperfecta is but one of many illustrations of how SNPs will be used to predict increased risk of disease. A major application is expected to be in detecting susceptibility to caries development in children so that early preventive treatment approaches can be initiated [5, 81]. Another example applicable to dental medicine is the finding that a combination of SNPs within the alcohol dehydrogenase gene (ADH) and the methylenetetrahydrofolate reductase gene (MTHFR) is associated with increased susceptibility to oral squamous cell carcinoma when the susceptible individual consumes alcohol [82]. Early detection of this susceptibility affords the individual the choice of taking steps that could prevent the disease from manifesting.

The gene for each protein involved in the various oral diseases provides the potential for susceptibility testing once the gene-disease associations have been adequately explored. As an increasing number of gene-oral disease associations are identified and their molecular mechanisms determined, the clinical utility of predictive genomics is expected to expand considerably.

Pharmacogenomics

Pharmacogenomics focuses on the genetic basis for the patient variability in response to drug treatment. Dental practitioners may prescribe medications (1) to control pain or anxiety, (2) as part of the treatment of specific oral conditions, or (3) to eradicate or prevent infection. The agents used may include nonprescription and prescription anti-inflammatory agents, narcotics as well as various milder analgesics, antibiotics and other antimicrobials, and muscle relaxants. These agents are typically metabolized in the gastrointestinal tract and the liver in a two-phase process referred to as Phase I and Phase II biotransformation. In many cases drugs require biotransformation for biological activity, but the endproduct of this process is the generation of a metabolite that can be more readily excreted (“cleared”) from the body than the original agent.

Phase I biotransformation involves the cytochrome P450 (CYP 450) family of oxidoreductases that generate a highly reactive intermediate. The majority of drugs marketed today are metabolized by the cytochrome P450 enzymes [83, 84]. The intermediate is subsequently conjugated by Phase II enzymes, either with a glutathione moiety (via the family of glutathione-S-transferases, GSTs), an N-acetyl group (via the N-acetyltransferase enzymes, NATs), or a glucuronic acid moiety (via the UDP-glucuronosyltransferases, UGTs). Sissung et al. [85] and Pacheu-Grau and colleagues [86] provide overviews of the pharmacogenomics of drug-metabolizing enzymes in general, and Hersh and Moore [87] address adverse reactions in medications used in dentistry.

As with any gene, those that encode the major drug-metabolizing enzymes can acquire changes that can affect the activity of these enzymes and, thereby, patient response to medications. Each patient’s set

of variants within the genes that encode the major drug-metabolizing enzymes provide a personalized profile in terms of response to medications. The response can vary from beneficial to neutral to harmful, depending upon the drug and the person's gene variants. Alterations in the Phase I or Phase II genes can influence the enzymatic conversions and either enhance toxicity or decrease it. For example, lidocaine, erythromycin, and the benzodiazepines are metabolized primarily by cytochrome P450 3A4. Impaired enzymatic activity will result in unmetabolized drug. Not only is this individual not receiving the drug effect intended, the unmetabolized molecule can accumulate and lead to toxicity. If Phase I activity were normal but Phase II impaired, the drug would still not be fully converted to its active metabolite so tissue levels would not reach the required concentration of drug. Additionally, the slow Phase II reaction causes accumulation of the reactive intermediate that, as a reactive oxygen species (free radical), is potentially harmful in itself. Fortunately, nutrition is an important component in the optimal functioning of Phase I and II enzymes from a number of standpoints and can be used to improve these reactions, as will be discussed in the "Nutritional Genomics" section.

There are other enzymes of importance beyond the Phase I and Phase II systems, such as the catechol-O-methyltransferase encoded by the *COMT* gene and the enzymes that provide defense against free radicals, such as the superoxide dismutases (SOD). The three main SOD enzymes—SOD1, SOD2, and SOD3—are slightly different in that they are coded for by distinct genes, differ in their coactivator molecules, and are located in different cellular compartments or in the extracellular matrix. The COMT enzyme is important in estrogen metabolism but is also involved in an individual's sensitivity to pain [88].

Although it is common to speak of adverse drug events as though the drug were the problem, the underlying basis for a patient's response is not necessarily something adverse about the drug but almost certainly an inappropriate match between the drug and the patient's genes that encode the drug-metabolizing enzymes. At a population level, there is typically a spectrum of responses to a particular drug at a specific dose. Often the response for an individual in that population is reproducible for a given drug taken at a given dosage because the response reflects that person's gene-directed ability to metabolize the drug. In the future it is likely that dental professionals will have as part of the dental record the genetic profile of a patient's drug-metabolizing enzymes, which can be helpful in selecting appropriate medications.

Nutritional Genomics

Nutritional genomics is a specialized application of genomics to diet- and lifestyle-related disease, which includes the majority of the chronic disorders of modern societies. At this point in the field's evolution, research is primarily focused on discovering the gene-disease-diet associations. With that knowledge and appropriately validated laboratory analyses it becomes possible to devise clinical applications of nutritional genomics. The expectation is that the field will enable improved management of existing diet-related disease as well as prevention of future disease [89].

Nutritional genomics describes the field itself. *Nutrigenetics* is the subdiscipline concerned with the effect of an individual's genetic variations on the ability to function within the environment in which the individual exists. Nutrition is an important component of an individual's overall "environment." An individual with a genetic alteration in a metabolic enzyme that reduces the production of an essential nutrient will likely suffer negative consequences if that nutrient is not consumed through the diet. Conversely, individuals may have a genetic alteration that impairs their gut and liver detoxification reactions. If toxin-free foods are not available to them, these individuals can be at increased risk of accumulating higher levels of toxins than their bodies can protect against, which can lead to impaired function of the liver as well as that of the mitochondria in various tissues throughout the body.

Nutrigenomics concerns the effects of diet and lifestyle on gene expression, which includes how diet affects the epigenetic signature of the genome (*nutritional epigenomics*). Food contains bioactive components that can influence the extent of gene expression, even preventing expression altogether. These bioactives may be traditional nutrients, such as vitamins, or nontraditional nutrients, such as phytonutrients. They may also be potential toxins that enter the food supply. An example of a bioactive that has positive implications for many chronic disorders is the essential fatty acid omega-3. This bioactive appears to modulate the expression of genes that promote inflammation, such as *PPARG* (peroxisome proliferator-activated receptor gamma), *IL1B* (Interleukin 1), *IL6* (Interleukin 6), and *COX2* (cyclooxygenase-2) genes [90, 91]. Another example with general application is the ability of bioactives in the cruciferous family of vegetables (the broccoli, cabbage, cauliflower family) to increase expression of genes involved in detoxification of potentially harmful molecules [92].

The communication between bioactive food components and the genetic material is an intricate web of events by which cells process the state of their environment. Signals from the environment make their way to the genetic material and affect gene expression, turning it on or off as appropriate. Environmental signals such as bioactive food components may serve as ligands for transcription factors or initiate signal transduction that ultimately results in transcription factors initiating or halting gene expression.

Conceptually nutritional genomics is similar to pharmacogenomics [93]. In the same way that genes determine drug-metabolizing capability, genes underlie the ability to digest, absorb, and use food to support health. Just as drug therapy is expected to become increasingly gene-directed, this same approach will be used to determine nutrient requirements for individuals. An important aspect of this work will be to investigate how human populations differ in their genetic characteristics (i.e., their gene variants) and to develop nutrient requirements and dietary recommendations appropriate for, first, each populations and, ultimately, each individual within a population. Attention is already being given to how dietary requirements for populations and individuals will be gene-directed and how best to stage such a significant change in approach [94]. Expect to see considerable research in the decade ahead that defines which components in food interact with the genome, the mechanisms involved, and the incorporation of this information into nutrition interventions. Numerous reviews of nutritional genomics and of its potential applications are available [95–102].

Applications of nutritional genomics specific to dental medicine have not yet been developed but three major emphases of current research will be of interest. One focus is on the role of nutrition in the Phase I and Phase II detoxification reactions. The second is on early detection of patient susceptibility to inflammatory disorders, such as periodontal disease. The third focuses on defining the microbial community within the oral cavity, known as the "oral microbiome."

Detoxification and Nutrigenetic Testing Applications

As explored in the Pharmacogenomics section above, the Phase I and Phase II detoxification system is a major pathway for metabolizing pharmaceuticals [103, 104]. The enzymes involved in Phase I are encoded by the *CYP* genes and those of Phase II by the *GST*, *NAT*, and *UGT* genes. Two aspects will be of interest to dental professionals from the standpoint of nutritional genomics. One is the emergence of nutrigenetic testing for the major *CYP* and *GST* genes and the association of nutrition approaches with particular gene variants. The other is the important role of nutrition in supporting the liver in general and the Phase I and Phase II reactions in particular.

In addition to metabolizing drugs, the enzymes produced by the *CYP* genes metabolize a host of other potentially toxic molecules that enter the body [105, 106]. As an example, the enzymatic product of the *CYP1A1* gene is an important defense mechanism against polyaromatic hydrocarbons and heterocyclic amines as well as excess estrogen exposure. The enzyme encoded by the *CY1A1* gene

also metabolizes residues from chargrilled meats and other proteins cooked at high heat for prolonged periods [107]. The enzyme encoded by the *CYP1A2* gene metabolizes carcinogenic arylamines from food as well as the majority of the caffeine ingested [108–110]. Variations in these genes can potentially change enzymatic activity. A decrease can lead to accumulation of nonmetabolized toxin, ultimately interfering with various aspects of metabolism. An increase could be beneficial if Phase II activity is sufficiently robust to conjugate the elevated load of reactive oxygen species (ROS) generated. These influences of variants in the Phase I genes not only affect the metabolism of medications used by dental professionals but also impact the general health of the patient. For example, variation in the CYP1A2 has been linked to increased risk for heart attack as well as for developing hypertension [111, 112]. Further, when the total load from medications and environmental exposure exceeds the body's enzymatic detoxification capacity, the patient is at risk of adverse events. Thus it is potentially helpful to the clinician to know the patient's genetically-determined capacity for detoxification as well as the current environmental load prior to prescribing medications.

The most commonly available nutrigenetic tests for Phase II metabolism center around the *GST* gene variants that conjugate the ROS intermediate with glutathione. Three isozymes of this sulfotransferase have been identified, encoded by the *GSTM*, *GSTP*, and *GSTT* genes, respectively. Variants that decrease Phase II activity have been identified for each of these genes [113–116]. Nutrigenetic analysis of Phase I and II variants helps predict the patient's ability to metabolize toxins and suggests appropriate diet-and-lifestyle support. For example, patients with a variant that leads to impaired *CYP1A1* activity will benefit from reducing their exposure to industrial pollutants, tobacco smoke, automobile exhaust and other airborne pollutants, and avoiding chargrilled meats. Women with a *CYP1A1* variant that increases activity would factor that information into their decision to use estrogen medications in light of the increased risk for developing breast cancer [117]. Those with variants in *CYP1A2* will want to minimize caffeine consumption. Similarly, those with a variant in one of the *GST* genes can increase the activity of this family of enzymes by consuming glucosinolates present in cruciferous vegetables. These bioactives can increase the expression of the remaining *GST* genes, essentially compensating for the presence of the gene variant [118].

Additionally, nutrition provides vital support for the liver where much of the detoxification activity occurs. Nutrients known to be required for Phase I activity include vitamins C, B2, B3, B6, B12, folate, glutathione, branched-chain amino acids, and various flavonoids. Nutrients that support Phase II include glycine, taurine, L-glutamine, and various sources of sulfur, such as L-cysteine, N-acetyl L-cysteine, and L-methionine. The enzymes involved in controlling levels of reactive oxygen intermediates generated by Phase I activity are dependent on cofactors such as selenium, copper, zinc, and manganese. Maintaining the body's acid-alkaline homeostasis through dietary choices is particularly important for detoxification [119]. For a comprehensive treatment of detoxification and biotransformation in the liver and the gut and the details of Phase I and Phase II reactions, see Liska et al. [103]; Jeffery [120], [121]; Lampe [122]; Yager and Davidson [117]; and Lampe [123].

Obviously, the translation of genetic variation into diet and lifestyle recommendations is in its infancy, but the potential is evident. With the understanding of how the components in food interact with the genes it becomes possible to use food judiciously to compensate for genetic limitations. This practice has actually been long carried out to use the diet to supply metabolites that humans are unable to synthesize due to genetic limitations of the species, such as supplying dietary vitamin C, essential amino acids, and essential fatty acids.

Inflammation and Nutrigenetic Testing Applications

Periodontal disease is characterized by chronic inflammation of the oral cavity and is associated with to a number of negative consequences, from bone loss and its sequelae to cardiovascular disease and cancer. The presentation of periodontal disease is variable and generally agreed to be linked to host-

based risk factors [124, 125]. Primary among those factors is the genetically-determined inflammatory capacity of the individual and its interaction with environmental factors, including the infectious bacteria that comprise the oral biofilm. Until recently, the diagnosis of periodontitis and the selection of therapeutic approaches have been based on the inflammatory features of the clinical presentation. The advent of molecular dental techniques and expanded knowledge of the underlying mechanisms at the biofilm-gingival interface are enhancing diagnosis and treatment [126]. In particular the biofilm composition, the nature of the host inflammatory and immune responses, the individual's inflammatory capacity, and the contribution of genotype to the clinical presentation of periodontitis as well as to the therapeutic response are providing insight into effective approaches to patient care. The contributions of specific genes and epigenomic processes are under investigation in a number of research laboratories and will likely challenge researchers for years to come [127, 128]. Among the expected applications is the use of genetic analysis to provide a new system for classifying periodontal disease as well as patient susceptibility and likelihood of effectiveness of treatment [124].

However, a more immediate application may be based on existing knowledge of the host inflammatory response, with the potential for detecting the genetic susceptibility of a given individual to inflammatory disorders, such as gingivitis and periodontitis. Accumulation of bacteria on the surface of the teeth and in the gingival sulcus leads to dental plaque at the gingival margin and proximal surfaces, which can promote gingival inflammation. Left untreated, periodontitis may result. In periodontal disease, the inflammatory response may expand to involve deeper periodontal tissues and progress to a chronic condition that is associated with pain as well as the potential for tooth loss. Sustained inflammation may also lead to additional chronic disorders such as cardiovascular disease, oral cancer, and bone resorption. Identification of those susceptible to a proinflammatory state could be helpful in early intervention and in effective use of nutrition approaches.

Inflammation increases the energy and nutrient requirements needed for the production of the acute phase proteins, inflammatory mediators, and antioxidant defenses involved in the inflammatory response as well as for tissue repair. More specifically, the individual's genotype affects the specific nutrient requirements for that individual and the susceptibility to inflammation, bone fragility, oral cancer, and numerous other disorders that can develop within the oral cavity. Additionally, the individual's genetic makeup interacts with bioactive food components and other environmental factors to alter the expression of various genes that can affect the health of the oral cavity.

For example, proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-alpha (TNFα) are known to be primary mediators of the inflammatory response [127, 129] and have been linked to periodontal disease as well as peri-implantitis [15, 18, 130–136]. Drugs that specifically block IL-1 or TNFα have been shown to decrease periodontal tissue destruction when the bacterial challenge is present [137]. Variants in the genes that code for these cytokines are being studied in order to detect individuals that overproduce cytokines and increase susceptibility to inflammatory disease, such as gingivitis and periodontal disease. Genetic testing exists for each of these variants and is expected to become clinically useful once the gene-disease-intervention studies have sufficiently established links between the variants and health outcomes.

At this time, variants of the *IL1B* gene, which encodes IL-1, are the best studied of the proinflammatory gene variants in terms of their impact on periodontal disease [22, 138–140]. IL-1 is one of the first cytokines produced in the acute inflammatory response. Certain variants of *IL1B* have been shown to overproduce IL-1 and to be associated with periodontal disease in multiple populations [141]. Elevated levels of this cytokine have also been detected in atherosclerosis and other inflammatory disorders [142]. A synopsis by Kornman et al. describes the association between IL-1 and chronic inflammatory disorders in humans as well as the impact of variants in the *IL1* gene cluster [143].

Given that genetic variations exist that result in overproduction of IL-1 and thereby increase susceptibility to developing periodontitis and other inflammatory disorders, researchers are interested in how nutrition therapy might be used to minimize the inflammatory impact on health. Among

the more promising bioactive dietary components are the omega-3 and omega-6 polyunsaturated fatty acids (PUFA) from food and dietary supplements and the association with decreased inflammation of the oral cavity. In pilot studies, omega-3 and omega-6 polyunsaturated fatty acids from food and dietary supplements attenuated oral inflammation [144, 145]. In a 5-year longitudinal study of 55 elderly Japanese men and women, Iwasaki and associates [146] found that those in the lowest tertile of intake of the omega-3 docosapentaenoic acid (DHA) had the greatest number of periodontal disease events, with a similar trend seen with the omega-3 eicosapentaenoic acid (EPA).

More recently Naqvi and coworkers used U.S. National Health and Nutrition Examination Survey data to examine whether intake of DHA, EPA, or alpha-linolenic acid (ALA), another omega-3 PUFA, was associated with decreased periodontal disease [147]. The main outcomes of this study were the findings that the higher levels of DHA consumption were associated with lower prevalence of periodontitis, that EPA showed a similar but less dramatic association, and that ALA had no effect. Further, modest levels of DHA and EPA such as those present from diet alone had the greatest effect in reducing periodontitis prevalence, which suggests that food alone may be sufficient to achieve clinically meaningful reductions in oral inflammation.

In terms of potential mechanisms by which inflammation in the oral cavity may be responsive to dietary PUFAs, studies suggest that omega-3 and omega-6 PUFA can influence cytokine gene expression and/or signaling pathways that lead to cytokine's pro-inflammatory actions [148–150]. Again, interaction of PUFA with the *IL1B* gene is the most studied of the various cytokine-producing genes at present. Transcription of the *IL1B* gene is controlled by a heterodimeric complex of two DNA-binding proteins that serve as transcription factors: the peroxisome proliferator-activated receptor gamma and the retinoic acid receptor, encoded by the *PPARG* and *RXRA* genes, respectively. The complex that activates transcription consists of these two transcription factors with their bound small molecular weight ligands. The complex binds to the appropriate DNA sequence (the response element) within the regulatory region of genes that are under the regulation of this heterodimeric complex. Omega-3 and omega-6 fatty acids serve as ligands that bind to the PPARG transcription factor and promote the conformational change that allows it to interact with the RXR transcription factor and the response elements. When the complex is appropriately bound to the regulatory region of the IL1B gene, transcription can proceed.

In addition to their ability to influence gene expression, the omega-3 and omega-6 fatty acids are precursors to anti-inflammatory and pro-inflammatory eicosanoids. The role of omega-3 fatty acids in anti-inflammation has been recently reviewed by Wall et al. [91] and by Calder and colleagues [149, 150]. Other bioactive food components that can influence the inflammatory response include various categories of polyphenols [151–154]. Clearly food contains numerous anti-inflammatory components that can potentially attenuate chronic inflammation from different points of intervention. For further information, the reader may consult publications by Enwonwu and Ritchie [148], Galli and Calder [149], Calder [150], de Pascual-Teresa et al. [151], Prasad et al. [152], Zhao et al. [153], Mastaloudis et al. [154], Lefevre and Jonnalagadda [155], and Rathee et al. [156].

The Oral Microbiome

The oral microbial community, also called the "oral microbiome," consists of bacteria, fungi, and viruses that contribute to the health status of the oral cavity [157]. The oral microbiome generates the biofilm that adheres to tooth surfaces and is responsible for fermenting sugars and other carbohydrates to various acids, including lactic acid. Repeated exposure to such acids leads to microscopic dissolution of minerals in tooth enamel. Colonization of the oral cavity with such pathogens can also lead to chronic oral infection that ultimately manifests as periodontal disease [20]. Further, their impact is not limited to the oral cavity; oral biofilms are thought to be able to

disperse throughout the body where they may promote the development of other chronic disorders, such as heart disease, lung disease, stroke, and diabetes [158].

Genomic implications of interest to dental professionals include the use of genetic testing to identify the microbial species present and the use of nutrigenomic interventions to target the expression of specific genes. The identification of the microbial makeup of the oral cavity would seem to be essential to selecting appropriate therapeutic approaches. Each species of pathogen has a signature genotype that can be detected [159]. This information would be important for drug therapy targeted against specific pathogens. It would also be useful in developing nutrigenomic interventions. Knowing an individual is susceptible to overproduction of pro-inflammatory cytokines would prompt the clinician to intervene with omega-3 fatty acids to downregulate the genes that encode these cytokines. Another approach may be more pathogen-specific. For example, detection of the caries-promoting bacterium *Streptococcus mutans* might suggest approaches such as incorporating bioactive polyphenols into fluoride mouth rinses or gels, which have been shown to down-regulate gene expression in *S. mutans* and in disrupting its development of cariogenic biofilms [160]. Yet another approach borrows from the successful use of orally administered probiotics to address pathogen-mediated gastrointestinal disorders. Reports have begun to appear of the successful use of probiotics for caries-protection in children and for halitosis, gingivitis, and periodontal disease in adults [161–163].

The oral microbiome is under active investigation, with the goal of identifying the greater than 600 microbial species estimated to inhabit the oral cavity [164–167]. The complexity of this community is thought to be surpassed only by that of the gut. That the microbiota of the human body is considered to be significant to human health can be inferred by the initiation in 2007 of the Human Microbiome Project (HMP), a 5-year feasibility study sponsored by the National Institutes of Health [168]. In this study, the microbial communities are being characterized in 250 healthy individuals in at least four body sites (the gut, mouth, vagina, and skin). A key objective is to demonstrate that changes to the microbiome are associated with health and disease. Once the importance of the microbiome is established and the global scientific community becomes involved in ongoing research, the expectation is that strategies will emerge for manipulating the microbiome to promote health. Details of the project can be found at www.hmpdacc.org. The challenge in dental medicine will be to determine what is the normal oral microbiome for each individual, detect the pathogens present and match therapeutic interventions to that profile, and identify the dental-related genetic susceptibilities of the individual and develop appropriate dietary interventions for controlling the balance of beneficial-to-pathogenic microflora.

Summary

Advances in genomics are bringing new knowledge and tools to dental medicine. Among the promises of genomics, pharmacogenomics, and nutritional genomics are new approaches to diagnosing oral disease, profiling patients' gene-directed drug-metabolizing capabilities, determining dietary requirements based on genotype, and making gene-directed food choices. As the role of the dental professional expands to encompass the overall health of the patient in addition to oral health, nutritional genomics will become increasingly valuable for its ability to detect gene variants associated with increased disease susceptibility, allowing for preventive measures as well as early detection of numerous chronic disorders. It is now well established that the two major oral diseases, dental caries and periodontal disease, are heritable and increasingly being studied from a molecular perspective [60–62, 169–173]. Additionally, the general health of the oral cavity is affected by genetic predisposition to a number of chronic diseases, such as heart disease, cancer, osteoporosis,

and inflammation. The early stages of nutrigenetic testing for such diseases are underway. Development of tests with clinical validity and utility [174] are expected to be increasingly integrated into various aspects of healthcare, including dental medicine.

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Part IV
Select Diseases/Conditions with Nutrition and Oral Health Relationships

Chapter 11
Diabetes

Ira B. Lamster, Maura Bruno and Riva Touger-Decker

Keypoints

- Oral complications of diabetes include increased risk of periodontal disease, root caries, and candidiasis as well as neuropathic conditions such as burning mouth and reduced salivary flow. Individuals with diabetes may have altered wound healing
- Diabetes is a vascular disorder with associated oral manifestations. Oral complications of diabetes can adversely affect metabolic control, identify a person with poor glycemic control, and ultimately affect a person's ability to masticate and maintain an appropriate diet
- Oral health care professionals have a role in screening for diabetes and identifying patients who are poorly managed
- The cornerstones of diabetes management are diet and lifestyle; medical nutrition therapy includes weight loss as appropriate and a focus on total caloric intake and macronutrient content

Keywords Diabetes mellitus · Nutrition · Oral health · Oral complications · Periodontal disease · Root caries · Candidiasis · Oral manifestations · Diabetes management · Diet · Nutrition therapy

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Introduction

Diabetes mellitus (DM) is a group of disorders associated with an elevation of the glucose concentration in blood. These disorders result from a reduction in the production of the peptide hormone insulin by the β cells of the pancreas, or a decrease in the responsiveness of insulin receptors on cell surfaces to the action of insulin. Insulin promotes the uptake of glucose by cells, where it can be utilized for energy. Glucose can be toxic when the blood levels are too high. Conversely, if glucose is not available as a source of energy, cells will utilize glycogen stored within the cells, and also metabolize fat stores resulting in a serious metabolic disturbance.

Diabetes mellitus is the most common endocrine metabolic disorder and its prevalence is increasing at an alarming rate [1]. It is associated with a significant morbidity and mortality. Classically, there are five clinical complications of DM, including nephropathy (leading to end-stage renal disease), retinopathy (leading to blindness), macrovascular disease (myocardial infarction and stroke), neuropathy (and a variety of neurological problems affecting sensory, motor or autonomic nerves), and poor wound healing (often manifesting as decubitus ulcers and circulatory problems of the extremities). DM is a chronic disorder, and the major cause of blindness in adults between the ages of 20 and 74, kidney failure, and non-traumatic lower limb amputations. It is estimated that in 2010, 25.8 million Americans representing 11.3 % of the population over the age of 20 had DM. The prevalence in men is slightly higher than in women (11.8% vs. 10.8%). Older adults ($\geq$65years of age) account for approximately 43% of the population with DM. More than 27% of individuals over the age of 20 with DM are unaware of their diagnosis. Prediabetes is a condition characterized by an elevated blood glucose level, or percent of glycosylated hemoglobin that is above normal but not high enough to be considered as diabetes mellitus. The interest in prediabetes centers on the absence of clinical complications, and the reversibility of the condition by decreasing the serum glucose concentration or HbA1c through diet and exercise alone and because of the need for follow-up of these individuals.

The oral health care professional (OHCP) is in a prime position to improve the detection of undiagnosed DM and the surveillance of glycemic control: nearly 70% of Americans visit the dentist each year [2] and there are several important oral manifestations of DM. Diet management is the cornerstone of diabetes management and, medical nutrition therapy (MNT) provided by a registered dietitian (RD), is an essential component of effective disease management. Effective healthcare partnerships among OHCPs, RDs, and physicians are supportive of optimal disease management. The role for each healthcare provider is included in the most recent recommendations for DM surveillance (see Table 11.1). Earlier detection, treatment, and management of diabetes will improve quality of life and reduce disease-associated morbidity and mortality.

As a chronic disease, DM must be managed over long periods of time. OHCPs are in an ideal position to assist in the management of individuals with diabetes for several reasons.

1. In the United States, more than two-thirds of the population see a dentist at least once a year, and considering the prevalence of diabetes in the United States and the even larger percentage of individuals 65-years old or older with DM, the aging of the population, and the expected increased need for dental services for older adults, the dental office can be a location where dental patients with undiagnosed DM can be identified, where patients with previously diagnosed DM can be monitored for metabolic control and oral complications can be diagnosed and managed.
2. There are several oral manifestations of DM, including increased severity of periodontitis, increased prevalence of root caries, *Candida* infection, hyposalivation, and oral burning sensation [3]. Patients may present to the dental office with an oral complaint that is related directly to DM.
3. Dental implants are increasingly used to treat total and partial edentulism. DM is associated with alterations in osseous healing and increased risk of fractures. Consequently, patients with diabetes will be evaluated for dental implants, and the OHCP must fully understand the nature of the patient's disease.

Table 11.1 Recommended Surveillance and Management Strategies of the *National Diabetes Education Program*

Diabetes Management Schedule
Adults with diabetes should receive medical care from a physician-coordinated team of healthcare professionals. Referrals to team members should be made as appropriate
At each regular diabetes visit
• Measure weight and blood pressure
• Inspect feet if one or more high-risk foot conditions are present
• Review self-monitoring glucose record
• Review/adjust medications to control glucose, blood pressure, and lipids. Consider low-dose aspirin for CVD prevention
• Review self-management skills, dietary needs, and physical activity
• Assess for depression or other mood disorder
• Counsel on smoking cessation and alcohol use
Quarterly
• Obtain A1C in patients whose therapy has changed or who are not meeting glycemic goals (twice a year if at goal with stable glycemia)
Annually
• Obtain fasting lipid profile (every 2 years if patient has low-risk lipid values)
• Obtain serum creatinine to estimate glomerular filtration rate and stage the level of chronic kidney disease
• Perform urine test for albumin-to-creatinine ratio in patients with type 1 diabetes >5 years and in all patients with type 2 diabetes
• Refer for dilated eye exam (if normal, an eye care specialist may advise an examination every 2–3 years)
• Perform comprehensive foot exam
• Refer for dental/oral examination at least once a year
• Administer influenza vaccination
• Review need for other preventive care or treatment
Lifetime
• Administer pneumococcal vaccination (repeat if over age 64 or immunocompromised and last vaccination was more than 5 years ago)
• Administer hepatitis B vaccination to patients aged 19 to 59 (use clinical discretion for patients ≥60 years)[a]

From the National Diabetes Education Program, NIH Publication NDEP-12, (www.ndep.nih.gov), updated March 2012

[a] CDC Morbidity and Mortality Weekly Report. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices. December 23, 2011/60(50);1709–1711

This chapter reviews the relationships among oral, systemic, and nutritional risk factors for DM and diabetes-related oral disorders. The relationship of DM and oral disease has been the focus of intense interest [3–7], but attention has not been placed on the role OHCPs can play in helping the patient with DM maintain proper diet and nutrition.

Clinical Classification of Diabetes Mellitus, Etiology, and Pathogenesis

Hyperglycemia is the hallmark of DM, and elevated levels of glucose in blood can be toxic. DM results in a vascular disorder, which can lead to a number of clinical complications that include microvascular disease and associated neuropathy, retinopathy, and nephropathy; increased

susceptibility to infection and delayed wound healing, the need for amputations, and accelerated atherosclerosis with associated myocardial infarction and stroke. The development of these clinical disorders in the patient with diabetes relates largely to the severity and duration of hyperglycemia.

Type 1 Diabetes Mellitus (TIDM)

T1DM, formerly referred to as insulin-dependent DM, constitutes approximately 3–5% of all cases of DM and is related to autoimmune-mediated destruction of the insulin-producing β cells of the islets of Langerhans in the pancreas. The absolute lack of insulin means that individuals with T1DM cannot utilize glucose in the blood, hyperglycemia results, and affected individuals utilize other energy sources. In general, the major classic findings of hyperglycemia with polyuria, polydipsia, polyphagia, weight loss, and fatigue occur in the setting of new-onset diabetes in young individuals whose disease is caused by profound insulin deficiency [7]. When fats and proteins are metabolized, the production of ketones is a by-product, which ultimately results in ketoacidosis, an acute and potentially life-threatening metabolic complication. Ketoacidosis may develop rapidly and lower the pH of the blood, leading to coma and death. The onset of signs and symptoms of DM in these individuals is relatively abrupt and usually occurs at a young age (mean of 15 years), although T1DM may occur at any age. The destruction of the β cells in T1DM has been linked to the presence of certain major histocompatibility locus antigens (HLA), some of which are also associated with other autoimmune diseases [7]. More than 60 genetic loci have been identified that increase the risk of developing T1DM. At present, however, this complex situation does not offer information to aid in management of patients with T1DM [8].

Type 2 Diabetes Mellitus (T2DM)

T2DM accounts for approximately 95% of all cases of the disease. The serum blood glucose level is elevated, but the insulin levels of affected individuals may be normal, increased, or decreased. There is no profound insulin deficiency. However, over many years, the majority of individuals with T2DM have shown a continual decrease in their insulin levels. The etiology and pathogenesis of T2DM is heterogeneous due to a complex interplay of lifestyle factors and genetic predisposition [7]. Lifestyle factors include diet, lack of physical activity, and obesity.

The hyperglycemia in T2DM is not caused by autoimmune destruction of β-cells; rather it is due to inadequate insulin production in the context of insulin resistance. These individuals are not generally prone to ketoacidosis and may not be dependent on exogenous insulin to sustain life. However, insulin treatment for people with T2DM (25–30% of cases) can improve glycemic control.

Obesity is a very important risk factor for, and is frequently associated with T2DM [9]. There is a close association between the increase in obesity in the United States and the increased prevalence of T2DM. Obesity increases insulin levels and decreases the concentration of insulin receptors and their sensitivity in tissue, including skeletal muscle and fat. Exercise increases the number of insulin receptors and improves insulin sensitivity, whereas a sedentary lifestyle is associated with glucose intolerance. Regular exercise with weight loss is associated with a decreased incidence of T2DM after adjusting for body mass index (BMI) [7].

There is a strong familial component in T2DM. However, a family history is not an absolute prerequisite for the development of the disease, as some patients develop DM without any known family history. Sixty percent of patients with T2DM have either a parent or a sibling with the

disease. T2DM is a complex disease, with multiple risk factors. An evaluation of the risk for T2DM in both monozygotic and dizygotic twins indicated that the coincidence was similar (monozygotic = 0.76, dizygotic = 0.71). The authors concluded that being a twin is associated with an increased risk, but that the fetal environment is of greater significance than genetic determinants of the disease [10]. Despite the high familial prevalence of T2DM, the precise mode of inheritance remains undefined. As also noted for T1DM, a large number of genes have been associated with increased risk of T2DM. The attributable risk for all of these loci is quite low, so genetic testing is not now useful in assessing a person's risk of developing the disease.

Gestational Diabetes Mellitus

Elevated levels of blood glucose are a recognized complication of pregnancy. This tends to develop in the second trimester, and is seen in 5–10% of women who have not had a previous diagnosis of DM [11]. The underlying mechanism is a lack of receptor responsiveness to insulin. The cause is unknown, but may relate to the effects of pregnancy hormones. Risk factors for gestational diabetes include previous dysglycemia, increasing age, race (African–American), being overweight/obese, and a previous pregnancy with a baby born with a birth weight of more than 9 lbs. Gestational diabetes is not generally associated with any symptoms, and is usually detected as part of a prenatal screening for the disease when women are 24–28 weeks pregnant. Following an 8 hour fast, an oral glucose tolerance test is typically done with subsequent blood glucose measurements 1 and 2 hours postprandially after drinking a 75 gram glucose solution. A fasting blood glucose of 92 mg/dL or greater or a 1 hour postprandial glucose of 180 mg/dL or greater, or a 2 hour postprandial glucose of 153 mg/dL or greater is diagnostic of the disease [58].

The goal of treatment of gestational diabetes is to reduce fetal and maternal complications. Reducing the glucose level in blood can be achieved in a number of ways, including reducing the risk by counseling prior to becoming pregnant (diet and lifestyle changes). The same approaches are the basis of management if a diagnosis of gestational diabetes is made [12]. Diet management is particularly important during pregnancy (see Chapter 2), and should be overseen by the patient's physician and an RD. Diet management approaches are addressed in Table 11.6 and Sections "Co-Morbidities and Diabetes" and "Nutrition and Diet Management of Diabetes" of this chapter. If diet and lifestyle changes are not sufficient, medication may be required. Insulin is often utilized.

An association of gestational diabetes and periodontitis has been proposed [13]. Women who were pregnant and had gestational diabetes were compared to a group of women who were pregnant but did not have gestational diabetes. Based on the established definition of periodontal disease, 77% of women with gestational diabetes also had periodontitis, versus 58% for pregnant women without gestational diabetes. Using logistic regression analysis, and controlling for many potentially important variables such as BMI, smoking, and family history of diabetes, the adjusted odds ratio was 2.6 (95% CI 1.1–6.1).

A case–control study of women with gestational diabetes and a group of pregnant women without DM examined clinical parameters and serum markers of inflammation [14]. Using their definition of periodontitis, half of the women with gestational diabetes had periodontitis, versus approximately half that percentage if gestational diabetes was not present (odds ratio = 3.0, 95% CI = 1.2–7.6). The women with gestational diabetes also demonstrated significantly higher blood levels of C-reactive protein. Using a fully adjusted logistic model that accounted for variables such as BMI and the amount of weight that was gained during pregnancy, the association between periodontitis and gestational diabetes remained significant.

Other Forms of Diabetes Mellitus

The fourth type of DM is referred to as "other," and includes a large number of generally uncommon entities such as those associated with a specific genetic basis, disorders of the pancreas (i.e., related to cystic fibrosis, or traumatic damage to the pancreas), endocrine disorders (i.e., Cushing syndrome), drug-induced diabetes (i.e., glucocorticoid usage), and diabetes resulting from infections of the pancreas (i.e., cytomegalovirus).

Oral Complications of Diabetes Mellitus

There are a number of oral complications of DM. These include, but are not necessarily limited to, increased severity of gingivitis and periodontal disease, xerostomia and increased incidence and severity of caries, candidiasis, burning mouth sensation, altered taste, and benign parotid hypertrophy [3]. The oral complications in patients with poorly controlled DM are most likely related to increased inflammation associated with the DM, as well as changes in the amount and constituents of saliva. A reduction of saliva production may reflect a neuropathy, which is a classical clinical complication of DM. Though not comprehensively studied, evidence suggests that oral complications of DM are more severe in patients with poor glycemic control. This would be consistent with the risk for the classical complications of diabetes, specifically nephropathy and retinopathy [15].

Periodontal Disease

Periodontal disease is a common oral manifestation of DM [6]. Furthermore, there is evidence that periodontal disease can adversely affect metabolic control in patients with DM. This bidirectional relationship has led to increased focus on the relationship of these two common, chronic disorders.

The fact that periodontitis is more severe in patients with DM is now established [16, 17]. The evidence suggests that this risk is approximately threefold [18]. The majority of these studies have been conducted in patients with T2DM, as both DM and periodontal disease are more common as individuals reach middle age and old age. As the duration of DM increases, so does the severity of periodontal disease [19]. Periodontal changes also occur in younger patients with T1DM [20, 21]. These findings have led to call for periodontal disease to be the "sixth clinical complication of diabetes" [22].

The pathophysiology of increased severity of periodontal disease in patients with DM is believed to be due to an enhanced inflammatory response. One important mechanism is the increased deposition of advanced glycation end-products (AGE; formed via a multi-step, non-enzymatic reaction between reducing sugar such as glucose and proteins). AGE binds to specific receptors (RAGE) found on a variety of cells, including macrophages and endothelial cells [23]. This receptor-ligand binding results in the increased production of proinflammatory mediators, including IL-6 and TNF-α. Oxidative stress also increases, and production of reactive oxygen species and release of degradative enzymes establishes a local environment that could promote damage to endothelial cells and degradation of non-mineralized and mineralized connective tissue.

Other host-specific changes that may account for the increased prevalence of periodontitis in patients with DM include abnormalities of polymorphonuclear leukocyte (PMN) function; both decreased chemotaxis [24] and an enhanced respiratory burst have been reported [25]. PMN migrate in large numbers into the gingival crevice and when present release proinflammatory mediators

(cytokines and catabolic enzymes) that can cause tissue damage. Further, there may also be reduced local repair capacity in the periodontal tissues. Infection with *Porphyromonas gingivalis* in mice that were diabetic demonstrated greater fibroblast apoptosis and reduced repair capacity [26].

Periodontal inflammation is driven by the presence of specific microorganisms in the subgingival environment. Periodontal pathogens such as A. *actinomycetemcomitans*, P. *gingivalis*, and P. *intermedia* have been shown to be important in periodontitis in the absence of the modifying effects of DM. Studies of the microflora in periodontitis in patients with DM have not identified any major differences in the microflora of patients with periodontitis who are not affected by DM [27].

The bidirectional relationship between periodontitis and DM is of major importance to all healthcare professionals who treat individuals with DM. Infection in patients with DM is recognized to result in adverse changes in metabolic control [28]. Subsequently, studies have found that periodontal therapy can improve glycemic control in patients with DM, and several meta-analyses have concluded that conservative periodontal therapy in patients with DM and periodontitis resulted in a decrease in HbA1c of 0.4% over a period of at least 3 months [29, 30].

Several population studies have suggested that periodontitis may be a risk factor for increased morbidity and mortality associated with DM. The Gila River Native American community has been extensively studied to gain an understanding of clinical complications of DM, as this population has a high prevalence of T2DM (approximately 50%). An analysis of renal complications that developed in patients with DM and periodontitis was reported [31]. None of the patients had renal disease at the beginning of the monitoring period. Following patients for as long as 22 years, those with DM and more severe periodontitis were at increased risk of developing renal disease. Compared to individuals with no or mild periodontitis, patients with moderate periodontitis, severe periodontitis, or who were edentulous were at 2.0, 2.1, and 2.6 times increased risk developing macroalbuminuria and 2.3, 3.5, and 4.9 times increased risk for developing end-stage renal disease. The study identified periodontitis as an independent risk factor for renal complications of DM. However, it is not known whether periodontal therapy would decrease this risk.

Another study [32] in the same community looked at periodontitis as a risk factor for death from cardiovascular or renal disease. With a mean follow-up period of 11 years, those with periodontitis were at increased risk of death. This was 3.2 times greater for those with severe periodontitis [32].

Other studies extend these findings, emphasizing the potential importance of periodontal disease in patients with DM. Using data from the NHANES, Demmer et al. [33], examined the transition to DM if periodontitis was present. With a mean follow-up of 17 years, compared to individuals with no or mild periodontitis, the risk of developing DM ranged from 1.5 to 2.3 for patients with moderate to advanced periodontitis. Further, the influence of periodontitis on the level of HbA1c has also been assessed [34]. Using data from a longitudinal trial in Pomerania, participants without DM were categorized by the severity of periodontitis at baseline. The change in HbA1c was examined. After 5 years, there was a fivefold increase in HbA1c when the participants with the greatest severity of periodontitis at baseline were compared to those with the least severe disease. Further, the increase in HbA1c for participants without periodontitis at baseline who did not demonstrate an increase in severity of periodontitis after 5 years was 0.005%. In contrast, patients with severe disease who demonstrated further progression demonstrated an increase in HbA1c of 0.143%.

These data position periodontal disease within the spectrum of disorders associated with dysglycemia. All healthcare professionals need to be aware of these associations, and urge patients with DM to be evaluated by a dentist at the time of their initial diagnosis, to be followed regularly by an OHCP, to practice ideal oral hygiene, and report any changes in the mouth to their health professionals.

Considering the increased prevalence of periodontitis in patients with DM, the provision of periodontal therapy should be a part of the dental healthcare services provided to affected patients. OHCPs must be aware of a variety of diet-related issues important for the appropriate management of patients. First, patient management in preparation for dental care should be concerned with

avoidance of hypoglycemia during dental care. Second, maintaining an appropriate diet following surgery in the oral cavity is important to ensure normal healing and repair. Dietary modifications may be necessary postoperatively to reduce pain and maximize healing while maintaining serum glucose levels. Chapter 17 (Oral Surgery and Nutrition) addresses diet and nutrition following oral surgery and Appendix 2E has post-surgical dietary guidelines for individuals with DM.

Dental Caries

Dental caries results from the interaction of specific bacteria (*S. mutans, Lactobacillus* species) that metabolize fermentable carbohydrates, the availability of the carbohydrate substrate, and a susceptible host, specifically a vulnerable tooth surface. The metabolism of the carbohydrate by the bacteria yields acid (primarily lactic acid) as a by-product, which when in contact with tooth structure for extended periods of time may lead to demineralization of the tooth substrate.

The relationship between dental caries and DM is poorly defined. This lack of clarity is due in large part to the differences in study design and a lack of clear definition of the study population (i.e., T1DM vs. T2DM, age, level of metabolic control).

The studies examining coronal caries in patients with DM have not identified DM as a risk factor for these lesions [35, 36]. A greater focus is on an association between DM and root caries. In periodontal health, the root surfaces of the teeth are not exposed to the oral environment. However, diabetes is a risk factor for periodontal disease, which is characterized by loss of periodontal attachment. One result is gingival recession and exposure of the root surfaces. Tooth root surfaces are covered with cementum, which is less densely mineralized, and much thinner than the enamel that covers the coronal portion of teeth, and in some individuals near the enamel margin, dentin is exposed. Increased root caries has been reported in patients with DM [37]. This study is noteworthy because confounders were considered, including exposed root surfaces, the level of oral hygiene, salivary gland function, and levels of cariogenic bacteria. The prevalence of root caries in patients with DM was more than twice that in the non-diabetic controls (40.0% vs. 18.5%, $p = 0.001$). Among the risk factors for root caries was poor buffering capacity of the saliva. Garton and Ford [38] have identified root caries as a potentially important future problem for patients with DM. As the population ages and the prevalence of DM and periodontitis increases, strategies will need to be implemented to prevent development of this complication of DM.

The importance of prevention in managing the risk of caries cannot be overstated. In addition to appropriate oral hygiene measures and the use of topical chemotherapeutic agents (e.g. fluoride), there should be a focus on salivary flow. Patients should also be counseled about the need to moderate their dietary intake of fermentable carbohydrates. Diet management for individuals with DM should be tailored to the patient's diabetes diet plan and focus on integrating oral hygiene practices with meals and snacks. Dietary guidelines to reduce caries risk are addressed in more detail in Chapter 1.

Xerostomia

Xerostomia is the subjective complaint of mouth dryness. Xerostomia is associated with hyposalivation, which is reduced production of saliva.

A complaint of xerostomia and reduced production of saliva has been reported in patients with DM. This complication occurs at all ages, including adolescents [39], adults [40], and older adults at least 60 years of age [41]. In case–control studies, the number of individuals with DM who complain

of xerostomia is 50–100% greater than individuals without DM. The proportional reduction in salivary flow was greater in the resting rather than the stimulated state [40].

Saliva has a number of important functions. This fluid lubricates the oral cavity, which allows comfortable oral function, i.e., softening the bolus of food and wetting the surfaces of the teeth and mucosa and reducing the chance of mucosal abrasion from hard or crusty food. The constituents of saliva also include amylase, which begins the process of digestion of starch in food. Saliva also contains different antimicrobial constituents such as lysozyme, peroxidase, and defensins, which helps to control the oral microflora. The buffering capacity and supersaturated calcium and phosphate of saliva are also critical, specifically to neutralize acids produced by bacteria when fermentable carbohydrates are metabolized and to remineralize teeth. This buffering affect is seen most strikingly with patients who lose salivary function secondary to radiation of the head and neck. Rampant caries can result.

When salivary flow is reduced, clinically important problems occur. As noted, the buffering capacity of saliva means that the fluid is an essential host mechanism to prevent tooth demineralization as a result of acid production following carbohydrate metabolism. Prevention includes diet instruction, plaque control, the use of topical fluoride, or fluoride delivered via mouth trays [42] and consideration for use of remineralizing products and chlorhexidine for antimicrobial effect. These measures may need to be considered for patients with T1DM or T2DM. Saliva provides a supersaturated calcium and phosphate source for remineralization of the dentition. Saliva also has antimicrobial and clearance functions. Bacteria and other microorganisms that are disrupted and separated from the plaque biofilm and degenerated epithelial cells are cleared from the oral cavity when swallowing occurs, and swallowing is far more efficient when there is a normal amount of saliva. A reduction or virtual absence of saliva may not only hamper digestion, but also makes eating difficult and less enjoyable. The absence of this lubricating effect of saliva and a reduction in enjoyment of eating are often the basis for patient complaints. Reduced salivary flow is a cause of reduced quality of life [39], and can be of major significance when patients with DM also suffer from medical complications of their disease.

Hyposalivation can have a significant impact on dietary intake and therefore nutritional status. Dietary management for patients with xerostomia and reduced salivary flow focuses on adequate fluid intake with all meals and snacks, avoidance of citrus fruits and juices, and other high acid foods and fluids as well as sugar sweetened beverages. Ingestion of moist foods is encouraged to reduce mucosal irritation (see Appendix 2C for dietary-guidelines for patients with xerostomia). Saliva secretion can be enhanced by taste, the chewing function, systemic sialagogues, and palliation provided with topical treatments. Therefore, it is critical that the OHCP and RD collaborate to develop an effective dietary management plan for patients with DM who have reduced salivary flow. It is important to remember that improved metabolic control of DM may improve salivary flow.

Candidiasis

Candida albicans, and to a lesser extent other *Candida* species, commonly exist as commensal organisms in the human oral cavity. However, in a number of conditions, including DM, acquired immunosuppression (e.g., HIV infection) and prolonged use of corticosteroids or antibiotics, *Candida* can cause disease in humans.

Candida infection in the oral cavity can present as a number of different lesions. This variability can make diagnosis a challenge. The lesions include:

Pseudomembranous candidiasis: erythematous (red) lesions with white patches. The white patches are accumulations of fungal organisms.

Atrophic or erythematous candidiasis: erythematous mucosa without white patches. If the dorsal surface of the tongue is involved in pseudomembranous or atrophic forms of candidiasis, the lesion has been referred to as medium rhomboid glossitis. When involving the hard palate, the lesion is often present under a complete upper denture or under partial denture bases. This lesion appears velvety and is referred to as denture stomatitis.

Hypertrophic candidiasis: mucosal hyperplasia with areas of increased keratin thickness. This lesion is a tissue response to an invasive *Candida* infection.

Angular cheilitis: fissures at the corners of the mouth. These lesions demonstrate fungal hyphae when a smear is taken.

Guggenheimer et al. found that a higher percentage of patients with T1DM versus control subjects have clinical manifestations of candidiasis, including median rhomboid glossitis, denture stomatitis, and angular cheilitis (15.1% vs. 3.0%) [43]. Subjects with T1DM were also more likely to have *Candida* pseudohyphae in their cytologic smears. Diabetic subjects with medium rhomboid glossitis had a longer duration of T1DM as well as the microvascular complications of nephropathy and retinopathy. Denture stomatitis was associated with smoking, retinopathy, higher counts of candidal pseudohyphae, poor glycemic control, and a longer duration of T1DM. Three factors in this study associated with the presence of candidal pseudohyphae were cigarette smoking, the use of dentures, and elevated HbA1c levels, indicative of marginal to poor metabolic control.

The overgrowth of oral *Candida* in patients with DM has been linked to the concentration of glucose in saliva [44] and altered PMN function (phagocytosis and intraoral killing of *Candida*) in patients with DM has also been identified [45]. Treatment with antifungal therapy and elimination of the *Candida* infection was accompanied by an improvement in PMN function. The improvement, however, was not to the level observed in normal individuals.

Increased oral colonization and overgrowth of *Candida* have been linked to the presence of a removable denture. Erythematous mucosa under the acrylic portion of the denture is the characteristic clinical finding (also referred to as denture stomatitis), and increased *Candida* colonization was reported in patients with DM and with a denture, and a higher percentage of patients with DM demonstrated denture stomatitis [46].

The presence of clinical infection due to *Candida* species (candidiasis) in the oral cavity should lead to a search for underlying risk factors. It is important to emphasize that many risk factors for intraoral candidiasis exist, and a thorough patient history is essential to establish the underlying cause.

Burning Mouth Symptoms

Burning mouth symptoms occur in patients with DM, but are not unique to these patients. This may be related to mucosal lesions, candidiasis, or dry mouth. Burning mouth syndrome (BMS) is characterized by a bilateral burning sensation without mucosal lesions. Patients affected with BMS commonly complain of burning or irritation, often involving the tongue and less often other sites on the lips and palate. Additional complaints include disturbances in taste, and a complaint of mouth dryness. Underlying oral disorders that may also be associated with DM should be ruled out such as *Candida* infection and lichen planus and treated if necessary. Burning mouth syndrome is rarely associated with vitamin and mineral deficiency, and anemia [47].

If other causes are ruled out, BMS may be a manifestation of diabetic neuropathy [48]. This case report illustrated a patient with these symptoms, and very poor metabolic control (fasting plasma glucose of 395 mg% and an HbA1c of 14.1%) was identified; oral symptoms improved with improved metabolic control. However, a study of BMS and diabetic neuropathy in patients with T1DM illustrates the challenges associated with identifying BMS as a manifestation of diabetic

neuropathy [49]. A total of 371 adults with T1DM and 261 individuals without diabetes that served as the control group were evaluated. The prevalence of BMS in the entire cohort was 4.6%. After eliminating the patients with identifiable causes (primarily candidiasis, with different clinical manifestations), the occurrence of BMS was 3.2% in the patients with T1DM and 2.1% in the control subjects. A more detailed analysis of the 12 patients with T1DM and BMS revealed that significant risk factors included a previous diagnosis of diabetic neuropathy ($p = 0.024$) and female gender ($p = 0.042$). Diabetic neuropathy is a challenge to treat; treatment focuses on improved metabolic control of diabetes and management of pain. Pain management strategies focus on the use of centrally acting medications used to treat neuropathic pain, including anticonvulsant, anti-anxiety and antidepressant medications [50]. Unfortunately, many of the medications have xerostomia as a side effect that may complicate the oral/dental management of these patients.

Other Oral Lesions Associated with Diabetes

There are a number of other oral lesions that have been associated with DM. These include aphthous stomatitis [51], lichen planus [52], and benign parotid enlargement [53]. These lesions have not been comprehensively studied, occur infrequently, or occur in association with many conditions, and when DM is not present. In addition, taste alterations/bad taste have also been identified as a complaint of patients with DM, which in at least some cases is related to reduced salivary flow, changes in salivary chemistry, *Candida* infection, or in association with BMS.

Management of the Patient with Diabetes Mellitus in the Dental Office

The OHCP, physician, and RD each have specific roles in caring for patients with DM. These are certain activities that can be considered overlapping, including surveillance for any subjective or objective signs and symptoms of DM, indicative of a change in metabolic status. Table 11.1 provides a recommended surveillance program for individuals with DM.

Interprofessional Practice

Considering the different oral lesions that have been associated with DM, evidence suggesting that untreated periodontitis can adversely affect metabolic management, and the increasing prevalence of diabetes in the U.S. population, OHCPs can have an important role in patients with diabetes and in identifying patients with undiagnosed or poorly managed DM. The outcome of dental care can be optimized by collaborating with other healthcare professionals to assure that patients maintain as close to an ideal blood glucose level as possible. For chronic disorders such as DM, where focus needs to be on lifestyle modifications (including diet, exercise, and weight control) as well as the use of oral medications and insulin, different contacts with the healthcare system provide opportunities for monitoring and reinforcement of therapeutic goals.

Team Approach to Diabetes Management

All health professionals must be cognizant of the medical, dental, and nutrition goals for management of diabetes, be aware of the resources available, and refer the patient to the appropriate healthcare provider. No discipline functions within a vacuum; in particular, in regard to dentistry and nutrition, there is a need for awareness of the important role each healthcare professional plays in the management of patients with DM.

It is incumbent on nutrition and oral healthcare professionals to screen individuals with DM for nutrition and oral health risks, provide appropriate education, and when necessary, referral to other health professionals. The relation between oral manifestations of DM and diet/nutrition is complex and bidirectional. Oral manifestations of diabetes challenge and compromise eating ability and consequently diet quality and nutrient intake, ultimately impacting nutrition status. A detailed review of oral nutrition risk assessment may be found in Chapter 19.

Screening for Diabetes Mellitus in the Dental Office

Population screening for DM is controversial. However, targeted cohort screening is indicated for high-risk individuals, especially when screening can occur as part of another healthcare activity, and when at-risk individuals gather in one location.

In recent years, there has been increasing interest in the idea of assessing the risk for diabetes in the dental office, and using oral/dental data to help with this assessment. This interest is driven both by the realization that nearly 70% of adults have seen a dentist in the past year [2], and that the dental disease and oral lesions associated with DM may be the reason that a patient seeks dental care.

Li et al. [54] used data from the third National Health and Nutrition Examination Survey (NHANES; conducted from 1988–1994) and the 2003–2004 NHANES survey to develop a questionnaire to identify dental patients who have undiagnosed DM. They employed classification and regression tree methodology, and developed predictive models. Their identified variables were self-reported waist circumference, age, weight, oral health status, and race/ethnicity. These data were incorporated into a flowchart to identify patients at risk for DM.

Strauss et al. [55] also used the 2003–2004 NHANES database to determine the percentage of patients with periodontitis (93.4%) who would qualify for screening based on criteria established by the American Diabetes Association. Lalla et al. [56] reported a prospective study of screening for DM in a cohort of patients seen in a dental clinic for routine dental care. Patients were screened based on age, race/ethnicity, and a positive response to at least one of four questions about their health history (family history of DM, ever told of being hypertensive, of having elevated cholesterol, or of being overweight or obese). For qualified individuals, the addition of specific dental disease criteria (at least 26% of teeth with at least one site with a periodontal probing depth of 5 mm or greater, and/or 4 or more missing teeth), 73% of cases of DM or prediabetes could be correctly identified. These data suggest that the dental office can be a place where undiagnosed DM can and should be detected, and by extension where poorly managed DM can be identified.

The Role of the RD

Medical nutrition therapy (MNT) for individuals with all types of DM is a recognized essential component of care [57]. The American Diabetes Association Clinical Practice Recommendations focus on treatment and prevention of diabetes and related complications [58] and are described in

the subsequent section of this chapter. MNT by the RD includes completion of a comprehensive nutrition assessment and diet evaluation along with planning, implementation, monitoring, and evaluation of a nutrition care plan. As part of that plan, the RD provides the patient with diet education and counseling. A nutrition focused physical examination, including an oral screen and questions on the oral sequelae of DM, is part of the nutrition assessment [59–61]. Questions about difficulties with biting, chewing, and swallowing, and the presence and severity of oral diseases should be asked [59, 61]. The oral screen completed by the RD should include an assessment of the head and neck area, cranial nerves relevant to eating and swallowing (V, VII, IX, X, XII), and oral cavity to note integrity of the soft tissue, dentition, and occlusion [61, 62] as well as any complaints of dysphagia. Although it is not the role of the RD to diagnose or treat oral diseases, it is incumbent on the RD to note any abnormal findings, determine their impact on eating ability, and refer patients to the dentist [62]. Chapter 19, Approaches to Oral Nutrition Risk Assessment, addresses nutrition screening in oral health.

The diet evaluation and history taken by the RD differs from that suggested for the OHCP. Provision of MNT is the role of the RD but all healthcare team members should be familiar with MNT recommendations for DM and encourage patient compliance. These recommendations are supported by the American Diabetes Association [57]. The outcome of the RD screen will be one or more of the following: provide MNT for the patient, refer the patient to a dentist for evaluation and treatment, refer the patient to his or her primary care provider, or refer the patient to another health professional.

Comorbidities and Diabetes

Individuals with prediabetes classified as either impaired fasting glucose (fasting plasma glucose levels 100 mg/dL to 125 mg/dL), impaired glucose tolerance (2-hour values in the Oral Glucose Tolerance Test of 140–199 mg/dL), or HbA1c of 5.7–6.4% have a high risk for the future development of T2DM [58]. Associated comorbid diseases include cardiovascular disease (CVD), obesity, dyslipidemia with high triglycerides, and/or low HDL cholesterol and hypertension.

Body mass index (BMI) values of 25 to 29.9 (overweight) and over 30 (obesity) can contribute to the risk of developing the insulin resistance that is characteristic of T2DM [58]. Weight loss of 7% or more of body weight can reduce insulin resistance and risk factors for CVD [58, 63, 64]. In the landmark trial led by the Diabetes Prevention Program Research Group, individuals with prediabetes who experienced weight loss ranges of 5–7% of body weight and who increased physical activity (2.5 hours per week or more) as part of a lifestyle change program reduced their chances of developing T2DM [65]. Waist circumference, an indicator of abdominal obesity, is an additional risk factor for T2DM [66]. Combined, a BMI greater than 24.9 and a waist circumference of greater than 35 inches for female patients and greater than 40 inches for male patients reflect increased risk for developing T2DM [54, 67].

Cardiovascular disease is the primary cause of morbidity and mortality in individuals with DM. Dyslipidemia and hypertension are common risk factors associated with CVD. Hypertension is often seen in individuals with DM and can impact the progression of micro and macrovascular complications. Lifestyle modifications including diet and physical activity are key to the management of DM as well as CVD, dyslipidemia, and hypertension [68–70] Weight loss, physical activity, and moderation of alcohol intake can help to prevent and manage hypertension [68]. The *DASH* (*Dietary Approaches to Stop Hypertension*) diet has been shown to lower blood pressure independent of medications and is advocated for the treatment of hypertension [71–74]. *DASH* emphasizes a diet plan rich in fruits, vegetables, low-fat dairy products, whole grains, poultry, fish, and nuts and promotes limiting intake of saturated and total fats, red meat, and added sugars along with

sweetened beverages [74] (www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf). Weight loss, along with aerobic physical activity such as brisk walking [75] have likewise been shown to be part of the lifestyle modifications to reduce risk of and manage hypertension and CVD. The American Heart Association supports a reduced sodium intake (<1,500 mg/day) for prevention and treatment of CVD [76]. Pharmacologic therapy, in addition to lifestyle therapy, is recommended for patients with confirmed blood pressure greater than or equal to 140/80 mmHg [58].

There is strong evidence for the role of a diet low in saturated and trans fats and cholesterol intake, increased in n-3 fatty acids, plant stanols/sterols, and viscous fiber; weight loss if required and increased physical activity as modifications to manage dyslipidemia [58, 76]. In addition to lifestyle changes, dyslipidemia in individuals with diabetes often requires pharmacologic therapy, particularly in individuals with CVD and those over the age of 40 with multiple risk factors (family history of CVD, hypertension, smoking, dyslipidemia) [57].

Goals of Medication Management of Diabetes Mellitus

Tight Control: Revisiting and Redefining an Established Concept

Current treatment goals for T1DM and T2DM are summarized in Table 11.2. Prolonged hyperglycemia is the primary factor responsible for the development of both acute and chronic complications of DM [77]. The common biochemical basis for complications is hyperglycemia-mediated formation of AGE. AGE are chemically irreversible, glucose-derived compounds that form slowly and continuously in plasma and tissues as a function of blood glucose concentration and have been linked to the development of complications such as renal failure [78].

HbA1c is used to assess glycemic control [79]. Its prognostic value was demonstrated in the Diabetes Control and Complications Trial (DCCT) in 1993 [80]; the randomized prospective 6-year study in Japan [81, 82]; and in the UK Prospective Diabetes Study Group in 1998 [83]. The HbA1c measures glucose that binds to hemoglobin within circulating erythrocytes and remains attached for the life cycle of the red blood cell. Thus, HbA1c is an indicator of the glucose concentration in blood during the preceding 2 to 3 months, as this is the half-life of red blood cells. Hence, it is the preferred test for the medical evaluation of diabetic control. HbA1c will be elevated significantly with prolonged, severe hyperglycemia. Target therapeutic ranges for the HbA1C are below 7% (American Diabetes Association) or 6.5% (American College of Endocrinology). Less stringent HbA1C goals (<8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, or extensive comorbid conditions; Table 11.3 summarizes the correlation between HbA1c and mean plasma glucose [58].

The DCCT demonstrated that other features of diabetic glucose control not reflected in the HbA1c might add to or modify the risk of complications [84]. Clinical data show that the risk and severity of complications may be more highly dependent on the extent of 1 to 2 hours postprandial (after meal) elevations in blood glucose (acute glycemia and toxicity) [78]. Hyperglycemia after a meal is associated with increased free radical production that can lead to tissue damage. Hyperglycemia 2 hours post-prandially is associated with an increased risk of death, independent of fasting blood glucose [85]. Data have also demonstrated that the risk of microvascular complications of DM (e.g., retinopathy, nephropathy, neuropathy) increase with progression in postprandial glucose levels from 180 to 260 mg/dL [81]. Hence, tight control now includes daily self-monitoring of blood glucose (SMBG) often before and after meals to target postprandial levels (Table 11.4) and minimize the occurrence of acute hyperglycemia and acute toxicity [86]. Battery-operated glucometers enable patients to obtain and record blood glucose data. Individual needs and goals of the patient should dictate the frequency and timing of SMBG. Patients using intensive insulin regimens (multiple dose

injections or insulin pump therapy) are at greater risk of hypoglycemia; more frequent SMBG is recommended to minimize risk. At a minimum, SMBG should be done before meals and snacks. Occasionally, additional SMBG is recommended postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until normoglycemic levels are achieved, and, prior to critical tasks such as driving. This will require testing 6–8 times daily for some patients, although individual needs may vary. Tight blood glucose control, where both hypoglycemia and hyperglycemia are avoided, is a challenge that requires a patient's commitment to self-management [58].

Table 11.2 Treatment goals for the ABCs of diabetes

$A_1C < 7\%$			
	Preprandial plasma glucose	70–130 mg/dL	
	Peak postprandial plasma glucose	<180 mg/dL	
Blood pressure (mmHg)			
		Systolic	Diastolic
	Hypertension definition	>140	>90
	Treatment goal	<130	<80
Cholesterol: Lipid profile (mg/dL)			
	LDL	<100	
	HDL	Men >40	Women >50
	Triglycerides	<150	

From Ref. [58]

Table 11.3 Correlation between glycosylated hemoglobin and mean plasma glucose level

Glycosylated hemoglobin (%)	Mean plasma glucose (mg/dL)
6	126
7	154
8	183
9	212
10	240
11	269
12	298

From Ref. [58]

Oral hypoglycemic agents and insulin preparations currently available for treating DM are summarized in Tables 11.4 and 11.5 [87, 88]. While achievement of normoglycemia remains the goal of the management of diabetes, pharmacologic treatment differs between individuals with T1DM and T2DM. Due to the complete destruction of β cells, treatment for individuals with T1DM requires exogenous insulin replacement. Despite the destruction of some β cells, most individuals with T2DM are still producing endogenous insulin at the time of diagnosis. However, the insulin resistance associated with T2DM in combination with a decreased insulin production, often requires pharmacologic intervention. The progressive destruction and dysfunction of β cells associated with T2DM requires ongoing re-evaluation of treatment to achieve glycemic control over time. Most individuals with T2DM achieve adequate blood glucose control with one oral hypoglycemic agent at the time of diagnosis, but as beta cell destruction continues, additional agents often become necessary and if normoglycemia cannot be achieved with non-insulin agents, exogenous insulin is

Table 11.4 Oral hypoglycemic agents

Class	Drug	Usual starting dosage	Doses/Day
Insulin secretagogues			
Sulfonylureas	Chlorpropramide	100–250 mg	1
Long-acting			
	Glipizide	2.5 or 5 mg	1–2
	Glyburide	2.5–5 mg	1–2
	Glimepiride	1–2 mg	1
Meglitinides	Nateglinide	60–120 mg	2–4
Short-acting	Repaglinide	0.5–2 mg	2–4
Insulin sensitizers			
Biguanides	Metformin	500–8,500 mg	2–3
Thiazolidinediones	Pioglitazone	15 mg	1
	Rosiglitazone	4 mg	1–2
Delay carb absorption			
α-glucosidase inh	Acarbose	25 mg	3
	Miglitol	25–50 mg	3
Bile acid sequestrants	Colesevelam	1,875 mg	2
Incretin mimetics			
GLP-1 receptor agonists	Exenatide	5–10 mcg	2
	Exenatide extended-release[a]	2 mg	Weekly
	Liraglutide	0.6 mg 1.2 mg 1.8 mg	1
Incretin enhancers			
DPP-4 inhibitors	Sitagliptin	100 mg	1
	Saxagliptin	2.5–5 mg	1
	Linagliptin	5 mg	1
	Alogliptin[b]	6.25–25 mg	1
SGLT-2 inhibitors	Canaglifozin[c]	100–300 mg	1

Adapted from Diabetes Health. November 2011. www.DiabetesHealth.com accessed March 7, 2013
[a] Package insert Amylin Pharmaceuticals, Inc. 2012
[b] Package insert Takeda Pharmaceuticals America, Inc. 2013
[c] Package insert Janssen Pharmaceuticals, Inc. 2013

needed. Hypoglycemia (plasma glucose level <70 mg/dL) is an associated risk of insulin therapy. Individuals requiring insulin treatment should receive proper education regarding insulin injection methods, insulin storage, monitoring, diet, and signs and treatment of hypoglycemia.

Hypoglycemia is the leading risk of DM management for individuals with T1DM and those with T2DM that are treated with insulin [58]. Hypoglycemia symptoms include but are not limited to sweating, shaking, confusion, and disorientation. Treatment requires the ingestion of glucose (preferred treatment) or foods containing carbohydrates. Over the counter glucose tablets (3–4 tablets) or 4 ounces of a sugared beverage such as soda or juice drinks will provide 15 gms of carbohydrate necessary to improve hypoglycemia symptoms. Added fat may slow down and prolong the acute glycemic response. When possible, blood glucose levels should be checked to confirm hypoglycemia at the onset of symptoms. Following treatment of hypoglycemia, the patient's blood glucose should be checked in 15 minutes to ensure the level is returning to normal. Left untreated, hypoglycemia will become severe, and the individual will require assistance of another person. If the patient becomes unresponsive, emergency services should be contacted immediately.

Table 11.5 Insulin preparations

Type	Action	Onset time (h)	Peak time (h)	Duration (h)
Human				
Regular	Short	0.5.0–1.0	2.0–4.0	5.0–8.0
NPH	Intermed	1.0–2.0	2.0–8.0	14–24
Analogs				
Lispro Insulin	Rapid	0.25–0.50	0.5–2.5	4–5
Aspart	Rapid	0.25–0.50	1.0–3.0	3.0–5.0
Glulisine	Rapid	0.25–0.50	0.5–2.5	4–5
Glargine	Long acting	1.5	None	>24
Detemir	Long acting	1.6	8–10	14–24
Insulin Mixtures				
Humulin 70/30	NPH 70% + Regular 30%	0.50–1.0	2.0–4.0	14–16
Novolin 70/30	NPH 70% + Regular 30%	0.50	2.0–12	14–16
Humalog 75/25	NPH 75% + Humalog 25%	0.25–0.50	0.5–2.5	14–16
Novolog 70/30	NPH 70% + Novolog 30%	0.25–0.50	2.4	14–20

Adapted from Diabetes Health. December 2011–January 2012. www.DiabetesHealth.com accessed March 7, 2013

Nutrition and Diet Management of Diabetes

Medical Nutrition Therapy

Diet management is an essential component of DM management. While there are several approaches to diet management of DM, independent of the strategy selected, is the need for MNT with a qualified and credentialed provider, namely the RD. The Certified Diabetes Educator (CDE) credential indicates the individual has specialist certification in diabetes management. Ideally, RDs providing MNT to individuals with DM should also be CDEs. The goals of MNT are outlined in Table 11.6 [57, 58]. MNT for DM includes a comprehensive nutrition assessment. Assessment should include the evaluation of current diet intake, eating patterns, lifestyle behaviors, readiness to change, goal-setting, diet instruction, and monitoring of response to therapy. Individuals with prediabetes or impaired glucose tolerance have a relatively high risk for the future development of diabetes and should receive this instruction [58]. Persons at risk for oral complications because of poor glycemic control and those with DM who may need dental (oral) procedures that will affect their functional ability to eat are at high nutrition risk. Examples include individuals undergoing oral surgical procedures that will compromise the ability to eat for several days or longer. If several days of impact on diet are expected, these individuals should be seen by an RD prior to the procedure for diet evaluation and counseling. If that is not feasible, OHCPs should provide diet guidelines customized for individuals undergoing such procedures, as outlined in Table 11.6.

In most states, MNT by an RD with several follow-up visits is a benefit covered by all third-party payers, Medicare and Medicaid, for individuals with DM. In addition to referring patients as appropriate to an RD, the OHCP should reinforce the need to adhere to diet and nutrition-related goals, integrate oral hygiene into daily routines, and modify diet as needed to manage oral conditions and dental treatment. Individuals referred to an RD should be encouraged to check with their insurance company for MNT benefits and necessary referral documentation. Registered Dietitians providing MNT can be found at most community hospital outpatient services or by contacting the Academy of Nutrition and Dietetics (www.eatright.org).

Table 11.6 Goals of medical nutrition therapy (adapted from Refs. 57, 58)

Goals for all persons with diabetes
• Attain and maintain desirable metabolic outcomes
• Achieve normal blood glucose values or as close to normal as is safely possible
• Achieve lipid profile consistent with risk reduction for vascular disease
• Maintain blood pressure levels in the normal or as close to normal as is safely possible
• Prevent and treat associated chronic complications of diabetes by modifying nutrient intake and lifestyle
• Maintain eating pleasure by only limiting food choices when indicated by scientific evidence
• Address individual nutritional needs considering personal and cultural preferences and lifestyle
Goals for specific situations
• In youth with T1DM, youth with T2DM, pregnant and lactating women, and older adults with diabetes, to meet individual nutrition needs of these times in the life cycle
• In individuals treated with insulin or insulin secretagogues, provide self-management education for treatment, and prevention of hypoglycemia, safe conduct of exercise and diabetes treatment during acute illnesses

Nutrition Goals of Diabetes Management

The diet and nutrition goals for DM management of the American Diabetes Association [57] are stated in Table 11.6. The evidence supporting these goals for each of the macro- and micronutrients, alcohol, and energy needs is stated as "A level" (strongest) to "C level" (weakest) [58].

General recommendations regarding energy intake for individuals who are overweight or obese focus on provision of calories to promote weight loss, reduce insulin resistance, and improve glycemic control in individuals with insulin resistance (A-level evidence). Lifestyle modification programs including education, reduced fat (<30% of total calories) and energy intake, regular physical activity, and ongoing contact between participant and provider can promote long-term weight loss. Behavior modification and exercise are important adjuncts to support weight-loss initiatives. A recommended energy intake (number of calories) should be determined by the RD; it will be based on the patient's current weight, physical activity and exercise patterns, other comorbid conditions, and weight management goals.

Expert consensus indicates that monitoring carbohydrate intake is a key strategy to achieve glycemic control [57]. However, the patient's metabolic profile and need for weight loss should be considered when determining the macronutrient composition. A-level evidence for carbohydrate indicates that dietary intake should include fruits, vegetables, whole grains, and non/low-fat milk. The total amount of carbohydrate at meals and snacks should be considered as more important than the source or type of the carbohydrate. Glycemic response is influenced by many factors including the type of sugar (fructose, glucose, lactose, sucrose), the amount of carbohydrate, food processing, and cooking as well as the presence of other food components. Sucrose-containing foods may be included but they should be substituted for other types of carbohydrates or covered with insulin. Nonnutritive sweeteners may be used. Individuals with diabetes or at risk for T2DM should be encouraged to achieve the U.S. Department of Agriculture recommendation for dietary fiber (21–38 gms per day) and foods containing whole grains (one-half of grain intake) [89].

Expert consensus also suggests that usual protein intake (15–20% of total energy) should be modified for individuals with DM and normal renal function [57]. The primary goal regarding dietary fat in the diet for DM is the limitation of dietary saturated and trans fatty acid, and, dietary cholesterol to reduce risk for CVD. B-level evidence indicates that saturated fat intake should be limited to less than 7% of total calories [58]. There is A-level evidence indicating that reducing intake of trans fat can lower LDL- cholesterol and increase HDL-cholesterol; therefore trans fat intake should be minimized [57]. There is B-level evidence to indicate that two or more servings of

fish per week provide n-3 polyunsaturated fatty acids and are recommended for the management of DM. Expert consensus indicates that individuals with DM should limit dietary cholesterol intake to <200 mg/day [57]. A-level evidence indicates that in the absence of a deficiency there is no evidence of benefit from vitamin, mineral, or trace-element supplementation [58]. The exceptions to this include folate for the prevention of neural tubular birth defects and calcium for prevention of bone disease, both recommendations for all individuals independent of DM. In addition, the A-level evidence indicates that routine supplementation of antioxidants is not advised as there are no data regarding the long-term efficacy or safety of supplemental doses [58]. Expert consensus regarding alcohol indicates that intake should be limited to one drink per day for women and two for men [58].

The reader is encouraged to consult the references for more detailed discussion on management of T1DM and T2DM. Other recommended clinical resources include the American Diabetes Association (www.diabetescare.org) and the Academy of Nutrition and Dietetics (www.eatright.org).

Dietary Interventions for Optimizing Glycemic Control

Individuals with DM should see an RD for MNT following their initial diagnosis in order to establish individualized goals and meal plans. In addition to the traditional diabetes exchange system diet, there is also carbohydrate counting, the MyPlate visual prompt, and the glycemic index. The choice of diet plan should be based on the individual's needs and goals as determined by the RD in consultation with the patient.

MyPlate replaced MyPyramid as the U.S. government's primary food group symbol [90] in 2011. It is a simple graphic designed to help consumers adopt healthy eating habits by encouraging them to build a healthy plate, consistent with the 2010 Dietary Guidelines for Americans. The familiar image of a place setting include fruits, vegetables, grains, protein foods, and dairy as the building blocks for a healthy diet. A care plan that includes an individualized diabetes diet will provide a specific number of servings from each food group depending on personal activity goals and nutrient needs. It is important to distribute servings from a variety of food groups at each meal and snack. For more detailed information on *MyPlate*, please see Chapter 1 of this book.

The diabetes exchange lists published by the Academy of Nutrition and Dietetics and the American Diabetes Association [91] are another guide often used for individualized meal planning. Exchange systems are also available for several nationalities to facilitate keeping to one's ethnic food preferences. The exchange system is based on distribution of foods on the basis of their macronutrient composition, including carbohydrates, proteins, and fats. The food group categories include foods that contain starch (bread, rice, pasta, cereals, starchy vegetables, and legumes), fruit (fresh, frozen, or fruit juice), milk and vegetable lists; a meat and meat substitutes group that includes categories based on the fat content; and a fat group. Lists are also included for vegetarian alternatives, fast foods, and other carbohydrates, including cakes, pies, puddings, and cookies.

Carbohydrate counting is a tool for individuals with DM to use in making food choices and planning meals [92]. It is based on the principle that total carbohydrate intake influences blood glucose greater than any other macronutrient. Using this method, individuals with DM calculate the grams of carbohydrate they eat at each meal and each snack during the day. Individuals must learn to use carbohydrate counting along with the principles of balanced nutrition and the food guide pyramid in planning their meals. Patients are encouraged to consistently consume moderate amounts of carbohydrates at meals and snacks.

The glycemic index (GI) of a carbohydrate is the rise in plasma glucose (above baseline) relative to that induced by a standard, usually 50 g, glucose or "white bread challenge" [93]. GI values are based on postprandial digestion and absorption. Clearly, dietary fiber content, dietary fat, and overall macronutrient composition of the foods eaten in combination influence the GI of individual foods.

There is no consensus as to its usefulness and practicality as a means of dietary management of DM. Additional information regarding the GI can be found at the American Diabetes Association website (http://www.diabetes.org/food-and-fitness/food/planning-meals/glycemic-index-and-diabetes.html).

Summary

There are a wide range of oral/dental disorders that occur in individuals with DM. In addition, these individuals may have compromised healing and increased risk of oral infection(s). To manage these problems, OHCPs and RDs must have an understanding of the etiology, prevalence, clinical complications, and medical management of patients with DM. The sequelae of periodontal disease and root caries may make mastication difficult, and BMS and *Candida* infection can lead to a loss of desire or ability to eat, thus reducing food intake and resulting in altered nutrition status. For a patient with DM, where metabolic control is so important, yet difficult to achieve over the decades that patients are afflicted with chronic diseases such as diabetes, OHCPs and RDs (and other health professionals), can have an important role in patient management. OHCPs, physicians, and RDs must work together to help patients with diabetes to achieve the best possible oral health and health outcomes. This begins with recognition and appreciation of the role of each discipline in the management of DM.

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Chapter 12
Oral Pharyngeal Cancer Epidemiology and Prevention

Joel B. Epstein, Heidi Ganzer and Riva Touger-Decker

Keypoints

- Cross-sectional studies have demonstrated inverse relationships between fruit and vegetable intake and incidence of oral and pharyngeal cancers
- Variable findings have been reported regarding associations between dairy and meat product intake and incidence of oral and pharyngeal cancers
- Dietary supplements have not been shown to be effective substitutes for the fruits and vegetables in regards to reduced risk of oral and pharyngeal cancers

Keywords Nutritional epidemiology · Oral cancer · Incidence · Dietary supplements · Oropharnygeal cancer

Introduction

Worldwide, approximately 500,000 new cases of cancer of the lip, oral cavity, oropharynx, and salivary glands (ICD-9 140–149) with approximately 300,000 deaths occur annually [1]. Cancer at these sites is important because the disease and its management can result in pain, disfigurement, speech impairment, and chewing and/or swallowing difficulties, thereby leading to nutritional

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compromise, a decreased quality of life, and reduced survival. While the primary risk factors for oral squamous cell carcinoma (OSCC) and oropharyngeal cancers (OPC) have historically been tobacco and alcohol abuse, and nutritional compromise in developing countries, more recently cases associated with Human papilloma virus (HPV), particularly OPC, are increasingly documented [2–4] This chapter reviews diet and nutrition in relation to OSCC/OPC risk.

Nutritional Epidemiology

Case-control studies have been conducted in developing countries comparing people with cancer to those of a control group. Information on past exposures of interest (e.g., tobacco use, alcohol consumption, and diet/nutrition) is obtained from the cases and controls, often using food frequency questionnaires based upon self-report. The level of macro- and micro-nutrients in the diet may be calculated by estimating the average nutrient content within a typical serving of each food item included on the questionnaire and summing across the foods eaten.

Findings from case studies of OSCC/OPC are often reported in terms of odds ratios (ORs). The OR serves as an estimate of the relative risk (RR). The RR relates the risk of disease among subjects with a reported exposure to the risk to those who do not have the exposure. Both ORs and RRs can range from 0 to infinity. An OR or RR equal to 1.0 suggests no relationship between exposure and the disease. An OR or RR greater than 1.0 indicates a positive association and an OR or RR less than 1.0 suggests a negative, or inverse relationship. An OR of 2.0 indicates a twofold (100%) increased risk among those persons who were unexposed. ORs and RRs are also often reported as having been adjusted for known risk factors such as smoking and alcohol consumption. The purpose of adjusting ORs and RRs is to remove potentially confounding effect of these factors from the relationship being studied [5]. For example, smoking is known to increase the risk of oral cancer, and smokers are more likely to drink coffee than are nonsmokers (i.e., an association between coffee drinking and oral cancer could be confounded by smoking). In studies of diet and nutrition and OSCC, OPC and cancers of the pharynx, it is imperative that potential confounders such as tobacco and alcohol be considered.

Studies based on dietary recall may have limited reliability. Therefore, nutritional epidemiologists often seek to obtain "best" estimates of dietary consumption and on the basis of those estimates form groups with various levels of reported ingestion. Although each subject's estimated consumption may represent a range of intake because these estimates are given by all participants, examining the risk (or odds) of developing a given disease with increasing consumption of a given food group or item (e.g., low, intermediate, and high), epidemiologists can evaluate whether that food is associated with an increased, decreased, or no risk of disease.

Studies of Oropharyngeal Cancer: Diet and Nutrition

A number of epidemiological studies have suggested that certain dietary factors are linked to the risk of OSCC/OPC. Early studies linked Plummer–Vinson syndrome, a disease related to deficiencies in iron, riboflavin, and other vitamins, to the development of primarily hypopharyngeal cancer in women [6, 7], but other investigations prior to the 1980s provided little evidence relating diet to cancer risk [8, 9]. Since the early 1980s, a number of studies in various regions of the world have suggested associations between the low intake of some foods or nutrients and the risk of OSCC/OPC [9].

Food Groups and Items

Fruits and Vegetables

Evidence suggests poor nutritional status and low consumption of certain foods or nutrients increase the risk of developing head and neck cancer. The most consistent findings have been inverse associations between OSCC/OPC and consumption of fruits and/or vegetables [10–27].

Fruits

In developing countries, high fruit consumption has been linked to a reduced risk of OSCC/OPC. In a large case-control study conducted in the United States [11, 13], risk reductions of 40–80% were observed for high versus low fruit consumption among both blacks and whites and between both genders. When fruit subgroups were analyzed separately, high intake of citrus, dark yellow, and other fruits, including watermelon, strawberries, apples, pears, and bananas, were associated with a reduced cancer risk [11, 13]. In a prospective cohort study of more than 34,000 Iowan women followed for 14 years, total fruit intake was associated with a protective effect in upper aerodigestive tract (UADT CA) (oral/pharyngeal, esophageal, gastric, and laryngeal) cancers, although the finding was not statistically significant [23]. A large Italian case-control study also linked fruit consumption with a reduced risk of OSCC/OPC, although the reduction associated with high consumption was greater for citrus (50%) than non-citrus (30%) fruits and statistically significant for citrus only [25]. The beneficial effects associated with citrus intake were seen from consumption of both the whole fruit and fruit juices.

A meta-analysis, involving 16 studies (pooled data, n = 65,802), concluded that fruit consumption significantly reduced the risk of oral cavity and pharyngeal cancer [28]. Combined adjusted OR estimates revealed that each serving of fruit consumed per day significantly reduced the risk of oral cancer by 49% (OR: 0.51; 95% CI: 0.40, 0.65); a stronger protective effect was observed for citrus fruit [28]. All 16 studies indicated that fruit consumption reduced the occurrence of OSCC/OPC cancer. Studies that included both men and women showed a similar significant decrease in the risk of oral cancer in regards to fruit. The authors did note that confounding factors in the relationship between cancer and diet varied considerably across studies. While all studies reviewed adjusted for age and sex, and 93.8% adjusted for smoking (tobacco), only 12.5% adjusted for tobacco chewing habits and 75% for alcohol consumption.

Vegetables

Findings regarding vegetable intake have suggested a protective effect in some studies. In the large US case-control study, OSCC/OPC risk reduction was seen for total vegetable consumption among black males, to a lesser extent among females, but was not seen in white males [11, 13]. In that study, however, vegetables most likely to be eaten raw, including lettuce, cucumbers, fresh tomatoes, carrots, and coleslaw, were associated with 60–80% reductions in OSCC/OPC risk among high consumers in both races and genders. In the cohort study of Iowan women, an inverse relationship was observed for total vegetable intake and risk of UADT cancer, although, again, the finding was not statistically significant [23]. That study found a statistically significant reduction in cancer risk when considering the intake of yellow and orange vegetables. In the Italian case-control study [25], a high intake of both raw and cooked vegetables was associated with approximately 50% reductions in OSCC/OPC risk.

Although individual vegetables have not been evaluated across studies, carrots [11, 14, 18, 22, 25, 27, 29] have been associated with a potentially protective effect in some studies. There is also evidence to suggest that diversity in terms of the fruits and vegetables consumed is inversely related to the risk of OSCC/OPC [20]. A large prospective observational study found an inverse association between total fruit and vegetable intake and risk of head and neck cancer (per serving/day/1,000 cal, HR; 95% CI: 0.94, 0.89–0.99). The association was stronger for vegetables than for fruits. The study further subclassified the fruits and vegetables into botanical groups and found the following to be most significant in decreasing the risk of HNC: legumes (dried beans, string beans, and peas), *rosaceae* (apples, peaches, nectarines, plums, pears, and strawberries), *solanaceae* (peppers and tomatoes), and *umbelliferae* (carrots) [30].

In studies that have examined the association between fruit and/or vegetable consumption and the risk of OSCC/OPC, findings suggest that the effects of both tobacco and alcohol may be attenuated with a diet high in these foods [10, 11, 13, 15, 26, 27, 29]. In a case-control study of OSCC/OPC in southern US women, smokers with a low consumption of fruits and vegetables had over a 300% increase in cancer risk relative to nonsmokers with a low intake of fruits and vegetables. However, smokers with a high consumption of fruits and vegetables had only a 60% increase in risk [10]. These studies showed that smoking increases the risk of OSCC/OPC among these women, but a high consumption of fruits and vegetables was associated with a reduction in risk.

A large meta-analysis (see above, [28]) concluded that there was a significant reduction in the risk of OSCC/OPC in 10 of 15 studies reviewed when evaluating vegetable consumption. The combination of all studies revealed an overall significant reduction in the risk of oral cancer of 50% (O: 0.50; 95% CI: 0.38, 0.65). Studies that included both men and women showed similar significant reduction in the risk of oral cancer and vegetable intake [28].

Low dietary folate intake is an independent risk factor for a number of cancers, including head and neck cancer [31]. There may be an association between folate-related gene polymorphisms and clinical outcomes for colorectal, gastric, and breast cancer [31]. A high pretreatment folate intake ($\geq$320 μg/day, n = 144) was identified as an independent prognostic factor for survival when compared to those consuming a low or medium folate intake (n = 278) (<320 μg/day). Survival was 79.1% in those with the highest intake of folate versus 68.2% (P = 0.020). The effect on prognosis was less clear in patients with a primary tumor of the oral cavity compared to primary sites within the oropharynx, hypopharynx, or larynx, which points out the need to report site specific cancer risks in the upper aerodigestive tract (UADT) in future trials.

Fruits and vegetables are abundant sources of phytochemicals, antioxidants, vitamins, minerals, carotenoids, and polyphenols. Comprehensive listings of sources can be found at http://www.nutrition.gov/whats-food/antioxidants-phytonutrients and http://preventcancer.aicr.org/site/PageServer?pagename=elements_phytochemicals. The nutritive compounds found in these foods may be responsible for reducing inflammation and oxidative stress which maintain the normal cellular processes in the body.

Breads, Grains, and Cereals

Some studies suggest that grain, bread, and cereal consumption may be related to the risk of OSCC/OPC. In the case-control study of OSCC/OPC among women living in the southern United States, a statistically significant protective effect associated with a high consumption of breads and cereals was reported [10]. However, a subsequent large US case-control study found no clear pattern in effect of grain consumption among Caucasians, while among blacks a statistically non-significant risk was reported [11, 13]. Other studies suggest that whole grain bread, pasta, and cereal intake may be associated with a protective effect [10, 11, 14, 23, 29, 32, 33]. A Swiss case-control study found

that high intake of whole grain foods was associated with a 40% reduction in the risk of OSCC/OPC [33], and the cohort study of Iowan women revealed a 50% reduction [23]. However, a large Italian study found no relationship between whole grain bread at least weekly and OSCC/OPC risk [25]. Further study is required to understand the possible associations between whole grain foods and cancer risk.

Lam et al. [34] followed subjects for roughly 11 years (n = 1867; 401 women/1,466 men); an inverse relationship was found between fiber and grain intake and head and neck cancer among women. The results showed that in women consuming a higher intake of total fiber and grains there was a lower risk of HNC (HR10 g/day = 0.77; 95% CI: 0.64–0.93; HR serving/1000 kcal = 0.89; 95% CI: 0.80–0.99, respectively). The inverse relationship was consistent across subtypes of fiber and grain. Notably, the inverse associations were weaker and nonsignificant among men [34]. Research assessing bread, grains, and cereals should classify these as whole food based versus refined or processed.

A longitudinal study (n = 542) of newly diagnosed patients with head and neck cancer identified two specific dietary patterns, a whole foods pattern (whole grains, fruit vegetables, fish, and poultry) and a western pattern (high intake of red/processed meats, refined grains, potatoes/French fries, high fat dairy products, desserts, etc.) [35]. The study concluded that a diet rich in whole foods before treatment was associated with a lower risk of recurrence and improved survival among patients with head and neck cancer. The authors also reported that being overweight or obese at the time of diagnosis was associated with better prognosis, independent of diet [35].

Meats

Some studies have reported increased risk of OSCC/OPC associated with consumption of meat high in animal protein [11, 20, 22, 24], while other studies have reported protective or inconsistent patterns [13, 15, 18, 29, 36]. In a Brazilian investigation, charcoal-grilled meat was linked to an elevated risk of oral cancer [12], but studies in the United States have failed to show this relationship [10, 11, 13]. Some studies have suggested that salted meat and fish [15, 36] or nitrite-containing [11, 13] or processed meats [25] could be associated with increased risks of OSCC/OPC, however, these associations have not been sufficiently corroborated. Although fish consumption has been identified as potentially reducing risk of OSCC/OPC risk in several studies [11, 13, 16, 18, 25, 27, 37], other investigations have not reported this relationship [10, 15, 22].

A large population-based case-control study (n = 1,176 cases of HNC and 1,317 age, race, and gender-matched controls) evaluated the association between dietary patterns and risk of HNC. The study concluded that a dietary pattern consisting of fried foods, high-fat and processed meats, and sweets were positively associated with laryngeal cancer (OR : 2.12; 95% CI: 1.21, 3.72). No relationship was observed in regards to OSCC/OPC. The food pattern deemed "fried foods, high-fat and processed meats, and sweets" included the following: beef (roast beef, burgers, and ground beef), fried chicken (dark and light meat), candy and chocolate, ice cream, desserts, sugar-sweetened beverages, sausage and bacon, pork products, processed meat products, and fried seafood [38].

Dairy Products

Dairy foods have not been consistently related to a risk of OSCC/OPC. Some studies have suggested high milk intake may reduce risk [18, 20, 29], while other investigations have not found a protective effect [25, 36]. Similarly, cheese intake has been associated with an increased risk in some [14, 22] but not other studies [25, 29]. A possible link between egg consumption has also varied by study [14,

18, 20, 25]. Similar inconsistencies have been observed with regard to the use of butter [14, 17, 25, 29]. Current evidence regarding milk and dairy products and the risk of HNC is inconsistent; however, studies do not appear to indicate a strong association. Further research is warranted.

Coffee and Tea

Coffee and tea are some of the most commonly consumed beverages worldwide. Both contain antioxidants, polyphenols, and biologically active compounds that may help prevent cancer or perhaps protect against the progression of cancer [39]. Hildebrand et al. [39] reported associations between caffeinated coffee, decaffeinated coffee, and tea intake with fatal oral/pharyngeal cancer. Intake of greater than 4 cups/day of caffeinated coffee was associated with a 49% lower risk of oral/pharyngeal cancer death when compared to no/occasional coffee intake (RR: 0.51; 95% CI: 0.40, 0.64). Notably, a dose-related decline in RR was observed with each cup/day consumed ($P_{trend} < 0.001$). The relationship was not modified by smoking status, sex, or alcohol use. An inverse association was suggested for >2 cups/day of decaffeinated coffee, however, no association was noted for tea consumption.

A pooled analysis (nine case-control studies of HNC; 5,139 cases and 9.028 controls) identified that caffeinated coffee intake was inversely related to the risk of OSCC/OPC, OR 0.96 (95% CI: 0.94–0.98) for an increase of 1 cup/day and 0.61 (95% CI: 0.47–0.80) in those consuming greater than $4 > 4$ cups/day compared to nondrinkers. The relationship was consistent for the following anatomic sites; oral cavity, oropharynx/hypopharynx, and oral cavity/pharynx not otherwise specified. There was no association found between caffeinated coffee intake and laryngeal cancer. No association was noted between decaffeinated coffee or tea intake and head and neck cancer [40].

Summary

To date, fruits and vegetables are the best established dietary links to OSCC/OPC risk, particularly in developing countries with some evidence in western studies. The associations generally remain after adjusting for known high risk factors of smoking, drinking, and other potential confounders. However, nutritional supplements in the form of vitamin and mineral supplements have not been shown to impact OPC risk [41]. Coffee consumption has increasing support for prevention in a number of cancers including OSCC and OPC.

Fiber and Micronutrients

Dietary Fiber

There is evidence that fiber intake is inversely associated with OSCC/OPC. Studies in the United States, Australia, China, and Italy have reported decreases in risk of 40% or more in persons with a high intake of total fiber [11, 13, 18, 42–44]. However, the observed reductions in risk may not be a function of the fiber per se; or whether this may represent markers of a diet high in fruits, vegetables, and whole grains.

Micronutrients

Dietary Micronutrients

Various dietary micronutrients, including vitamins, provitamins, and minerals, have been investigated for potential associations with OSCC/OPC risk. Findings from studies reported in the early to mid-1980s suggested a possible inverse relationship between dietary vitamin A and OSCC/OPC risk among men [45, 46], but not among women [45]. In those studies, however, the researchers were limited by the existing US Department of Agriculture (USDA) food composition tables, which did not differentiate between retinol (vitamin A from primarily animal sources). Provitamin A and carotenoids, such as β-carotene, derived primarily from plants [47]. Subsequent studies, aided by more advanced food composition tables, have facilitated evaluation of dietary retinol and carotene intake in relation to OSCC/OPC risk.

Inconsistent findings of retinol intake and its association with OPC risk have been reported. In the large US study, increased risk was observed with increasing dietary retinol among black and white males and among white females [11, 13]. For black females, however, no clear patterns of risk were observed [13]. Similarly, retinol intake was not clearly associated with a risk of OPC in a case-control study conducted in Italy and Switzerland [48].

Dietary carotene has been examined with some studies suggesting a protective association [18, 39], while other investigations have been equivocal or shown no effect [11, 13, 15, 24, 42]. On the basis of the large US study, McLaughlin et al. [11] reported a 60% reduction in cancer risk among high consumers of fruit carotene, but little risk reduction for persons with a high intake of carotene from vegetable sources. However, findings from a Chinese study showed 40% and 50% reductions in oral cancer risk with high, relative to low, dietary intakes of carotene from fruits and vegetables, respectively [18]. A similar study in Shanghai revealed no evidence of a protective relationship [15]. During the early 2000s, findings from two European case-control studies were reported. Although a Greek study found no relationship between carotene intake and OSCC/OPC risk [24], a large investigation conducted in Italy and Switzerland revealed strong protective effects that generally increased with the amount of carotene consumed [48].

In addition to carotene, the dietary intake of various other antioxidants, primarily vitamins C and E, have been investigated in relation to OSCC/OPC risk. Dietary intake of vitamin C has generally been associated with a decreased risk of OPC in studies conducted in various regions of the world, including the US, China, Australia, Greece, Switzerland, and Italy [11, 13, 18, 24, 43, 46, 48, 49], although some studies have found only little [42] or no effect [15]. In the large US case-control study, for example, men and women who consumed a high level of dietary vitamin C had a 40% or more reduction in their risk of OSCC/OPC compared to persons with a low intake [11, 13]. On the other hand, evidence for an association between vitamin E is generally weak, although one case-control study did report on a moderate-to-strong inverse relationship [48].

The dietary intake of B vitamins (thiamin, niacin, riboflavin, pyridoxine, and folic acid) has been evaluated in terms of OSCC/OPC risk [11, 13, 24, 42, 48]. Each of these vitamins has been identified as protective in some studies; however, conflicting findings have been reported, and therefore more research is needed before any conclusions can be drawn.

Recent studies have assessed the beneficial effect of dietary folate. Folate is essential for DNA synthesis and repair and for the methylation of biological substances. Alcohol interferes with many aspects of normal folate transport and metabolism. Although the effect of alcohol on folate is primarily related to its influence on folate metabolism in the liver, metabolism of acetaldehyde from ethanol occurs locally in the oral cavity as well. This may decrease the beneficial effect of folate, which, in turn may increase cancer risk by disrupting the DNA synthesis, repair and methylation of the squamous epithelial oral cell [50]. In addition to the previous study [51], a study including a cohort of women within the Nurses' Health Study concluded that higher alcohol intake was

associated with significantly increased risk of oral cancer, especially in women with low folate intake. Cancer risk for those women with a high alcohol intake (>30 g/day) and low folate intake (<350 μg/day) was significantly increased (RR: 3.36; 95% CI: 1.57–7.20) compared to non-drinkers with a lower folate intake. The risk associated with a higher intake of alcohol was reduced to 0.98 (0.35–2.70) in the high folate intake group (>350 μg/day), compared to non-drinkers with high folate [52]. Foods high in folate content include beans, lentils, edamame, and green leafy vegetables.

Some minerals, including calcium, iron, phosphorous, and potassium, have each been assessed in relation to OSCC/OPC risk [11, 13, 18, 24, 42, 48], but limited data and conflicting outcomes do not allow association with these cancers.

Vitamin Supplementation

The relationship between vitamin supplementation and OSCC/OPC risk has received limited attention. Our society readily accepts the concept of vitamin and mineral supplementation by tablet; unfortunately, this is often based on limited or no evidence of effect. In studies carried out in the United States assessing supplementation, little evidence of an association between cancer risk and multivitamins use is seen [49, 53, 54]. On the other hand, in the largest and most comprehensive of the three studies, persons who reported taking one or more individual supplements for vitamins A, C, E, or B-complex for at least 6 months had a 30% reduction in risk [53]. Only vitamin E demonstrated statistically significant risk reduction (OR: 0.5) after taking into account the fact that persons who use one vitamin supplement may also be using another. The 50% reduction in risk with vitamin E supplementation was remarkably consistent across levels of tobacco and alcohol use, and fruit and vegetable consumption. In persons with a high use of tobacco and alcohol, those who took vitamin E supplements had half the risk of those who did not. A protective effect with vitamin E supplementation was observed in another study [54]. Given the equivocal and historical nature of these studies, additional research is necessary [41].

Serum Micronutrients

Studies have assessed serum micronutrient levels in persons with and without cancer. Three studies in the 1990s assessed possible protective relationship between high serum β-carotene levels and the subsequent development of OSCC/OPC, although the findings were not always statistically significant [55–57]. In addition, and although evaluated in only two of the three studies, serum levels of other carotenoids, including α-carotene and β-crytoxanthin were also lower in cases than in matched controls [56, 57]. Serum levels of vitamin E, including α- and γ-tocopherol showed inconsistent findings across studies.

The potential mechanisms of action of β-carotene and other carotenoids include oxygen scavenging and capture of free radicals that may prevent genetic mutations and immune dysfunction and potential activity at the retinoic acid receptors and second messenger generation. Vitamin C has been shown to reduce the formation of nitrosamine and act as an immune response enhancer. It is less clear, how various nutrients function together. For example, although there is evidence suggesting that certain antioxidants can act synergistically in some cancers, Negri et al. [48] found evidence of antagonism when the relationship between various antioxidants are evaluated in relation to OSCC/OPC risk. Additional research and improved methodological tools are needed in order to further our understanding as to how nutritional factors influence the risk of OPC.

Supplements of beta-carotene and alpha-tocopherol were shown not to prevent lung cancer in men who smoke and may increase cancer risk and are therefore to be avoided (see below, [58, 59]).

Studies of Precancerous Oral Lesions and Conditions in Relation to Diet and Nutrition

One of the concerns of studies that investigate the relationships between diet and OSCC/OPC risk is that symptoms associated with cancer in the region could impact dietary intake and thereby influence the reporting of pre-illness diets in case-control studies [59]. Such reporting could give rise to the identification of misleading associations between risk and dietary and/or nutritional factors due to potential bias. The study of precancerous oral lesions such as leukoplakia and erythroplakia (i.e., a white or red lesion of the oral mucosa that cannot be categorized as any other definable lesion [60] and those with epithelial dysplasia may be useful in addressing this concern because such lesions are generally asymptomatic and therefore less likely to initiate dietary changes. The challenge in the lesions present is the unpredictable nature of progression or regression of the clinical lesion or histologic dysplasia and progression to cancer. The highest risk of progression to cancer of these lesions are those seen in patients who have had prior UADT cancer and specifically prior OSCC/OPC. These populations have been assessed in preventive trials ([61–63]; see below). The relationship between diet and nutrition and oral submucous fibrosis (OSF), a precancerous condition seen most often in individuals living in or migrating from areas in Asia, particularly the Indian subcontinent (see below). Unlike oral leukoplakia commonly seen in western countries, OSF is associated with use of betel nut and often presents with a burning sensation when consuming spicy foods, a characteristic that could lead to dietary alterations. Due to differences in etiology and site of lesion, mucosal changes associated with betel nut should be assessed separately from oral and pharyngeal lesions of different etiology including tobacco, and human papilloma virus.

Some investigations focusing on potentially malignant oral lesions have evaluated a possible link between the oral lesions or conditions and the intake of specific foods or food groups [61–63]. One study in India of male tobacco users revealed marginally significant protective effects with the consumption of fruits (OSF) and vegetables (leukoplakia) as well as a significant inverse relationship between fiber intake and the risk of leukoplakia and OSF [61]. Another Indian study of oral leukoplakia and OSF involving tobacco users and a US investigation of oral epithelial dysplasia risk each reported findings consistent with a protective effect associated with fruit and/or vegetable consumption [62, 63]. It is important to recall that leukoplakia in patients at risk due to use of betel nut have a different distribution of lesions favoring the buccal mucosa and an association with OSF may not be representative of more common lesions of the tongue and floor of the mouth with tobacco use and alcohol abuse in western countries.

Among those investigations studying the potential link between various precancerous lesions or conditions and selected dietary micronutrients, vitamin C [61, 62, 64, 65] and β-carotene, iron, and zinc [62, 63] have been identified as having potentially protective effects. However, further research is required to verify and understand the mechanisms through which such associations are manifest.

Studies of Cancer Chemoprevention

Cancer chemoprevention is the use of chemical agents to prevent cancer. Potential chemopreventive agents have been identified by molecular modeling, in vitro and in vivo models, and by studies discussed above. The study of chemoprevention in OSCC/OPC may also be instructed by studies in chemoprevention of other epithelial cancers such as lung and colon. Intervention trials for OSCC/OPC have evaluated effectiveness in reversing oral leukoplakia and oral lesions with dysplasia and in preventing second primary and recurrent cancers in those who have had prior UADT cancers. Common agents evaluated include vitamin A derivatives (13-cis-retinoic acid, fenretinide, and

etretinate) and naturally occurring vitamins including vitamins A, C, and E, β-carotene, and selenium, which are generally administered as pills or capsules at high supplemental levels [66, 67]. There are also limited trials of topical vitamin A acid [68], but these will not be discussed further because they are outside the focus of this chapter. While several chemoprevention trials of oral premalignancy have focused on vitamin A and β-carotene, and both nutrients have been shown to reverse oral leukoplakia [69–74], more comprehensive study has not shown effective chemoprevention by systemic supplements without toxicity [66]. Systemic vitamin A supplements are not recommended due to limited effect and risk of side effect/toxicity [67, 75–77].

Large studies of β-carotene were conducted to assess prevention of second primary and recurrent cancers among persons diagnosed with a previous OSCC/OPC [58, 59]. One trial [59] after a mean follow-up of 51 months found the β-carotene group experienced a 30% decrease in the risk of second or recurrent head and neck cancers, and a 15% reduction in total mortality, but a 45% increase in the risk of lung cancer, although none of those findings were statistically significant. The increased risk of lung cancer associated with β-carotene supplementation has also been observed in earlier cancer chemoprevention trials focusing on endpoints other than OPC [66, 75–77] and underscores the fact that there is still much to learn regarding the role of nutrients in cancer and cancer prevention. B-carotene has since been abandoned in chemoprevention for HNC.

Due to findings of significant adverse events with systemic vitamin A supplementation, topical application for premalignant oral lesions was assessed. In a small trial, approximately 50% of lesions responded clinically and did not recur in approximately half, and that if recurrence was seen this was reversed with resuming topical treatments [68]. This may therefore represent a local means of leukoplakia control without the risk of the adverse events associated with high dose vitamin A supplementation.

There are other non-nutritional and non-vitamin approaches that have been studied in patients at high risk for OPC, but these are not the topic of review in this chapter.

Summary: Recommendations for Clinicians

Around the world, OSCC/OPC affects hundreds of thousands of individuals each year. In the United States and other Western countries, tobacco use and alcohol consumption are the recognized causative agents, and increasing importance of HPV as an essential risk factor for OSCC/OPC is recognized. Diet and nutrition also appear to play a potential role. Most studies investigating a link between diet and OSCC/OPC, and to a lesser extent potentially malignant oral lesions have reported a protective effect associated with the consumption of fruits and vegetables. Dietary recommendations for OSCC/OPC risk reduction [78, 79] are also consistent with general diet recommendations addressed in Chapter 1 of this text. Table 12.1 addresses practice guidelines for oral health care professionals and nutrition professionals in regards to risk reduction for OSCC/OPC.

To date, nutritional supplements in the forms of vitamin and minerals have not shown preventive effects, other than vitamin A and B-carotene that have significant adverse effects or other systemic health risks that have led to recommendations against use of systemic supplementation. Some investigations also suggest that the consumption of whole grain foods as well as a diet high in fiber intake may also be protective. Studies investigating specific dietary micronutrients in relation to OPC have suggested that vitamin C may be associated with a reduced risk. It is not clear, however, whether these micronutrients are directly responsible for the risk reduction, or whether they are markers for some other responsible factor and the adverse effects seen to date do not allow recommendations for use. Multivitamins have not emerged as protective in terms of OSCC/OPC, and while two case-control studies have suggested that vitamin E supplementation may be protective, it is too early to recommend this supplement to patients. Coffee consumption has been assessed in large population studies, with

Table 12.1 Guidelines for practice

Oral health professional
- Complete head and neck and oral exam
- Reinforce tobacco cessation, moderate alcohol consumption; balanced diet

Manage
- Dental status: functional occlusion, dental pain/infection, dental breakdown, pain
- Dental prevention: oral hygiene, caries prevention
- Jaw continuity: postsurgery, osteonecrosis
- Hyposalivation
- Mucosal lesions/pain/sensitivity
- Functional pain (e.g.,: TMD)
- Limitation of opening (pain, fibrosis)
- Diet recommendations:
  - Balanced meal plan, adequate in vitamins, minerals, and nutrients (calories, protein, and fluid)
  - Modify diet texture for specific limitations (e.g.,: dental and jaw condition, xerostomia, mucosal sensitivity)
  - Instruction on limiting simple sugar intake, diet texture
- Taste

Nutrition professional
- Reinforce tobacco cessation, moderate alcohol consumption
- Balanced meal plan, adequate in vitamins, minerals, and nutrients (calories, protein, and fluid)
- Modify diet texture for specific limitations (e.g.,: dental and jaw condition, xerostomia, mucosal sensitivity)
- Encourage selecting foods from all food groups; American cancer Society Guidelines for Cancer Prevention
- Encourage 5–9 servings of fruits and vegetables; including citrus fruits, dark green, deep yellow vegetables
- Encourage whole foods, high fiber foods (e.g.,: whole grain breads and cereals)
- Encourage healthy fats, limit saturated fats
- Preparation: encourage fresh, baking or broiling
- Encourage low-fat milk and dairy options
- Limit salt-cured, smoked and pickled foods
- Limit alcohol intake, encourage moderation
- Minimize consumption of simple sugars (frequency and quantity)
- Weight maintenance, weight gain, weight loss: discuss achievable goals and give direction on achieving goals (i.e., increase activity if no limitations; discuss a new exercise with physician). If goals not met, discuss and address barriers were possible

beneficial effects attributed to plant phenols and antioxidants. Finally, although various potential oral cancer chemopreventive agents have been and are being evaluated for their effectiveness and safety, the use of these agents remains experimental at this time. Although patients and consumers may self-prescribe dietary supplements for prevention of OSCC/OPC, it is up to clinicians to advise patients about the lack of supportive evidence and risks associated with some dietary supplements. Chapter 9 in this book addresses dietary supplementation in greater depth.

Sources for Additional Information

Further information regarding diet and nutrition in relation to OSCC/OPC can be obtained by accessing the websites for the National Cancer Institute and the American Cancer Society (ACS). (http://www.cancer.org/docroot/PED/content/PED_3_2X_Recommendations.asp?sitearea=PED; http://www.cancer.org/docroot/MBC/MBC_6_1_things_to_think_about.asp).

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Chapter 13
Nutrition Management of the Cancer Patient

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Keypoints

- The locoregional nature of head and neck cancers along with their associated therapies (chemotherapy, targeted therapy, radiation therapy, and surgery) can impact appetite and dietary intake
- Nutrition assessment and management of patients with head and neck cancer should be initiated early and monitored before, during, and after cancer treatment
- Mechanical and sensory functions may be affected and should be assessed and managed in order to maximize oral intake
- The interprofessional team approach including oral health care professionals and registered dietitians is essential in managing patients with head and neck cancers

Keywords Nutrition management · Head and neck cancer · Dietary intake · Nutrition assessment · Dietary impact

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Introduction

According to the American Cancer Society one out of two American men and one out of three American women will develop cancer at some point in their lifetime [1]. In 2013 this translates to more than 1.6 million Americans being diagnosed with cancer; of which approximately 3% were head and neck cancer (HNC) [1].

Although the proportion of individuals with HNC is small, the number of cases are increasing and the population is distinct in regard to the adverse impact of treatment which may involve surgery, chemotherapy, radiation therapy, or a combination of these modalities [1–4]. Changes in the epidemiology and advances in treatment and the use of multimodal therapy have improved outcomes, however, acute and late-term side effects have increased [5]. It is estimated that greater than 90% of all HNC cancer patients will develop mucositis and oral complications during their course of treatment with oral mucositis being the most debilitating acute toxicity [6, 7]. Oral health problems are often underappreciated and require continuing research; however, they have a profound impact on a patient's quality of life and impact overall health [8].

The anatomic location of HNC is such that side effects of the tumor or its treatment may impact mouth opening, biting, chewing, or swallowing, resulting in compromised oral consumption of foods, fluids, or medications. Specific toxicities affecting the oral cavity include mucositis, hyposalivation, taste changes, mucosal sensitivity, odynophagia, dysphagia, mucous production, and edema [9–12]. The oral mucosa is particularly vulnerable to side effects of concurrent chemoradiation (CCR); 90–100% of patients with HNC that undergo CCR develop oral complications related to their cancer therapy [12, 13]. Severe mucositis is the most common acute toxicity [14, 15]. Late treatment effects may also result in decreased oral intake. In an analysis of three Radiation Therapy Oncology Group (RTOG) studies, Machtay et al. evaluated clinical factors associated with late toxicity of CCR; 43% of patients with HNC had severe late toxicity post-CCR [16]. Significant factors identified were age, advanced T stage, cancer site, and neck dissection and cancer treatment provided [16]. Dysphagia is a common, debilitating late effect of CCR that may prolong patient recovery and require long-term feeding tube reliance. If it occurs post-CCR, dysphagia may be silent and the use of swallow studies may be required to identify and provide rehabilitation to patients with HNC post-CCR [17]. Post-treatment neck dissection can increase swallowing dysfunction secondary to fibrosis which may limit mobility of the laryngopharynx and CCR [20, 21]. In a study of patients with locally advanced HNC (Stages III and IV) post-CCR (median time of follow-up was 17 months), 45% of the patients developed severe dysphagia requiring prolonged use of a feeding tube (>3 months) or repeated dilatation related to pharyngeal or esophageal stenosis. Aspiration was often unrecognized, and discovered only by barium or modified barium swallow studies [17]. Assessment of symptom and functional deficits is clinically relevant for both patients and healthcare professionals [18].

A multidisciplinary team approach is essential and include otolaryngologists, medical, and radiation oncologists, dentists, and registered dietitians (RD) along with oncology social workers, speech and language pathologists, physical and/or occupational therapists, and oncology nurses as essential team members [2, 3]. This chapter addresses diet management, nutrition screening and assessment of the patient with HNC, and provides suggestions for health professionals to potential nutrition impact symptoms for both acute and late treatment effects resulting from HNC and associated therapies to treat the disease.

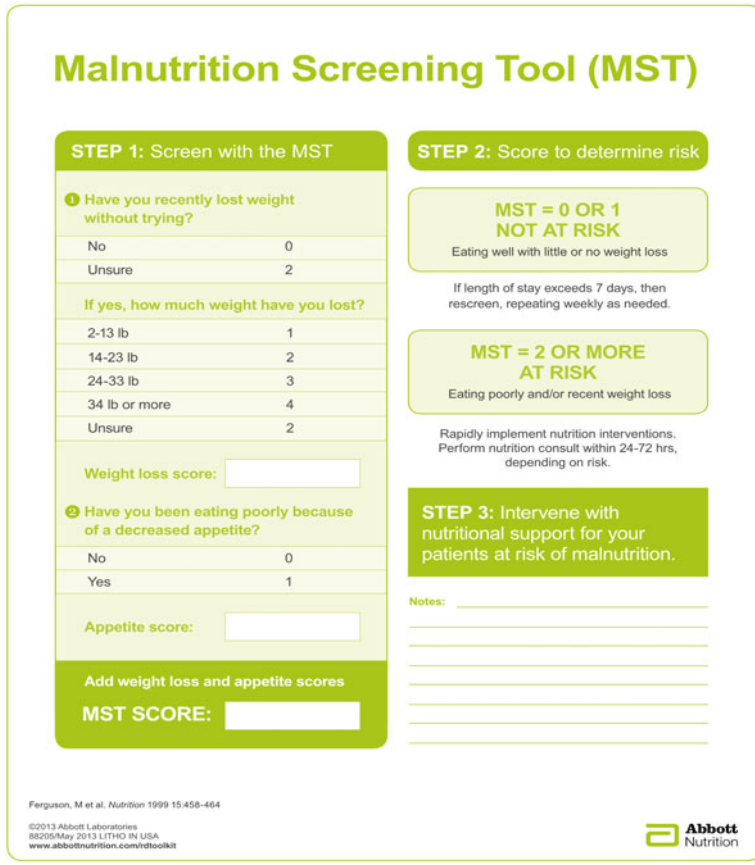
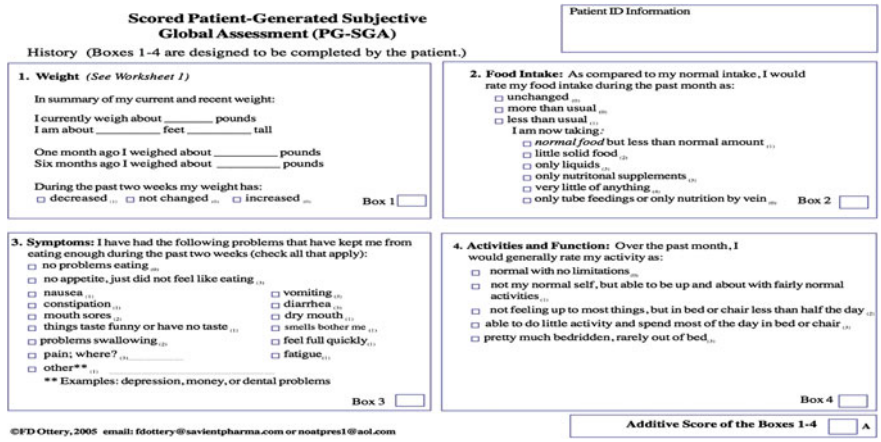


Fig. 13.1 Malnutrition screening tool http://static.abbottnutrition.com/cms-prod/abbottnutrition.com/img/Malnutrition%20Screening%20Tool_FINAL.pdf

Head and Neck Cancer Nutrition Screening, Assessment, and Referral

The primary diet and nutrition goals for patients with HNC are to achieve optimal nutrition, prevent weight loss, maintain lean muscle mass, and resume optimal oral intake post-treatment [4]. In order to reduce treatment-related nutrition challenges, patients with HNC should be seen by an RD prior to initiation of, during, and post-treatment to maximize nutritional status [19]. Nutrition screening is the first step in the identification of nutrition risk and it allows the practitioner to identify those patients who are malnourished or at nutritional risk. A screening tool includes objective data (i.e., height, weight, weight change, comorbidities) and should be cost-effective, easy to use, valid, reliable, and sensitive [5]. The *Malnutrition Screening Tool* (MST) (Fig. 13.1) has been validated as a nutrition screening tool for adults with cancer [6, 7]. It includes three questions that address weight, weight change, and appetite.

A nutrition assessment is more comprehensive than screening and includes a medical history, a nutrition focused physical examination including oral examination, anthropometric measurements, and laboratory values. This assessment provides the RD the means to diagnose nutrition problems and identify and address nutritional problems and potential deficiencies prior to treatment initiation, throughout the course of treatment and following treatment. The Patient-Generated Subjective Global Assessment (PG-SGA) (Fig. 13.2) is a nutrition assessment tool that has been validated for use in adults with cancer [8]. The patient generated portion (PG) of the PG-SGA is a



Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased ☐ not changed ☐ increased

Box 1

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:
☐ unchanged
☐ more than usual
☐ less than usual
I am now taking:
☐ *normal food* but less than normal amount
☐ little solid food
☐ only liquids
☐ only nutritonal supplements
☐ very little of anything
☐ only tube feedings or only nutrition by vein

Box 2

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):
☐ no problems eating
☐ no appetite, just did not feel like eating
☐ nausea
☐ constipation
☐ mouth sores
☐ things taste funny or have no taste
☐ problems swallowing
☐ pain; where? _____
☐ other** _____
☐ vomiting
☐ diarrhea
☐ dry mouth
☐ smells bother me
☐ feel full quickly
☐ fatigue
** Examples: depression, money, or dental problems

Box 3

4. Activities and Function: Over the past month, I would generally rate my activity as:
☐ normal with no limitations
☐ not my normal self, but able to be up and about with fairly normal activities
☐ not feeling up to most things, but in bed or chair less than half the day
☐ able to do little activity and spend most of the day in bed or chair
☐ pretty much bedridden, rarely out of bed

Box 4

©FD Ottery, 2005 email: fdottery@savientpharma.com or noatpres1@aol.com

Additive Score of the Boxes 1-4 ☐ A

Fig. 13.2 Patient generated subjective global assessment (PG-SGA) for cancer http://www.accc-cancer.org/oncology_issues/supplements/pgsga.pdf

self-administered four-item questionnaire which includes weight history, symptoms, food history, and activity level. The practitioner completes the remainder of the worksheet and calculates a score based on the physical examination, diagnosis, metabolic demand, and comorbidities. Although nutrition screening would be the initial component identifying those at nutrition risk in all healthcare settings, a healthcare organization must determine what tool is utilized, who is at risk, and how often reassessment is to take place [5]. A referral process is necessary to ensure patients who are identified at-risk are seen by the RD in a timely manner.

Head and Neck Cancer Treatment and Nutrition Impact Symptoms

Treatment options selected determine the immediate, intermediate, and long-term impact on nutrition status (see Table 13.1). HNC treatment approaches are chosen based upon disease factors (site, extent of disease, pathologic findings), presence or absence of comorbid conditions, and patient preference. Treatment is often aggressive involving surgery, chemotherapy, radiation therapy, or a combination of modalities. Potential nutrition complications resulting from the tumor, surgery, chemotherapy, and radiation therapy in the treatment of HNC are identified in Table 13.1 [4, 12, 20–25]. The size and location of the tumor may affect oral function, particularly if involving the oral tongue, base of tongue, and oropharynx. In addition to mass effects and affect on function of the involved site, pain may affect oral intake. Localized oral lesions (Stages I and II) are primarily treated surgically, whereas those of the oropharynx are primarily treated by radiation therapy. For locally advanced cancer and those with locoregional disease (Stage III/IV disease) multimodality therapy is required.

Oral toxicities, those symptoms that occur secondary to cancer treatments often coexist and are interdependent; they may be classified as acute or late effects. An acute toxicity typically occurs early in the course of treatment and generally resolves by treatment completion. For example, patients who undergo concurrent chemoradiation therapy experience acute effects that create nutritional challenges. However, it is possible that an acute toxicity may fail to resolve and may persist as a late effect toxicity [26]. Early nutrition screening and assessment and prevention and management of oral complications in patients with HNC are essential. The Vanderbilt Head and Neck Symptom Survey 2.0 (VHNSS) allows practitioners to assess, qualify, and quantify symptom

Table 13.1 Nutrition considerations for treatment modalities in head and neck cancer [4, 12, 20, 22–25]

Nutrition complications after head and neck cancer surgery						
Surgery	Compromised swallowing and aspiration potential	Delayed swallow (>10 seconds)	Dysphagia, odynophagia, postoperative swelling	Dental extractions/ altered dentition	Dry mouth/altered taste	Inability to meet energy needs
Base of tongue resection	X	X	X			X
Total glossectomy	X	X	X		X	X
Partial glossectomy	X		X			
Floor of mouth resection		X	X	X		X
Hypopharyngeal resection	X	X	X			X
Total laryngectomy		X	X			X
Partial laryngectomy	X		X			X
Total maxillectomy	X		X	X		X
Pharynogo-laryngectomy		X	X			X
Oropharyngeal resection	X	X	X	X		X
Mandiblectomy			X	X	X	X
Buccal/mucosal resection			X	X	X	
Loss of 7th cranial nerve	X	X			X	X
Thyroidectomy			X		X	

(continued)

Table 13.1 (continued)

Oral complications related to chemotherapy

Complication	Direct risk factor	Indirect risk factor
Oral mucositis	Mucosal cytotoxicity	Decreased local/systemic immunity
	Physical/chemical/microbial irritation	Local infections, reactivation of herpes simplex virus
Oral infections		
Viral		Decreased systemic immunity
Fungal	Antibiotics, steroids, salivary gland dysfunction, and local immunity	Decreased systemic immunity Altered oral flora
Bacterial	Inadequate oral hygiene Mucosal breakdown Acquired pathogens	Decreased systemic immunity Salivary gland dysfunction
Taste dysfunction	Taste receptor toxicity, neural toxicity	Salivary gland dysfunction Mucosa and taste receptor damage
Xerostomia	Salivary gland toxicity	Xerogenergin medications: (e.g.,: anti-hypertensive, anticholinergic, antianxiety drugs, opioids)
Neuropathies	Vinca alkaloid drug use; specific drug toxicity (platinum, taxanes, etc.); surgical neuropathy, radiation toxicity	Anemia, dental hypersensitivity
Gastrointestinal mucositis causing secondary changes in oral status including taste, hygiene, and dietary intake	Mucosal cytotoxicity: radiation and chemotherapy	Nausea and vomiting
Hemorrhage	Oral mucositis Physical trauma Infections	Thrombocytopenia Decreased clotting factors

(continued)

Table 13.1 (continued)

Oral complications related to radiation therapy		
Acute complications	Chronic complications	Results of significant toxicities caused by radiation to the head and neck region
Anorexia	Ageusia/dysguesia/dysosmia	Dehydration
Dysgeusia	Cachexia	Dental complications
Dysosmia	Dental demineralization/caries	Discontinuation of treatment
Dysphagia	Infection—fungal or bacterial	Dose limitations
Infection—fungal or bacterial	Mucosal fibrosis and atrophy	Extreme fatigue
Odynophagia	Muscular/cutaneous fibrosis	Hospitalization
Oral mucositis	Osteonecrosis	Oral complications and pain
Salivary gland dysfunction	Soft tissue necrosis	Taste alterations
Sore mouth and throat	Trismus	Treatment interruptions
Taste dysfunction	Xerostomia	Weight loss
Xerostomia		Ultimately poor outcome

burden and duration in a timely manner [27, 28]. Symptom burden is a concept that refers to the combination of both the severity of symptoms and the patient's perception of the impact of the symptom. The VHNSS was designed for use in a clinic setting by health professionals to identify specific symptoms associated with HNC including acute and late stage toxicities and to help guide clinical care. There are 50 questions within 13 domains that are specific to the HNC population. Questions are ranked on a scale of 0–10 with 0 indicating no issue and 10 indicating severe symptom issues. The VHNSS 2.0 addresses the possible adverse effects of treatment such as mucosal sensitivity, dental health, and trismus [27, 28]. OHCPs and RDs as well as other health professionals can use this tool during initial and periodic patient visits to determine symptoms impacting the ability to eat and drink and quality of life. The value of its use lies in the information gleaned that can be used to guide changes in treatment plans and management strategies.

In dentate, patients with xerostomia, the frequency of fermentable carbohydrate (carbohydrates that can be metabolized by salivary amylase) (e.g., fruits and juices, sugar-sweetened foods and beverages) intake must also be considered because they can increase the caries risk in already at-risk patients [29]. Some suggestions are to complete appropriate oral hygiene procedures (e.g., brushing teeth) before or immediately following consumption of sugar-sweetened foods and fluids including those with natural sugars such as fruits and juices/sweetened beverages, limiting these foods to mealtimes, and to maintain caries prevention strategies on a daily basis. In addition, acidic products in liquid form (e.g., citrus beverages including sugar-sweetened and sugar-free: fruit drinks, carbonated beverages, and ice tea) and in foods should be limited as they can irritate soft tissue and increase risk of tooth demineralization and caries. Common nutrition impact symptoms resulting from treatment and recommendations for management of diet and nutrition for individuals with acute toxicities are described in Table 13.2 [12, 20, 22, 30–32].

In addition to severe acute oral complications, treatment may cause a debilitating long-term impact on nutritional and functional status, including mechanical as well as sensory aspects of eating and drinking and overall quality of life [2, 3, 12, 20, 21, 33]. A late effect is defined as an adverse effect which develops at least 90 days posttreatment [26]. These may include hyposalivation, xerostomia, thick secretions, dysgeusia, dental caries, dental sensitivity, advanced periodontal disease, ulcers, osteonecrosis, soft tissue necrosis, trismus, limited movement of lips/tongue, mucosal sensitivity, dysphagia, odynophagia, esophageal stricture, anorexia, and dysomia [31, 33].

Late effects of treatment may go unrecognized by the patient and hence be underreported to the health provider as patients unconsciously compensate for the impacts. Such compensation may be adaptive or maladaptive. An example of adaptive compensation would be a patient reporting no xerostomia with eating, however, a dietary recall indicates the patient is drinking 32 ounces of milk with each meal (adapting for the xerostomia). In contrast, a patient who avoids meat as a protein source due to taste loss or aversions, difficulty chewing or xerostomia, or avoids fruits and vegetables as a result of mucosal sensitivity would be exhibiting maladaptive behaviors. These behaviors have the potential to lead to nutritional deficiencies that may impact long-term health [28]. It is essential that oral health care professionals (OHCPs) and RDs identify possible late effects of treatment. Suggestions for diet and nutrition management of potential late effects of treatment are given in Table 13.3 [12, 20, 22, 30–34].

Patients who undergo CCR are at risk for significant mucositis and dysphagia which may require the use of a feeding tube to achieve energy, fluid, and nutrient needs [35–38]. Currently, no standard criteria exist for placement or timing of placement of feeding tubes in patients with HNC [35, 39]. Feeding tube placement may decrease incidence of weight loss, prevent delay in treatment, and decrease hospitalizations in patients with HNC [35, 37, 39, 40]. Lewis et al. found that adults with stage III/IV HNC treated with CRT at one U.S. Veterans Affairs hospital who had a feeding tube placed before treatment lost less weight and completed chemotherapy at a greater rate than those who had a feeding tube placed after treatment began or who had no tube [40]. Most patients in this study resumed oral diets by 1-year posttreatment independent of whether they had a feeding tube.

Table 13.2 Nutrition impact symptoms and nutrition management [12, 20, 22, 30–32]

Common nutrition impact symptoms during treatment	Nutrition management	Comments for healthcare professional (RD)
Anorexia	• Consume small, frequent meals or snacks • Fortify food and fluids versus increasing the volume (i.e., add protein powder to foods, smoothies) • Drink nutrient-dense beverages (drink between meals to avoid feeling too full) • Make the most of eating when energy is greatest • Incorporate light exercise to stimulate appetite as feasible	• Identify symptoms that contribute to anorexia (i.e., pain, constipation, taste, etc.) • Discuss pharmacological options with MD (i.e., Megace, Marinol, etc.) • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalances
Aversion to food	• Use protein sources other than meat (a common aversion) such as cheese, cottage cheese, nut butter, eggs, etc. • Use low odor food and fluids; cold or room temperature foods and fluids are often better tolerated • Season foods to increase palatability (i.e., if food is too salty, add a sweet taste) • Avoid favorite foods to prevent long-term avoidance posttreatment • Purchase small quantities of any new item (it may be palatable one day, not the next. Taste can change on a daily basis) • Cleanse the palate using baking soda/salt water rinses	• Utilize a dietary recall to identify foods that are tolerated well; offer suggestions to maximize intake • Monitor weight status • Monitor hydration status
Candida	• Use medications as prescribed • Use excellent oral care; soft tooth brush • Consume soft, moist, non-acidic foods and fluids • Avoid spicy, dry, course, or rough food • Avoid alcohol containing mouthwash • Use a straw to avoid oral cavity (if swallowing function is intact) • Consider the use of liquid high calorie, high protein oral nutrition supplements	• Encourage excellent oral care • Reinforce the use of mouthwash or medication prescribed by healthcare provider • Encourage patient to assess oral cavity at home • Monitor weight status • Assess for taste changes, decrease in intake
Constipation	• Utilize medications as prescribed • Consume adequate fluid (8–10 cups/day) • Eat foods high in fiber if consuming adequate fluid • Eat at regular intervals • Consume warm/hot fluids to stimulate bowel • Try prune juice or prunes • Integrate physical activity or light exercise as feasible	• Reinforce medication prescribed by healthcare provider • Assess fluid intake; discuss estimated needs • Determine date of last bowel movement • Assess for nausea, anorexia • Monitor weight status

(continued)

Table 13.2 (continued)

Common nutrition impact symptoms during treatment	Nutrition management	Comments for healthcare professional (RD)
Dehydration	• Consume small, frequent meals and snacks • Consume fluids as able • Use foods that are higher in fluids (i.e., soup, gelatin, melons, hot cereal) • Avoid alcohol and caffeine • Use Sippy cups or bottles that have a cover if smell is creating an aversion to drinking fluid • Use lemon, lime, cucumber or mint in water if water tastes "off"	• Identify barriers to fluid intake • Reinforce use of medications (i.e., anti-emetics) • Assess actual oral intake of fluid • Offer suggestions to increase fluid intake (i.e., foods that are higher in fluid such as soup, ice cream, gelatin, etc.) • Consider IV fluids if oral intake goals are not attainable • Monitor weight status • Monitor for electrolyte imbalance • Assess blood pressure, skin turgor, etc., for signs of dehydration • Discuss signs of dehydration with patient (i.e., dark urine, skin turgor, lightheadedness)
Diarrhea	• Use medications as prescribed • Use soluble fiber; limit insoluble fiber • Increase fluid intake • Consume small, frequent meals • Consume cool or room temperature food and fluids • Avoid dairy if lactose intolerant • Avoid greasy, fried, or fatty foods • Avoid spicy or rich foods • Avoid excessive amounts of sweetened beverages • Limit foods and fluids containing sorbitol/xylitol or sugar substitutes	• Reinforce medication prescribed by healthcare provider • Evaluate medications • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalance • Discuss foods that are high in soluble fiber • Encourage adequate fluid intake; discuss estimated need and assess barriers to meeting goals • Consider IV fluids if oral intake goals are not attainable
Dysphagia	• Utilize swallowing exercise/techniques provided by speech language pathologist (SLP) • Use foods suggested by registered dietitian (dysphagia diet per National Dysphagia Diet guidelines); soft, moist or pureed foods • Avoid bread, cakes, cookies (dry or crumbly/course foods) • Avoid temperature extremes • Use thickened liquids as suggested by SLP	• Referral to SLP • Provide suggestions for foods and fluids determined to be safest texture (per SLP) • Assess oral intake • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalances • Collaborate with healthcare team regarding need for a feeding tube
Fatigue	• Use foods and fluids that require little effort to prepare • If available, have family or friends prepare meals • Consider use of Meals on Wheels or other community-based program • Prepare meals when not feeling fatigued; freeze and use at a later time when fatigue is present • If possible, use light activity to lessen fatigue • Rest as able; maintain adequate sleep	• Assess for cause of fatigue such as anemia, pain, depression, weight loss, etc. • Provide suggestions for easy to prepare foods • Monitor weight status • Monitor hydration status • Possible referral to community-based nutrition program • Collaborate with healthcare team for possible cancer rehabilitation if appropriate (occupational therapy, physical therapy, etc.)

(continued)

Table 13.2 (continued)

Common nutrition impact symptoms during treatment	Nutrition management	Comments for healthcare professional (RD)
Mucositis	• Use medication(s) recommended by healthcare provider • Rinse mouth with baking soda/salt water rinses (½ teaspoon of baking soda, ½ teaspoon of salt mixed in 1 cup of warm water) • Try sparkling water with a spring of mint • Consume soft, moist foods • Use sauces or gravies to moisten food • Use smoothie or oral nutrition supplements • Puree food if required • Avoid acidic foods • Avoid alcohol and caffeine • Avoid dry, course, rough, or spicy foods • Avoid hot temperatures • Avoid smoking	• Reinforce the use of medication prescribed by healthcare provider • Offer suggestions for foods and fluids that would be well tolerated • Monitor oral intake • Monitor weight status • Pain management • Oral hygiene maintenance
Myelosuppression	• Use good hand washing technique • Use safe food handling practices such as hot foods hot, cold foods cold • Wash fruits and vegetables • Avoid raw eggs, raw meat, raw fish	• Educate on food safety
Nausea/vomiting	• Use medication as recommended by healthcare provider • Consume small, frequent meals and snacks • Consume liquids between meal • Eat low odor foods/fluids (potatoes, rice, plain pasta, chicken, cereal, etc.) • Eat cold food or room temperature foods • Try ginger or peppermint products (Gingerale, gingersnaps, ginger or peppermint tea, or candies) • Avoid sweet or rich foods • Avoid strong odor foods • Avoid taking pain medication(s) on an empty stomach	• Reinforce the use of anti-emetics as prescribed by healthcare provider • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalances • Provide suggestions for low odor foods/fluids
Pain	• Use medication(s) as prescribed • Take pain medication with food unless otherwise directed • Use small frequent meals • Be aware of possible constipation with pain medication	• Reinforce the use of pain medications prescribed by healthcare provider • Assess oral intake • Assess weight status • Assess hydration status • Assess bowel status; collaborate with healthcare team as needed in regard to bowel routine
Sensitivity to smell	• Use low odor foods and fluids • Consume room temperature or cold foods • Chose foods that smell and taste good, even if the food is unfamiliar • Eliminate cooking smells by cooking on a grill or turning on the exhaust fan • Consider buying precooked foods • If possible, have family or friends prepare meals away from the home • Use covered cups or bottles for fluids	• Provide suggestions for low odor food and fluids (i.e., plain pasta, potatoes, rice, hot cereal, cold cereal, pancakes, or waffles, etc.) • Monitor oral intake • Monitor weight status • Monitor hydration status

(continued)

Table 13.2 (continued)

Common nutrition impact symptoms during treatment	Nutrition management	Comments for healthcare professional (RD)
Taste changes	• Use medication as recommended by healthcare provider • Try protein sources other than meat; chicken, fish, eggs, dairy, etc. • If mouth is not sensitive, marinate food in seasonings and spices • If metallic taste is present use finger foods, plastic silverware, or chop sticks to alleviate metallic taste • Add lemon, lime, tart cherry, vinegar, or salt to foods that are too sweet • Add a source of sweetness to foods that are too salty (honey, agave, maple syrup, etc.) • Rinse the mouth with baking soda and salt water (½ teaspoon baking soda, ½ teaspoon salt, 1 cup warm water) • Consume fresh or frozen food; avoid canned food if metallic taste is present • Olives and pickles may be well tolerated	• Assess oral cavity for possible candida or other infection • Collaborate with healthcare team if non-normal findings observed • Encourage the use of spices or seasoning appropriate to situation (i.e., basil, parsley or dill are options that will be well tolerated if mucositis is present) • Assess what the patient taste the patient is experiencing (i.e., salty, metallic, lack of taste, etc.). Offer suggestions to counter taste issues • Monitor oral intake • Monitor weight status
Thick secretions	• Drink adequate fluid (8–10 cups/day) • Use medication as recommended by healthcare provider • Rinse with baking soda and salt water • Carry a water bottle or fluid daily • Avoid dry, crumbly, course foods • Puree foods if required • Use moist foods • Utilize excellent oral care • Sparkling water may thin secretions if carbonation is not bothersome	• Assess oral intake • Encourage the use of mouth rinses • Offer suggestions for food and fluids that would be well tolerated • Monitor weight status • Monitor hydration status • Sialagogues, mucolytics
Trismus	• Therapy and exercises recommended by healthcare provider • Utilize excellent oral care • Dental caries prevention • If pain with eating use easy-to-chew foods • Utilize high calorie, high protein oral nutrition supplements to help meet nutritional needs	• Reinforce exercises recommended by speech and language pathologist • Assess patient's ability to take oral intake • Provide suggestions for diet that will be well tolerated • Assess oral intake • Monitor weight status • Monitor hydration status
Weight loss	• Eat small, frequent nutrient-dense meals and snacks • Fortify foods and fluids versus increasing the volume of food • Consume higher calorie, higher protein oral nutrition supplements or smoothies • Ensure adequate fluid; use foods that are higher in fluid to maximize caloric intake and fluid (i.e., hot cereal, soup, popsicles, etc.) • Add cream, butter, gravies, etc., to maximize caloric intake	• Assess cause of weight loss (inadequate oral intake or cancer cachexia) • Assess actual oral intake • Provide suggestions to maximize nutritional intake • Assess barriers to patient meeting nutrition goals • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalance • Collaborate with healthcare team if nutrition support is required

(continued)

Table 13.2 (continued)

Common nutrition impact symptoms during treatment	Nutrition management	Comments for healthcare professional (RD)
Xerostomia	• Drink adequate fluid (8–10 cups/day) • Chewing and taste stimulation of saliva • Suck on ice chips or frozen grapes • Use medication as prescribed • Use oral hygiene measures as directed by dentist following meals and snacks • Add extra gravies and sauces, to food to moisten • Use sips of warm fluid between bites of food (broth works well) • Use pureed or soft, moist foods such as casseroles • Consume high calorie, high protein oral nutrition supplements or smoothies • Drink adequate fluid (8–10 cups/day) • Use sugar-free candy or gum to moisten mouth • If edentulous, try acidic or tart foods to help stimulate saliva • Avoid dry, crumbly, course foods • Moisten breads, crackers, and cereals • Avoid caffeine, alcohol, mouthwashes with alcohol and tobacco; they can exacerbate the xerostomia • Use a humidifier while sleeping to increase moisture in the environment • Consider acupuncture, low-level laser therapy	• Reinforce the use of medication prescribed by healthcare provider • Provide suggestions for foods and fluids that will be best tolerated • Assess oral cavity • Discuss the need for adequate oral care • Assess oral intake • Monitor weight status • Monitor hydration status

Percutaneous endoscopic gastrostomy (PEG) tubes may be placed before treatment is initiated in patients with HNC who may or may not have nutritional deficiencies in anticipation of compromised oral intake and subsequently nutritional status [39, 40]. The American Gastroenterological Association recommends that PEG tubes should be used if the tube feeding is anticipated to last for more than 30 days which is most often the situation for patients with HNC [39]. Conversely, the American Society for Parenteral and Enteral Nutrition Cancer Guidelines indicate that "because the evidence is not clear nutrition support therapy should not be used routinely in patients undergoing head and neck irradiation" however, it is "appropriate in patients who are already malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrition for a prolonged period of time" [39]. Patients should be encouraged to take as much by mouth and do swallowing exercises while on PEG tubes and to discontinue use as soon as possible to facilitate return to normal swallow function as soon as possible.

Summary

HNC research continues to explore alternative treatment modalities, preventive approaches, and management of outcomes. This is best accomplished by multidisciplinary healthcare teams including OHCPs and RDs. In addition to research, best patient care practices requires knowledgeable and integrated healthcare teams that include physicians, oncologists, oral healthcare providers, registered dietitians, and physical occupational and speech therapists.

Table 13.3 Possible late effects related to treatment for head and neck cancer [12, 20, 22, 30–32]

Common late effects related to HNC treatment	Nutrition management	Comments for healthcare professional (RD)
Anorexia	• Consume small, frequent meals or snacks • Fortify food and fluids versus increasing the volume (i.e., add protein powder to foods, smoothies) • Make the most of eating when energy is greatest • Drink nutrient-dense beverages (drink between meals to avoid feeling too full) • Incorporate light exercise to stimulate appetite as feasible	• Identify symptoms that contribute to anorexia (i.e., pain, constipation, taste) • Discuss pharmacological options with MD (i.e., Megace, Marinol, etc.) • Utilize a dietary recall to assess oral intake • Monitor weight status • Monitor hydration status • Monitor for electrolyte imbalances
Dental caries	• Use oral hygiene measures as directed by dentist following meals and snacks • Use sodium fluoride daily, as recommended per dentist (i.e., fluoride trays); maintain mineralization of teeth (Calcium, phosphate source) • Brush teeth before and after eating • Avoid sugar-sweetened beverages or, limit to mealtime • Limit use of sugar-sweetened candies and gums to mealtime and follow with oral hygiene measures • Use cariostatic/anticariogenic foods such as nut butters, cheese, artificial sweeteners (e.g.,: xylitol)	• Reinforce suggestions and recommendations provided by healthcare team • Discuss caries risk reduction through diet • Discuss cariostatic/anticariogenic foods (protein, nut butters, healthy fats, sugar-free gum, etc.)
Dysgeusia	• Use medication(s) as recommended by healthcare provider • Try protein sources other than meat; chicken, fish, eggs, dairy, etc. • If mouth is not sensitive, marinate food in seasonings and spices • Use Umami flavors (savory); garlic, soy sauces, sweet, and sour sauce, etc. • If metallic taste is present use finger foods, plastic silverware, or chop sticks to alleviate metallic taste • Add lemon, lime, tart cherry, vinegar, or salt to foods that are too sweet • Add a source of sweetness to foods that are too salty (honey, agave, maple syrup, etc.) • Rinse the mouth with baking soda and salt water (½ teaspoon baking soda, ½ teaspoon salt, 1 cup warm water) • Consume fresh or frozen food; avoid canned food if metallic taste is present • Olives and pickles may be well tolerated	• Assess oral cavity for possible candida or other infection • Collaborate with healthcare team if non-normal findings observed • Encourage the use of spices or seasoning appropriate to situation (i.e., basil, parsley, or dill are options that will be well tolerated) • Assess what the patient taste the patient is experiencing (i.e., salty, metallic, lack of taste, etc.). Offer suggestions to counter taste issues • Utilize a dietary recall to assess oral intake, possible deficiencies • Identify adaptive or maladaptive behaviors • Monitor weight status

(continued)

Table 13.3 (continued)

Common late effects related to HNC treatment	Nutrition management	Comments for healthcare professional (RD)
Dysphagia	• Utilize swallowing exercise/ techniques and therapy provided by physical therapist, speech language pathologist • Use foods suggested by R.D. (dysphagia diet); soft, moist or pureed foods • Avoid bread, cakes, cookies (dry or crumbly/course foods) • Avoid temperature extremes • Use thickened liquids as suggested by SLP	• Referral to SLP • Provide suggestions for foods and fluids determined to be safest texture (per SLP) • Utilize a dietary recall to assess oral intake, possible deficiencies • Monitor weight status • Monitor hydration status • Collaborate with healthcare team regarding need for a feeding tube or continued use of feeding tube • Prior to feeding tube removal (if determined possible by SLP) ensure patient is meeting estimated calorie, protein and fluid needs orally
Dysomia (olfactory dysfunction)	• Use low odor foods and fluids • Consume room temperature or cold foods • Choose foods that smell and taste good, even if the food is unfamiliar • Eliminate cooking smells by cooking on a grill or turning on the exhaust fan • Consider buying precooked foods • If possible, have family or friends prepare meals away from the home • Use covered cups or bottles for fluid	• Provide suggestions for low odor food and fluids (i.e., plain pasta, potatoes, rice, hot cereal, cold cereal, pancakes, or waffles, etc.) • Utilize a dietary recall to assess oral intake • Monitor weight status
Mucosal sensitivity (sensitivity of the oral mucosa to acidic, spicy, sweet or dry foods; also temperature)	• Use medication(s) recommended by healthcare provider • Rinse mouth with baking soda/salt water rinses (½ teaspoon of baking soda, ½ teaspoon of salt mixed in 1 cup of warm water) • Consume soft, moist foods • Use sauces or gravies to moisten food • Try sparkling water • Avoid acidic or citrus foods • Avoid alcohol and caffeine • Avoid dry, course, rough, or spicy foods • Avoid hot temperatures • Use smoothie or oral nutrition supplements • Puree food if required • Avoid smoking	• Reinforce the use of medication prescribed by healthcare provider • Offer suggestions for foods and fluids that would be well tolerated for described symptoms • Utilize a dietary recall to assess oral intake, possible deficiencies • Assess for adaptive or maladaptive behavior • Monitor weight status
Odynophagia	• Use medication recommended by healthcare provider • Incorporate soft foods (i.e., hot cereal, pudding, ice cream) • Consume high calorie, high protein oral nutrition supplements or smoothies • Puree food if required • Avoid rough, crumbly, dry foods • Avoid alcohol and caffeine • Avoid smoking	• Identify possible causes of symptom (ulcer, stricture, candida) • Collaborate with healthcare team as needed • Referral to SLP as indicated • Provide suggestions for foods/fluids that would be best tolerated • Utilize dietary recall to assess oral intake, identify possible deficiencies

(continued)

Table 13.3 (continued)

Common late effects related to HNC treatment	Nutrition management	Comments for healthcare professional (RD)
Osteoradionecrosis	• Use treatment regimen recommended by healthcare providers (i.e., hyperbaric oxygen chamber, antibiotics when indicated, etc.) • Continue with excellent oral care • Limit alcohol, tobacco, and caffeine (irritants) • Symptom management	• Reinforces regimen recommended by healthcare providers • Reinforce the need for excellent oral care • Provide suggestions for food and fluids that are best tolerated • Utilize a dietary recall to assess adequacy of oral intake, possible deficiencies • Monitor weight status
Pain	• Use medication as recommended by healthcare provider; for oral pain consider topical agents in addition to systemic • Take pain medication with food unless otherwise directed • Use small frequent meals • Be aware of possible constipation with pain medication	• Reinforce the use of pain medications prescribed by healthcare provider • Utilize a dietary recall to assess oral intake, possible deficiencies • Assess weight status • Assess hydration status • Assess bowel status; collaborate with healthcare team in regard to bowel routine
Thick secretions	• Use medication as recommended by healthcare provider; • Drink adequate fluid (8–10 cups/day) • Rinse with baking soda and salt water • Carry a water bottle or fluid daily • Avoid dry, crumbly, course foods • Puree foods if required • Use moist foods • Utilize excellent oral care • Sparkling water may thin secretions if carbonation is not bothersome	• Reinforce prescribed sialagogues and mucolytics • Assess oral cavity • Utilize a dietary recall to assess oral intake, possible deficiencies • Discuss the need for adequate fluid • Encourage the use of mouth rinses • Offer suggestions for food and fluids that would be well tolerated
Trismus	• Use exercises and physical therapy recommended by healthcare provider • Utilize excellent oral care • If pain with eating use easy to chew foods • Utilize high calorie, high protein oral nutrition supplements or smoothies to help meet nutritional needs	• Reinforce exercises recommended; active exercise device use • Use a dietary recall to assess oral intake, possible deficiencies • Provide suggestions for diet that will be well tolerated • Monitor weight status
Ulcers	• Use medications as prescribed • Avoid acidic foods • Avoid alcohol and caffeine • Avoid citrus foods • Avoid dry, course, rough, or spicy foods • Avoid hot temperatures • Use smoothie or oral nutrition supplements • Puree food if required • Avoid smoking	• Reinforce recommendations provided by healthcare provider (i.e., dental professional or MD) • Provide suggestions for foods and fluids that are best tolerated • Utilize a dietary recall to assess oral intake, possible deficiencies • Monitor weight status

(continued)

Table 13.3 (continued)

Common late effects related to HNC treatment	Nutrition management	Comments for healthcare professional (RD)
Xerostomia	• Use medications as prescribed • Use oral hygiene measures as directed by dentist following meals and snacks Add extra gravies and sauces, to food to moisten • Use sips of warm fluid between bites of food (broth works well) • Use pureed or soft, moist foods such as casseroles • Consume high calorie, high protein oral nutrition supplements, or smoothies • Drink adequate fluid (8–10 cups/day) • Use sugar-free candy or gum to moisten mouth • If edentulous use lemon, lime, or tart foods to help stimulate saliva • Sip on liquids throughout the day • Suck on ice chips or frozen grapes • Avoid dry, crumbly, course foods • Avoid bread products unless moistened • Avoid caffeine, alcohol and tobacco all dry the mouth • Avoid mouthwash with alcohol • Use a humidifier while sleeping to increase moisture in the environment • Consider acupuncture, low-level laser therapy	• Reinforce the use of medication prescribed by healthcare provider • Provide suggestions for foods and fluids that will be best tolerated • Assess oral cavity • Utilize a dietary recall to assess oral intake, possible deficiencies • Assess for signs of adaptive or maladaptive behavior • Reinforce the need for excellent oral care • Monitor weight status

Although the effects of surgical, chemotherapy and radiation therapy may not be preventable in the acute and long-term phases of recovery, early identification of these effects including those that impact functional and sensory ability to eat and drink can reduce the negative consequences including weight loss, malnutrition, delayed wound healing, and compromised quality of life. The goal of prevention remains, but when present early diagnosis and intervention is needed, and in this way improved quality of life can be achieved. The tables and figures in this chapter are presented as resources for health professionals in caring for patients with head and neck cancer.

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Chapter 14
Human Immunodeficiency Virus/AIDS

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Keypoints

- Oral manifestations of HIV are often early signs of the disease and represent clinical manifestations of immune suppression
- Oral lesions associated with HIV may be viral, bacterial, or fungal in etiology; inflammatory (stomatitis, apthous-like ulcers) and neoplastic conditions also occur
- In conjunction with dental care, nutrition and diet management is essential to prevent and treat associated weight loss and nutrient deficits
- Oral manifestations may impact functional and senory ability to eat and drink; dietary manipulations are critical to ensure adequacy of intake

Keywords Human immunodeficiency virus · HIV · Oral manifestations · Immune suppression · Oral lesions · Dietary manipulations

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Introduction

Oral health is an integral component of overall health and well-being in all patients and may have particularly important implications for an immunocompromised patient. Many common oral conditions significantly impact patient's quality of life. Intraoral pain, which is a common complaint among patients with human immunodeficiency virus (HIV), compromises adequate oral intake. Furthermore, the polypharmacy used to treat HIV and associated opportunistic infections may increase incidence of oral pathologies such as caries and oral candidiasis, in part by inducing hyposalivation. This can be further aggravated by disease of the salivary glands that affects people living with HIV [1]. Decreases in salivary flow and increases in intake of high sucrose containing supplements and medications may play significant roles in the progression and severity of dental caries and risk of fungal overgrowth.

Oral manifestations of HIV disease may be the initial signs of the disease and represent clinical signs of progressive and continuous immune suppression. Side effects of medications and underlying systemic and local opportunistic infections may also manifest oral changes. Because there is a strong correlation with immune status and the manifestation of oral lesions, any abnormal oral finding may significantly influence clinical treatment decisions [2]. The use of oral lesions as clinical markers for immune suppression and disease progression can be utilized for intervention therapy, as well as in staging protocols [3].

Unfortunately, most oral lesions are symptomatic and may also be refractory to conventional therapy. As a consequence, oral manifestations can greatly hamper nutritional intake, negatively enhancing calorie and protein intake and influence general well-being. It is of vital importance that oral health care providers, physicians, and nutritionists work together in the management of HIV-infected patients. Children who are HIV positive suffer oral health consequences of nutritional factors as well as do adults. Manifestations include "reduced appetite, malabsorption, and increased requirements for nutrients and soft foods" leading to consequences of "increased caries, ulcers, soreness, mucosal inflammation and candidasis" [4]. These consequences may lead to negative impact on children's growth and development [5].

Particular concerns occur among people living with HIV in locations with poor food access, such as much of Africa and some Carribean countries. Oral manifestations, candidiasis especially, have had significant roles in limiting nutrition intake and as potential markers of immune failure monitored for food program impact [6–8].

A Cochrane Systematic Review has been conducted regarding aspects of nutrition and HIV status. The 2013 update of the 2007 review of macronutrient intervention found the status of data too weak to draw conclusions about effectiveness [9].

HIV/Acquired Immunodeficiency Syndrome

HIV, the etiologic agent of acquired immunodeficiency syndrome (AIDS), is a lentivirus belonging to the larger family of retroviruses. This is a family of RNA viruses notable for its viral reverse transcriptase (a RNA-dependent DNA polymerase) that transcribes viral RNA into proviral DNA, which is then incorporated into the host-cell genome. The T-helper lymphocytes, generally referred to as CD4 cells, are infected by HIV, and are subsequently depleted during progression of HIV disease. These cells are essential for the coordination of many critical immunological functions and consequently, the loss of these cells results in the progressive loss of immune functions [10].

In 1981, the Centers for Disease Control and Prevention (CDC) noted an increase in a rare form of cancer accompanied by progressive immune deterioration among homosexual and bisexual men.

Later the condition was recognized as Kaposi sarcoma (KS), a disease which was not usually seen in young males and which was subsequently associated with Acquired Immune Deficiency Syndrome (AIDS) [11].

HIV infection is characterized by the development of opportunistic infections, malignancies, neurological dysfunction, and other conditions associated with immune deterioration. AIDS is defined as a clinical stage where individuals infected with HIV have developed specific diseases and conditions, according to a surveillance case definition put forth by the CDC, or have reached a level of immune deterioration determined by a specific level of remaining CD4 cells [3].

Transmission of HIV requires contact with body fluids containing free virions or infected cells. HIV may be present in any fluid or exudates that contain plasma or lymphocytes, blood, semen, vaginal secretions, breast milk, saliva, or wound exudates. This virus is not transmitted by casual contact. HIV is caused by two similar retroviruses, HIV-1 and HIV-2. Both viruses are found primarily in different geographical areas, yet infection with either virus may ultimately result in AIDS. HIV-1 is known to cause most of the AIDS cases in the Western hemisphere; Europe; Asia; and central, south, and east Africa; whereas, HIV-2 is the primary agent of AIDS documented cases in West Africa [3].

The HIV/AIDS epidemic in the United States has entered its fourth decade; 1.2 million people are living with HIV and 1 in 5 are unaware of their infection [11]. It is estimated that around 50,000 new infections occur annually in the United States [12], a number which has stubbornly refuses to drop despite numerous prevention initiatives. Because of the increase incidence in these populations, it has been recommended that prevention initiatives be targeted to young [13–15], African Americans, and men who have sex with men (MSM). At risk behaviors, which appeared to be reduced before 2000 in susceptible populations, appear to have resumed, as experience with morbidity and mortality of HIV infection and AIDS has diminished with improved therapy [12].

While there is currently no cure for HIV infection, medical breakthroughs such as highly active antiretroviral therapy (HAART) have reduced morbidity and mortality and extended the life of those living with HIV. Moreover, single-tablet once daily regimen have significantly contributed to improved clinical results by reducing pill burden and improving adherence and treatment outcomes [10, 16]. With this achievement, new issues have emerged in an aging HIV-infected population. These issues include metabolic concerns which seem to be the results of unexpected toxicity associated with viral suppressing treatments [17]. In that regard, nutritional counseling has become an essential element in the management of HIV as cardiovascular and bone health have taken an increased significance in the health of people living with HIV [18].

Oral manifestations during initial HIV infection while still common have seen a significant decrease in their prevalence with HAART possibly with the exception of human papillomavirus associated diseases (discussed below) [19, 20]. Oral manifestations of HIV have been reported among the earliest documented cases of the disease [21]. Patients may present with nonspecific oral ulcerations, a sore throat, exudative pharyngitis, and oral candidiasis, which may be clinical presentations of the acute seroconversion syndrome [22–24]. Signs of fever, fatigue, weight loss, and myalgia are also related to initial HIV infection [25]. Occasionally, a macular erythematous nonpruritic rash may be found on the trunk and extremities [24]. A thorough patient history, including sexual history, is one of the key factors in the differential diagnosis of sexually transmitted disease including HIV. An HIV antibody test is strongly recommended for patients engaging in high-risk sexual activity or sharing needles, or if there are reasons to assume that HIV infection has occurred. The duration of the acute phase of this nonspecific illness usually lasts from a few days to 14 days [25]. The patient should be referred to an infectious disease clinic for a comprehensive evaluation and referred for treatment of oral lesions and conditions that may appear during the course of HIV disease and during treatment.

Oral Lesions

A number of classification systems have been suggested for characterizing oral changes that may occur in patients with HIV [3, 26, 27]. Most commonly, oral lesions are described according to etiology.

Viral Etiology

Table 14.1 summarizes the potential viral caused oral lesions common in HIV disease [26].

Herpes Simplex Virus Infections

Eight different herpes viruses that are known to infect humans have been identified; of these, six have been associated with lesions in the oral cavity [28]. Oral lesions caused by herpes simplex viruses are commonly recognized by the clinical manifestations of infection [29]. Lesions associated with cytomegalovirus (CMV), varicella zoster virus (VZV), and human herpes virus 8 are uncommon in non-HIV-infected individuals and pose more of challenge to recognize [28, 30].

Although both herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) can cause oral ulcerations, HSV-1 ulcers are generally found in and around the oral cavity, whereas HSV-2 ulcers are more commonly associated with genital manifestations, although this distinction is becoming less common and either can affect either site. When, HSV-2 produces oral ulcerations, the recurrence rate tends to be higher than those caused by HSV-1. Oral ulcerations produced by HSV-1 are more common than HSV-2 in HIV-infected individuals [29].

The lesions may present as single or multiple, localized or generalized vesicles that breakdown to result in ulcerations on intraoral surfaces and/or on the lips. The ulcers are usually small, round or oval, and shallow, with a diameter of 1–4 mm. In the immunocompromised patient, coalescent lesions may form large ulcers that can be hemorrhagic and covered by a pseudomembrane. A raised white border may surround chronic ulcers that have persisted for more than 3 weeks [29].

In the immunocompromised patient, lesions may occur on any intraoral surface including attached keratinized and unattached nonkeratinized mucosa [31]. However, in the immunocompetent individual the lesions are generally restricted to the more keratinized surfaces.

Ulcerations associated with HSV can be painful and tend to make eating, swallowing, and speaking difficult. As a consequence, this may lead to dehydration, weight loss, and restricted oral intake, which could compromise or alter medication and nutritional regimens [29].

In the immunocompromised host, the healing time of HSV-associated ulcers may be delayed and may be misdiagnosed as aphthous ulcers or CMV-associated ulcers. A precise diagnosis is of great importance, as treatment, prognosis, and significance of the lesions may relate to a disseminated disease state of the herpes virus.

A diagnosis can be established by: a cytologic specimen and staining for multi-nucleated giant cells or HSV, viral culture from the lesion, biopsy for detecting occurrence of viral intranuclear inclusions, or the use of monoclonal antibodies and by PCR. As a rule, HSV-associated intraoral lesions are not used as markers for changes in immune status, although frequent or large confluent ulcers may indicate progressing or advanced HIV disease. To reduce the severity of lesions, the recommended treatment is either acyclovir 800 mg five times a day or valacyclovir 500 mg two to three times a day. Caution should be used when prescribing valacyclovir for immunocompromised patient, as this medication may produce bone marrow suppression impacting white cell and/or platelet count and hemolytic uremic syndrome in this patient population [30, 31].

CMV

CMV, human herpes virus 5, can cause multiorgan dysfunction in an immunocompromised patient [32, 33]. The intraoral presentation of CMV is usually seen with a severe immunosuppression, as measured by the CD4 cell count of less than 100 mm^3 and may be associated with disseminated CMV infection [2, 34]. The lesions are generally nonspecific ulcers that range from a few millimeters to 1–2 cm in diameter, primarily on the gingiva or the palate, but they can also be found on other mucosal surfaces. The ulcers may be shallow or deep with an eroded base, may have elevated borders and tend to be extremely painful [35]. Because of the ulcers, the nutritional status of the patient may be severely compromised. Pain added to slow healing of the ulcers may cause dehydration because of inadequate oral and nutritional intake.

The differential diagnoses should include recurrent aphthous ulcers and HSV lesions, and ulceration associated with neoplasia. A definitive diagnosis requires a biopsy demonstrating perivascular inflammation and large basophilic intranuclear inclusions of CMV. A diagnosis of oral CMV requires additional workup to rule out ophthalmologic or other CMV-related disease and/or lesions [36]. Intraoral manifestations of CMV can be treated with ganciclovir and foscarnet [34].

VZV

VZV causes two well-defined diseases: chickenpox (varicella) and shingles (herpes zoster). After an initial infection, the virus remains latent in the dorsal root ganglia with reactivation resulting in shingles in adult and immunocompromised patients. Shingles may commonly be seen during the progression of HIV disease. If lesions appear intraorally, they are typically found unilaterally along a division of the fifth cranial nerve, generally on the palate or the tongue [30]. A significant correlation between intraoral VZV presentation and the immune status of an individual with HIV has yet to be shown [37]. Because of the painful nature of the lesions, especially in the acute phase, oral intake and consequently nutrition status may be affected. Treatment is usually supportive and preventive in nature and the prescription of oral valacyclovir has been utilized, intravenous acyclovir may be indicated in severely immunocompromised patients [30].

Epstein-Barr Virus

Initially described in HIV-infected males, oral hairy leukoplakia (OHL), a lesion associated with Epstein-Barr virus (EBV), was initially thought to be an HIV-specific manifestation [38, 39]. However, OHL is found among other immunocompromised groups, and occasionally in immunocompetent individuals [40–42]. For an individual presenting with OHL and an unknown HIV status, an HIV test is strongly recommended, as the occurrence of OHL in individuals with HIV far exceeds the incidence of the lesion among other groups of patients and in many cases the cause of immunosuppression is known, such as following hematopoietic stem cell transplant.

OHL is commonly seen on the lateral borders of the tongue as white, vertical, hyperkeratotic striae sometimes extending onto the ventral or dorsal surfaces. The lesion cannot be wiped or rubbed off. As it is asymptomatic, the patient may not be aware of the lesion and it may be found incidentally during a routine intraoral examination. Occasionally, the lesion may appear as white patches on other intraoral surfaces. A definitive diagnosis of OHL must demonstrate the presence of EBV in the lesion [26]. A differential diagnosis of OHL includes hyperplastic or chronic candidiasis. Candida albicans has been shown to be present in over 50% of the lesions [37]. In HIV, OHL is usually found in patients with CD4 cells below 200 cells per mm^3 and is further associated with a viral load of 20,000 copies/mL or greater, irrespective of the CD4 cell count and the use of an antiretroviral regimen [43].

Since OHL lesions are painless and not transmissible, treatment for OHL is generally initiated based on the patient's request when the lesion causes aesthetic problems or impairs masticatory functions. Therapy with acyclovir 800 mg five times a day for at least 10 to −14 days is usually successful. In some individuals, recurrence is common and prophylactic therapy of acyclovir 800 mg daily is recommended [37]. Other interventions have included use of podophylum resin applied to the lesion and other keratolytic applications.

Human Herpes Virus 8

Kaposi sarcoma (KS), traditionally known as an angiomatous neoplasia, was first described in 1872 by Moritz Kaposi. This form of tumor was known to predominantly affect men of Mediterranean decent in their sixth decade of life. However, since the onset of the HIV epidemic, the epidemiology of KS in the United States has changed dramatically and has become recognized as the most common neoplasm associated with HIV disease, mostly affecting homosexual and bisexual men. Because of its presence in men with multiple sexual contacts, it was hypothesized that KS may be caused by a transmissible pathogen even prior to viral identification, studies have confirmed this suspicion, implicating the HHV8 as the etiologic agent for KS [44, 45]. The presence of HHV8 in practically all KS lesions strongly suggests that this virus is associated with the development of the lesion [46].

More than 90% of KS lesions are found either on the hard and/or soft palate, with the gingivae being the second most common site, although it also occurs at other oral sites [47]. Lesions usually present as red, purplish, or blue macules, or nodules. In the early macular stage, the lesions are mostly asymptomatic and the patient may not be aware of their presence. Larger lesions may interfere with normal oral functions and become painful, from secondary trauma or ulcerations. KS lesions may grow to such an extent that they may interfere with a patient's ability to eat, speak, and/or swallow.

Although lesions have been noted during all stages of HIV disease, intraoral KS generally presents when the patient's CD4 cell count drops below 100 cells per mm^3. Extrapalatal lesions and the change from a macular to a nodular presentation represent a progression and poorer prognosis. Similar to cutaneous lesions, intraoral KS is more frequently found in patients with increased incidence of sexually transmitted diseases [47].

A differential diagnosis must include physiologic pigmentation, bacillary (epithelioid) angiomatosis, salivary gland malignancy and lymphoma. A biopsy is required for a definitive diagnosis of KS [47].

Therapies are aimed primarily at reducing the size and number of lesions. Treatment is chosen based upon the degree and extent of involvement. Systemic chemotherapy is chosen for disseminated disease, regional therapy (including radiation) for loco-regional disease and intralesional therapy for localized disease. The most common treatments are systemic chemotherapy, radiation therapy, and surgical interventions. Smaller localized lesions can be treated by direct injection into the lesion with chemotherapeutic agent such as vinblastine sulfate 0.1 mg/mm^2 or sodium tetradecyl sulfate 0.1 mg/mm^2. Such local therapies are generally successful, although lesions may recur [48–50].

Human Herpes Virus 6

HHV6 has emerged as an additional herpes virus who may contribute to carcinogenesis especially in T cell related blood dyscrasia such as T-primary effusion lymphoma [51]. HHV6 is T-cell tropic and its genome is endowed with oncogenic regions. The possible role played by HHV6 in carcinogenesis remains to be fully understood and so its hypothesized implication in numerous conditions including neurological diseases [52, 53]. The contribution of HHV6 to HIV associated diseases is unknown and requires ongoing laboratory and clinical studies.

Human Papilloma Virus

Human papilloma virus (HPV) is a known etiologic agent that causes warts in the oral cavity. Multiple lesions can occur in large areas of the mouth. The lesions are generally asymptomatic, unless traumatized. However, they frequently tend to interfere with mastication and may be disfiguring. HPV can present on all oral mucosal surfaces, although they have a predilection for the inside of the lips and the gingival [37, 54]. Various clinical forms have been described as hyperplastic, papillomatous, or verrucous. Oral squamous cell papillomas manifest as solitary or multiple, exophytic, pedunculated papules with a cauliflowerlike or pebbled surface. Condyloma acuminata are larger, white to pink nodules, with a cauliflower-like or pebbled surface. The common wart, or verruca vulgaris, may appear as a firm and sessile, exophytic, white lesion. This lesion has a hyperkeratinized superficial epithelium with a slight invagination at the center of the lesion. Heck's disease, or focal epithelial hyperplasia, may appear as areas that are smooth, pebbled, or cauliflower-like; large; solitary or multiple; whitish; hyperplastic; and slightly elevated. The differential diagnosis of oral HPV includes traumatic fibromas.

Although the incidence and prevalence of oral lesions have decreased since the institution of more effective anti-HIV medications, there has been a rise in the incidence of oral HPV associated warts [19, 20]. It has been proposed that the increased incidence of HPV-warts among patients with HIV who are taking highly active antiretroviral therapy (HAART) may be related not to immune suppression, but rather to immune reconstitution [55].

The prevalence of oral HPV infection in the general adult population is estimated to be around 6.9% as demonstrated by the detection of HPV viral DNA in oral rinses [56]. Sexual contacts including the age of first sexual experience, the number of lifelong sexual partners and oral sex partners and the number of open-mouthed kissing partners have been shown to be associated with a higher risk of oral HPV infection [57]. Other studies have indicated that people living with HIV have a higher rate of oral HPV infection. This may be due to an increased persistence of HPV infection related to immune suppression [58]. This observation is concerning as an increased incidence of HPV related oropharyngeal cancer associated with HPV-16 and -18 [59]. The higher rate and chronicity of oral HPV infection could compound with the observed improved life expectancy of people living with HIV resulting in a future dramatic increase in the incidence of HPV-associated cancers of the head and neck in this population.

Multiple successful treatment regimens have been reported [54]. Surgical removal with a scalpel, laser ablation, cryotherapy, topical application of keratinolytic agents, and intralesional injections of antiviral agents have been used. Podophyllum resin 25% may be used topically to reduce the size of the lesion and for removal of smaller lesions. Larger lesions can be treated using intralesional injections of interferon-α once or twice a week with 1million IU per cm^2 of the lesion, accompanied with subcutaneous injections of 3 million IU two to three times a week for up to 3 months [54]. Eradication of the lesions is possible over time using a combination of therapies, even though the recurrence rate is high.

Fungal Etiology

Table 14.2 describes the fungal oral lesions common in HIV disease [26].

Candidiasis

Candidia albicans is common in the normal oral flora in many immunocompetent individuals, generally without any signs of clinical manifestation. Candidiasis, or candidosis, has been recognized as one of the most common and earliest intraoral manifestations of immune suppression [60].

Table 14.1 Viral infections

Lesions	Clinical presentation	Differential diagnosis	Treatment	Significance	Marker for HIV	Nutritional implications
HSV	Solitary, multiple, or confluentvesicles; keratinized mucosa; painful	Apthous ulcers, CMV	Acyclovir 800 mg five times a day or valacyclovir 500 mg BID for 14 d	Increases in frequency and severity based on progression of HIV	Not generally; indicates disease progression	Dehydration, restricted oral intake
CMV	Nonspecific >5 mm ulcers, nonkeratinized mucosa; painful	HSV, recurrent aphthous ulcers	Ganciclovir; acyclovir (solely for oral lesions)	CD4 cell count <200 mm^3	Not generally; indicates disease progression	Dehydration, restricted oral intake
VZV	Unilateral, generally on palate, along division of 5th cranial nerve; similar to HSV lesions; painful	HSV	Supportive and preventive; occasionally with oral or, if needed, intravenous acyclovir	No relation found	Not generally	Dehydration, restricted oral intake
EBV	Lateral borders of the tongue; a white, vertical, hyperkeratotic striae; cannot be wiped or rubbed off; asymptomatic	Hyperplastic or chronic candidiasis	Acyclovir 800 mg five times a day for 14 d	CD4 cell count <200 mm^3; viral load >20,000 copies/mL	Yes	None
HHV8	Red, purplish-blue macules or nodules; hard/soft palate, gingival; painful; caused by trauma	Bacillary (epithelioid) angiomatosis, lymphoma	Radition, surgical intervention; vinblastine sulfate 0.1 mg/mm^2 or sodium tetradecyl sulfate 0.1 mg/mm^2	CD4 cell count <100 mm^3	Yes	Difficulty eating with larger and/or traumatized lesions
IIPV	Hyperplastic, papillomatous or verrucous	Fibroma	Topical podophyllum resin 25%; intralesional injections one to two times a wk with 1 million IU/cm^2 of the lesion, along with subcutaneous interferon-α injection of 3 million IU two to three times per wk	No relation found	No	Interference with chewing

HSV herpes simplex virus; *CMV* cytomegalovirus; *VZV* varicella zoster virus; *EBV* Epstein-Barr Virus; *HHV8* human herpes virus 8; *HPV* human papilloma

While, not pathognomonic for HIV disease, oral candidiasis may be an early sign of infection and a marker for disease progression, independent of CD4 lymphocyte count [61]. The clinical diagnosis should be verified by laboratory tests such as cytological smear with potassium hydroxide, culture or biopsy and staining for tissue infiltration of pathogenic agents (spores or hyphae). Oral candidiasis may present in different forms including: pseudomembranous, erythematous, hyperplastic, angular chelitis and occasionally invasive oral ulceration. Differences in the risk factors associated with the different types of candidiasis in HIV may reflect distinct pathological mechanisms and it is possible that each form of oral candidiasis may denote a different stages of immune suppression [62].

The Intervention Review conducted via the Cochrane HIV/AIDS Group regarding "prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children" was based primarily on treatment trials [63]. The review found only one trial using food products in the form of lemon juice or lemon grass but no benefit was seen [63].

Pseudomembranous Candidiasis

Commonly known as thrush, pseudomembranous candidiasis presents as white or yellowish, plaque (s) that can be rubbed off the oral mucosa leaving an erythematous or bleeding surface. The plaques may be found on any intraoral surface. Patients may not be aware of the intraoral presentation or may be symptomatic with sensitivity and taste change that may affect oral feeding and, consequently, impact nutritional status. Oral candidiasis, particularly in immunocompromised and myelsuppressed patients may extend regionally to the throat and esophagus. The manifestation is an early indication of immune suppression, with CD4 cell counts below 400 cells per mm^3 [64].

Erythematous Candidiasis

Erythematous candidiasis (also known as atrophic candidiasis) presents as red or atrophic patches that may affect any intraoral mucosal surface but has a predilection for the tongue and the hard palate. On the dorsal surface of the tongue, it manifests as areas of depapillation resulting in smooth, erythematous patches. The erythematous form of candidiasis presents alone or in combination with the pseudomembranous form. Lesions may be accompanied with a burning sensation and rarely ulceration [30]. The lesions can appear throughout the course of HIV disease, although they are generally seen during the earliest stages of immune suppression [37].

Treatment of both the pseudomembranous and erythematous forms of candidiasis is usually effective although recurrence is common in people where the underlying risk for infection is not effectively managed. Troches and mouth rinses are beneficial for patients with CD4 cell counts above 150 to 200 cells per mm^3. In patients with more severe immune suppression, systemic medications should be instituted. Systemic medication may be more convenient that topicals [65].

Several factors should be considered when selecting the medication to be used. Troches are more convenient and practical than mouth rinses, but may not be dissolved in those with excessively dry mouth. Rinses sweetened with sugar should be avoided especially in dentate patients with dry mouth. The type and use of systemic medications are dictated by patient's immune status, liver status, and compliance and the potential for drug interactions. Topical antifungal agents include nystatin oral pastille, one or two or pastilles dissolved slowly four or five times daily; clotrimazole oral troche 10 mg, one troche dissolved five times a day; and nystatin or itraconazole oral suspensions. It is important to note that nystatin suspension is highly sucrose sweetened. When these are chosen, patients need to be instructed in oral hygiene and home fluoride applications. Topical agents with low sugar content are vaginal preparations of clotrimazole or nystatin. One vaginal troche is dissolved in the mouth three times a day. However, the taste of the vaginal formulation is

less agreeable to patients and may affect compliance. A new product with slow release intraorally is Oravig®. The most frequently used systemic antifungal agents are fluconazole one or two 100 mg tablets daily [65, 66].

Oral candidiasis has a high recurrence rate, and maintenance therapy may be indicated. In resistant cases, resistant speicies or selection of resistant Candida albicans may be overcome with increased dose of fluconazole or other agents such as voirconazole. Liver function and drug interaction must be considered with use of these systemic antifungals [65].

Hyperplastic Candidiasis

Hyperplastic candidiasis is uncommon among HIV-infected patients. This form of candidiasis may be seen in patients with severe immune suppression, represented by CD4 cell counts below 100 cells per mm^3. Patients with hyperplastic candidiasis have a high predilection for having, or developing, esophageal candidiasis, which is an AIDS-defining illness [2].

Hyperplastic candidiasis presents as white or discolored plaques that may be solitary or confluent but, in contrast to pseudomembranous candidiasis which cannot be wiped or rubbed off the mucosa. The differential diagnosis includes oral leukoplakia and squamous cell carcinoma. The lesions may be found on any intraoral surface but have a high prevalence on the hard or soft palate [65].

Hyperplastic candidiasis is often misdiagnosed as leukoplakia or, when it presents on the tongue, as OHL. Even though the clinical manifestation of the lesion is pathognomonic, the presence of hyphae and blastospores on biopsy confirms a diagnosis. Treatment for this type of candidiasis involves systemic antifungal agents, which may include intravenous formulations [65].

Angular Chelitis

Angular chelitis presents as radiating red fissures, and occasionally with a pseudomembrane, in the corners of the mouth. This condition is frequently observed in older individuals with ill-fitting complete dentures and is not pathognomonic for HIV disease. It is commonly associated with xerostomia, a habit of licking the corners of the mouth, chronic use of petrolatum on the lips, overclosure of the jaw and systemic risk factors noted above [67, 68].

Treatment of angular chelitis is accomplished by application of a topical antifungal agent such as clotrimazole, miconazole, ketoconazole cream, or nystatin ointment in combination with a topical antibacterial agent. As the source of the organism is commonly oral, treatment of the oral cavity is often required. Nutritional deficiency can both contribute to angular cheilitis and be exacerbated by it [69].

Histoplasmosis

Infections with histoplasmosis may occur in endemic areas, such as the Ohio and Mississippi valleys, and the inland areas of California. Histoplasmosis is caused by inhaling the spores of Histoplasma capsulatum, found in the soil throughout the world. Although rare in areas that are nonendemic, endemic areas have exhibited prevalence rates of approximately 70% of the adult population having a positive histoplasmin test [70]. In the immunocompetent host, infections by H. capsulatum are usually subclinical and self-limiting. However, in immunocompromised patients, H. capsulatum can cause a serious opportunistic infection. Although not correlated with CD4 cell count, histoplasmosis was included in the AIDS-defining illnesses category in 1985 [3]. Many cases of histoplasmosis are disseminated by the time of oral manifestations [71]. The clinical presentations

Table 14.2 Fungal infections

Oral manifestations	Clinical presentation	Differential diagnosis	Treatment	Significance	Marker for HIV	Nutritional implications
Pseudomembranous candidiasis	White or yellowish, single or confluent plaques; easily rubbed off; any surface		Nystatin oral pastille, one to two pastilles dissolved slowly four to five times a day; clotrimazole oral troche 10 mg, 1 troche dissolved five times a day; nystatin oral suspension; fluconazole one to two 100 mg tables QD	CD4 cells below 400 cells/mm^3	Not generally indicates early immune suppression	In severe cases, eating abd swallowing can be uncomfortable
Erythematous candidiasis	Red or atrophic patches on any surface, however, greater on the tongue and hard palate		Same as pseudomembranous	Any stage of HIV	Not generally, indicates early immune suppression	Longstanding lesions may produce a burning sensation
Hyperplastic candidiasis	White or discolored plaques; solitary or confluent; cannot be rubbed or wiped off	Leukoplakia, OHL	Fluconazole, one to two 100 mg tablets QD; ketoconazole one to two 200 mg tablets QD taken with food; itraconazole two 100 mg capsules QD	CD4 cell count below 100 cells per mm^3 high predilection for either having or developing esophageal candidiasis	Yes, severe immune suppression	Burning sensation and a feeling of having a "large ball of cotton in the mouth";xerostomia eating and swallowing may be uncomfortable
Angular chelitis	Radiating red fissures; commissures of the lips		Ketoconazole ointment 2%;apply to affected areas four times a day for 14 d		No	Difficulty opening the mouth because of pain

vary along a spectrum of ulcerations to granulomas. A definitive diagnosis is based on clinical examination, serology, biopsy and culture [71]. The treatment of choice is forms of intravenously delivered amphotericin B, however itraconazole and ketoconazole have also been used successfully to treat disseminated histoplasmosis in immunocompromised patients [71, 72]. Newer agents such as voriconazole, micfungin may play an important role in treatment.

Bacterial Etiology

Periodontal disease

Periodontal disease is common in both HIV-positive and HIV-negative individuals. HIV-infected individuals may have more rapidly progressive periodontal disease, but this is not a consistent feature. Acute, rapidly progressive periodontal conditions may be early signs of immune suppression and HIV infection [37]. An association between aggressive periodontal conditions in HIV-infected individuals and a progressive deterioration of individuals' immune status has been suggested [73, 74]. These periodontal conditions in the HIV-infected individual are linked to the person's immune status, not change in the microflora [37]. There are three types of periodontal conditions that have been associated with HIV disease: linear gingival erythema (LGE), necrotizing ulcerative gingivitis (NUG), and necrotizing ulcerative periodontitis (NUP) [27, 75].

Linear Gingival Erythema

An erythematous 2–3 mm red band at the gingival margin, disproportional to plaque accretion, characterizes LGE with an equal distribution around the teeth without ulceration, and no increase in pocket depth with periodontal attachment loss, and minimal bleeding on probing [37]. Occasionally, punctuated or diffuse erythema is noted on the attached gingiva near the alveolar mucosa. The condition may be asymptomatic. This presentation does not have a strong correlation with HIV disease [37]. The differential diagnosis includes localized effect secondary to hyposalivation and dry mucosa, localized candidiasis, oral lichen planus, mucous membrane pemphigoid, hypersensitivity reaction presenting as plasma cell gingivitis, Geotrichum candidum infection, and thrombocytopenia. The presentation of LGE may be associated with subgingival Candida infection [37].

LGE will typically not respond to routine dental scaling and root planing. However, concomitant use of chlorhexidine gluconate (0.12%) mouth rinse generally causes improvement. The patient should be advised to swish with 15 mL of the solution for 30 seconds and expectorate. Addition of a topical antifungal agent may be advantageous. Meticulous oral hygiene is essential for treatment and maintenance [37].

Ulcerative Gingivitis and Ulcerative Periodontitis

Both NUG and NUP may represent stages in a spectrum of the same severe periodontal condition. NUG is classically limited to the gingiva, whereas NUP is recognized by the loss of periodontal attachment and ulceration of the adjacent alveolar mucosa. Both lesions manifest in the acute phase and may vary from initial lesions with restricted necrosis at the top of the papillae to involvement of the complete attached gingiva, accompanied by tooth mobility and bone sequestering, [73], and both may become chronic. Individuals with NUP generally experience deep-seated jaw pain, spontaneous bleeding, and, in chronic cases, tooth movement [26, 76, 77]. Bad taste or bad breath may be present.

Left untreated, NUP may progress with 1–2 mm of soft and hard tissue destruction per week. NUP has been linked with severe immune suppression and CD4 cell counts below 100 cells per mm^3 [73]. During the acute phases, oral intake may be severely limited.

Differential diagnosis may include: mucous membrane pemphigoid, erythema multiforme, and acute leukemia [37].

The first step in the treatment of both NUG and NUP is debridement and antibiotic therapy with metronidazole 250–500 mg or tetracycline 250–500 mg QID for 7 days. Pain relief is rapid and tissue healing begins quickly. Concomitant antifungal therapy is recommended. Chlorhexidine gluconate 0.12% mouth rinse, twice a day swish for 30 seconds and then expectorate, is recommended for treatment and maintenance therapy [37].

Conditions with Nonspecific Etiology

Necrotizing Stomatitis

Necrotizing stomatitis is a rapidly progressive localized necrosis of oral soft tissue overlying bone [78]. The lesion may be extremely painful and interfere with eating, speech, and swallowing, seen in severely immunosuppressed, with the CD4 cell counts below 100 cells per mm^3 [2].

Differential diagnosis should include aggressive forms of aphthous ulcers, traumatic ulcers and malignant disease. It has been hypothesized that necrotizing stomatitis may be representing a widespread form of NUP [37].

Treatment includes debridement of the necrotic areas. A stent should be fabricated to cover the affected area to protect from trauma and as a carrier for topical application of medication. Topical glucocorticosteroids such as clobetasol or fluocinonide gel, or steroid mouth rinse may be used. In more severe and resistant cases, systemic steroid such as prednisone up to 80 mg day for 7 days may be indicated. The patient should be instructed to use chlorhexidine gluconate 0.12% rinse twice a day. Concurrent systemic antibiotics, metronidazole or tetracyclines (minocycline, doxicycline) may prevent bacterial super-infections and promote healing [37]. Pain management should be provided as needed.

Aphthous Like Ulcers

People living with HIV may experience ulcerations clinically resembling aphthous ulcers but lacking the usual early age predilection [79]. Minor recurrent aphthous ulcers generally manifest as 2–5 mm diameter small ulcers and resolve within 5 to 7 days. Recurrent aphthous stomattis (RAS) typically appear on non-keratinized tissue of the oral cavity, such as inside the lips or on the floor of the mouth or buccal mucosa. Minor RAS are characterized by frequent recurrence rate, often at the same site, and are generally associated with stressful events [37]. These lesions may be particularly painful and when large lesions develop may heal with scarring. Minor ulcerations may be misdiagnosed as recurrent herpes virus infection. Anesthetic or analgesic mouth washes or coating agents may ease local pain. Pain management may restore a patient's ability to eat, drink, chew, and swallow.

Recurrent ulcers that present as greater than 10 mm in diameter, with a crateriform and deeply eroded base, are known as major recurrent aphthae. These ulcers persist for more than 3 weeks and may heal with scarring. Major RAS severely impact oral intake, speech and swallowing [80]. Although no clear etiology has been established for these ulcers, several theories have been put forth: stress, vitamin deficiency, diet, hormonal changes, trauma, and immune dysfunction [30, 81]. In patients with HIV disease, major RAS have been correlated with severe immune suppression and severe persisting lesions associated with CD4 cell count below 100 cells per mm^3 [80].

Treatment of major RAS is crucial to maintaining oral intake. Topical glucocorticosteroids may be administered as the first step in therapy. If severe lesions are present, systemic prednisone may be provided. Topical steroid rinses such as dexamethasone elixir 0.5 mg/5 mL, 15 mL four times a day or other topical steroid rinses compounded may be used when multiple oral sites or those not amenable to local application of gel or ointment, such as in the posterior oropharynx. Antibiotic and an antifungal may be prescribed to prevent superinfections. Thalidomide 100–200 mg/d has been used to treat oral and esophageal ulcerations with limited success [82, 83]. There are some adverse reactions with use of thalidomide,and specific precautions required in its prescription and use [83]. Other topical immunosupporesives may be considered as may agents that reduce TNF production. Pain management is an important consideration in management to support comfort and oral intake.

Neoplastic Conditions

The association between HIV, immunusppression and non-Hodgkin's lymphomas (NHLs) was recognized early in the HIV epidemic and in 1985 it was added to the list of AIDS-defining diseases [3]. This neoplasm is rare, appearing in approximately 3% of AIDS diagnoses worldwide [84]. The lesion may present as a large, painful, ulcerated or exophytic mass on any mucosal surface and may be accompanied with tooth mobility, jaw pain, widened periodontal ligament, and progressive paresthesia [30, 37]. The average CD4 cell count in patients diagnosed with NHL is below 100 cells per mm^3 [30]. Prior to HAART, NHL represented the second most common neoplasm associated with AIDS, after KS [85]. With the implementation of HAART, the incidence of KS cases has decreased, whereas the number of patients developing NHL remain the same and with extended survival may be seen more commonly [85].

A biopsy is required for a definitive diagnosis of NHL, and an appropriate referral to an oncologist is indicated for initiation of treatment. Therapy may include surgical excision, chemotherapy, and/or radiation therapy [30]. NHL in HIV infected individuals used to be associated with a poor prognosis [86]. Progress in the treatment of NHL has significantly improved the prognosis of this disease in HIV but the survival rates for HIV patients with NHL remain below that of non-HIV patients [87].

A patient, with or without HIV infection, who has a neoplastic diagnosis will likely have impact on the oral cavity in numerous ways that require dietary and nutritional consideration. A series of recent reviews for head and neck cancer by Epstein and Huhmann portray needs while undergoing therapy [88] and post therapy [89]. The impacts include assuring adequate caloric and nutrient intake. Much of the focus need be on adapting diets to the functional limitations resulting from chemo- or radiation therapy. Obvious preference would be for cancer prevention, for which diet and nutrients have been shown to play a role, particularly through the consumption of fruits and vegetables [90].

Nutritional Management of Oral Manifestations of HIV

Dental intervention in conjunction with nutrition management is an essential component of care at the earliest stage of HIV infection because of the magnitude and impact of HIV-associated oral diseases on dietary intake and nutritional status. In addition, during the extended survivorship, nutritional support continues to be of great importance.

Oropharyngeal fungal infections and viral diseases, along with stomatitis and periodontitis, are associated with pain and can lead to reduced oral intake. Esophagitis and oral and esophageal candidiasis can cause painful mastication, drinking, and swallowing, further compromising appetite and food intake. Taste change due to infection or other causes such as oral secretion of medications

may impact appetite and food selection. Tumors including lymphoma, KS, and SCC depending on the size and location in the oral cavity, has the combined effect of compromising oral intake and increasing nutrient needs.

Oropharyngeal fungal infections may cause a burning painful mouth, taste change and dysphagia. Very hot and cold foods or beverages, spices, and sour or tart foods also may be painful and should be avoided. Consumption of temperate, moist foods without added spices should be encouraged. Small, frequent meals followed by rinsing with lukewarm water or brushing to reduce the risk of dental caries are helpful. Once the type and extent of oral manifestations are identified, a nutrition care plan can be developed.

Stomatitis can cause severe pain and ulceration of the gingiva, oral mucosa, and palate, which makes eating painful. Xerostomia, or dry mouth, secondary to medications or other concurrent disease can further compromise intake. Efforts to stimulate saliva production using pharmacologic agents and citrus-flavors (although acidic products may be poorly tolerated and may damage the dentition), sugar-free candies or chewing gum may ease dry mouth. Dietary guidelines focus on the use of moist foods without added spices or umami flavors, increased fluid consumption with and between all meals and snacks, and judicious food choices. Problems with chewy (steak), crumbly (cake, crackers), dry (chips), and sticky (peanut butter) foods are common in individuals with severe xerostomia, and avoiding these foods may help a great deal with eating. Water with a lemon-lime twist, citrus-flavored seltzers, and sucking on frozen grapes may help. Good oral hygiene habits are important to reduce the risk of tooth decay and should be practiced after all meals and snacks. Xylitol-flavored gums and mints may help reduce the risk of associated decay. If nutritional drink supplements are used, the high levels of surcrose may be best managed by consuming with meals, and tooth brushing prior and following intake. Educational resources in the appendices of this book are available for several of these topics.

Nutritional Consideration in HIV

Oral function and systemic status associated with HIV may affect nutrition of patients and may have impact on cardiovascular and bone health. It is evident that given the susceptibility of people living with HIV to lipid dystrophy or insulin resistance, careful dietary counseling must be integrated in HIV care. Other considerations in the diet of people living with HIV include the known nutritional deficiency especially in micronutrients [91]. The World Health Organization (WHO) advocates the intake of micronutrients at recommended dietary allowance amounts for healthy people living with HIV [92].

Medical nutrition therapy (MNT) is recommended for individuals living with HIV infection since health outcomes improve when MNT is provided [93–98]. A comprehensive evidence-based, HIV/AIDS MNT guideline can be found at the Academy of Nutrition and Dietetics, Evidence Analysis Library [99]. The guideline recommends six or more MNT sessions per year for individuals with oral or gastrointestinal issues. The HIV/AIDS MNT guideline purpose is to provide a reference for registered dietitians to provide evidence-based recommendations to maintain optimal nutrition status and prevent and manage other nutrition-related diseases and co-morbidities in people with HIV infection. Features of the HIV/AIDS guideline include evidence review methods, recommendations with a series of guiding statements that propose a course of action for practitioners, and algorithms with flowcharts for treatment of specific conditions. Table 14.3 provides a summary of the major nutrition and HIV MNT recommendations from the guideline.

Of specific interest to oral health, vitamin D deficiency, a prevalent condition in people living with HIV especially among African women [100], was shown to correlate with an increased risk of oral candidiasis. This finding was reported in a study conducted in an established cohort of women living with HIV [101]. The significance and generalization of this finding remain however to be

Table 14.3 Executive summary of Academy of Nutrition and Dietetics HIV/AIDS Medical Nutrition Therapy Guideline http://andevidencelibrary.com/topic.cfm?cat=4458

Nutrition care process stage and topic	Level of evidence	Recommendation
Screening and Referral • MNT	Strong	Medical nutrition therapy (MNT) provided by a registered dietitian (RD) is recommended for individuals with HIV infection. Four studies regarding MNT (with or without oral nutritional supplementation) report improved outcomes related to energy intake, symptoms and cardiovascular risk indices. Two studies regarding nutritional counseling (non-MNT) also report improved outcomes related to weight gain, CD4 count and quality of life
Screening and Referral • Frequency of MNT	Consensus	The Registered Dietitian (RD) should provide at least one to two Medical Nutrition Therapy (MNT) encounters per year for people with HIV infection (asymptomatic) and at least two to six (or more) MNT encounters per year for people with HIV infection (symptomatic but stable, acute or palliative), based on the following: • Appropriate disease classifications • Nutritional status • Comorbidities • Opportunistic infections • Physical changes • Weight or growth concerns • Oral or gastrointestinal symptoms • Metabolic complications • Barriers to nutrition • Living environment • Functional status • Behavioral concerns or unusual eating behaviors Studies regarding MNT (with or without oral nutritional supplementation) report improved outcomes related to energy intake, symptoms, and cardiovascular risk indices, especially with increased frequency of visits
Screening and Referral • Screening	Consensus	The registered dietitian (RD) should collaborate with other health care professionals, administrators and public policy decision-makers to ensure that all people with HIV infection are screened for nutrition-related problems, based on referral criteria regardless of setting, at every visit. People with HIV infection are at nutritional risk at any time-point during the course of their illness

explored. What is more, it is uncertain whether vitamin D supplementation would have any effect on the risk of candidiasis or any other aspect of oral health.

Summary

Oral manifestations are commonly the first signs of an underlying systemic disease in a patient. This chapter discusses some of the more frequently found oral lesions associated with HIV disease, their clinical presentations, and current treatment modalities. Furthermore, HIV disease may be associated with "wasting syndrome" and therapy of HIV with lipodystrohy that may impact general health, and require dietary considerations and perhaps dietary modification. The integration of dental management with nutrition care contributes to improved systemic, oral, and nutritional well-being and response to treatment. Collaboration across disciplines in detection, referral, and early

Table 14.4 Guidelines for practice

Oral health professional		Nutrition professional
Prevention	• Conduct regular screening examinations for oral disease	• Conduct oral screen as part of comprehensive nutrition assessment; refer nonnormal findings to a oral health care profession
	• Assess nutrition risk and provide appropriate referrals for medical nutrition therapy (MNT) in all individuals with HIV and AIDS	• Provide MNT to patients along with referrals for dental care on a routine basis
Intervention	• Provide dental care and prophyaxis as needed	• Routinely conduct oral screen on all patients and refer for and reinforce importance of dental treatment
	• Review appetite, weight change, intake, and oral factors affecting eating ability at all visits and refer as needed for MNT by a registered dietitian	• Provide MNT dietary guidelines consistent with symptoms to promote attaining and maintaining nutritional well-being

intervention of oral and nutrition-diet-related problems are important for comprehensive care of the individual with HIV or AIDS. Table 14.4 provides guidelines for practice for oral health care and dietetics/nutrition professionals.

Additional Resources

Ryan White AIDS Education and Training Centers (AETCs), which are funded through Part F, train clinicians and service providers, including dental providers, on HIV and oral health. For more information on dental resources for clinicians visit, http://www.aidsetc.org and search for dental materials (www.aidsetc.org/aidsetc?page=home-search&post=1&SearchEntry=dental).

The HIV/AIDS Bureau's TARGET Center site also includes numerous technical assistance documents on oral health. To view these visit, http://www.careacttarget.org and search the TA library for keyword "dental".

HIVdent has up to date treatment information and shares expertise in development, training, integration, and evaluation of oral health services for PLWHA. To peruse this resource visit, http://www.hivdent.org.

The New York State Department of Health AIDS Institute has a number of educational resources dedicated to oral health care. To learn more visit, http://www.health.ny.gov/diseases/aids/about/hlthcare.htm#ohc.

HRSA has devoted an entire Webpage on oral health (including HIV and oral health) and its importance in an effective public health strategy underscoring the importance of access and entry into these services. To read the page visit, http://www.hrsa.gov/publichealth/clinical/oralhealth/.

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Chapter 15
Autoimmune Diseases

Herve Sroussi, Joel B. Epstein and Riva Touger-Decker

Keypoints

- Autoimmune diseases vary in their signs, symptoms, and management; the need for early and continuous monitoring and intervention by oral health care and nutrition professionals is essential
- Organ specific autoimmune disorders and their associated treatments can impact oral motor and sensory functions
- There are several types of pemphigus with oral manifestations that are often painful; frequent monitoring, assessment, and management of current disease manifestations as well as prevention of future symptoms is essential
- Nonspecific autoimmune disorders including systemic lupus erythematosus, rheumatoid arthritis sjogren syndrome, and pernicious anemia have oral sequallae and impact nutrition status

Keywords Autoimmune diseases · Oral health · Systemic lupus erythematosus · Rheumatoid arthritis · Sjogren syndrome · Pernicious anemia · Nutrition status · Oral sequallae · Organ-specific autoimmune disorders

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Introduction

Autoimmune diseases can directly impact the oral mucosa, masticatory, and salivary gland function, indirectly impact the dentition and periodontium, and cause oral pain, affecting oral function and sensation. For some disorders, the earliest signs of systemic illness are found in the oral cavity, and these remain significant manifestations of the primary immune disorder. In others, oral involvement may be the primary or only site of symptomatic involvement. Additionally, the medical management of autoimmune diseases can alter oral immune surveillance as well as introduce significant metabolic and nutritional complications. This chapter explores the impact on oral health and nutrition of the following autoimmune diseases: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), pernicious anemia (PA), and Sjogren syndrome (SS), and the mucocutaneous disorders of pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP); Type 1 Diabetes Mellitus, another important autoimmune disorder, is discussed in Chapter 11. The oral healthcare professional (OCHP) may be the first to diagnose some of these conditions due to their oral presentation, and is responsible for management of oral complications of the disease and its treatment as well as identification of oral health promotion strategies to minimize long-term sequelae. Referral to dental or medical specialists and to a registered dietitian (RD) may be important in achieving optimal patient care and provide the best strategy for optimal disease management and health promotion.

General Features of Autoimmune Diseases and Their Treatment

Autoimmune diseases share features of an immunologic disorder resulting in production of antibodies directed against normal tissue and/or in the activation of autoreactive cellular immunity. The signs and symptoms of each disorder depend on the target tissue or tissues involved. In addition to the presence of an autoantibody or evidence of other self-reactivity, criteria for autoimmune disease include the presence of the autoantibody or lymphocytic infiltrate in the pathologic lesion. These disorders generally occur more frequently in women than in men and usually in individuals over age 40. Autoimmune diseases may be restricted to one organ (e.g., PV, MMP) or may involve several distinct organ systems (SLE, SS, RA). Individuals with one autoimmune disease are more likely to develop another; thus, it is not uncommon to find that patients have overlapping symptoms and multiple diagnoses (e.g., SLE, SS, mixed connective tissue disorder (MCTD)). Table 15.1 summarizes the target antigens of the autoimmune disorders discussed in this chapter, and each disorder is explored in greater detail in the subsequent sections.

In general, autoimmune disorders are incurable but may be manageable and require continuous or periodic treatment to minimize disease-related sequelae. Treatment may be directed primarily at the immune system with the objective of reducing autoantibody production or immune activation, at protection or replacement of the affected target tissue or cell, at relieving symptoms, or a combination of the above. The common long-term use of immunosuppressant and immunomodulating medications presents significant risk for complications such as opportunistic infection, increased risk for cancers, and a myriad of potentially serious metabolic and biochemical problems. Therefore, when possible, local, topical therapy may be used for oral and skin lesions and when effective, may reduce the risk of broader complications when systemic therapy is used. Progress in the development of gene therapy, tissue transplantation, and monoclonal antibody therapy provides the promise of more specific treatments with fewer side effects. Table 15.2 summarizes the spectrum of therapies

Table 15.1 Target antigens of selected autoimmune disorders

Presence in autoimmune disease (% of cases)						
Non-organ-specific autoimmune disorders					Organ-specific disorders	
Auto-antibody type	SLE	RA	SS	PA	PV	BMMP
Antinuclear	96–100	30–60	95			
Anti-native DNA	60	0–5	0			
Anti-rheumatoid factor	20	72–85	75			
Anti-Sm	10–30	0	0			
Anti-Ro	15–25	0–5	60–70			
Anti-La	5–20	0–2	60–70			
Anti-intrinsic factor				60		
Anti-gastric parietal cell				90		
Desmoglein 3					100	
Desmoglein 1					50	
Bullous pemphoid antigen 2						100

Table 15.2 Selected therapies for autoimmune disorders

Drug	Class	Common indications					
		PA	PV	BMMP	SLE	SS	RA
Prednisone	Glucocorticoid		1	1	2	3	2
Mycophenolate mofetil	Immunosuppressive		1	2	2	3	3
Azathioprine	Immunosuppressive		2	2	2	3	3
Dapsone	Antileprosy/disease modifying		2	1	2	3	2
Cyclophosphamide	Alkylating agent		2	2	2		3
Cyclosporin	Immunosuppressive		2	2	2		2
Methotrexate	Immunosuppressive; Antimetabolite		2	2	2		2
Gold	Disease modifying		4	3	3	3	2
NSAIDs	Anti-inflammatory		4	3	1	2	1
IVIg	N/A		2	3		4	
Hydroxychloroquine	Antimalarial			3	2		2
Plasmapheresis	N/A		3	3	3		
Topical, injectable therapies	Immunosuppressive	1	2	1	2		2
Replacement therapy (B_{12})						1	3
Palliative therapy (e.g., artificial tears, sialagogue, analgesic)							

1 first-line therapy, *2* second- or third-line therapy or in combination with 1, *3* on rare occasions, *4* not applicable

for treating the autoimmune disorders discussed in this chapter, and Table 15.3 shows the related systemic, oral, and nutritional complications of these medications; details are discussed in the subsequent sections.

Organ-Specific Autoimmune Disorders

Pernicious anemia (PA), pemphigus vulgaris, and mucous membrane pemphigoid represent autoimmune diseases with organ-specific antigen targets (see Table 15.1). Each has implications for oral, systemic, and nutritional aspects of the disease itself as well as for its therapy.

Table 15.3 Selected adverse effects of therapies for autoimmune disorders

Drug	Class	Selected adverse effects		
		Oral	Systemic	Nutritional
Prednisone	Glucocorticoid	Candidiasis	Adrenal insufficiency Psychosis Mood swings Peptic ulcer Osteoporosis Edema Insomnia Hyperglycemia Hypertension	Appetite change Weight gain Dyspepsia Osteoporosis Hyperglycemia
Mycophenolate Mofetil	Immunosuppressive	Candidiasis	Leukopenia Thrombocytopenia GI ulceration Hypertension Edema Anemia Headache Abdominal pain Constipation Insomnia	Dyspepsia Diarrhea GIulceration Constipation Anemia
Azathioprine	Immunosuppressive	Candidiasis	Leukopenia Thrombocytopenia Anemia GI hypersensitivity Hepatotoxicity Malaise	Anorexia Vomiting Diarrhea Anemia
Dapsone	Antileprosy/disease-modifying drug	Erythema multiforme	Hemolytic anemia Hepatotoxicity Fever Malaise Arthralgia	Anorexia Vomiting Nausea Albuminuria
Cyclophosphamide	Alkylating agent	Candidiasis Stomatitis	Cardiomyopathy Malignancy Heart failure Leukopenia Thrombocytopenia	Nausea Vomiting Anorexia Diarrhea
Cyclosporine	Immunosuppressive	Gingival hyperplasia Candidiasis	Seizures Leukopenia Thrombocytopenia Nephrotoxicity Hepatotoxicity Diabetes Hypertension	Diabetes Nausea Vomiting Diarrhea
Methotrexate	Immunosuppressive Antimetabolite	Candidiasis Erythema multiforme Stomatitis	Anemia Leukopenia Thrombocytopenia Hepatotoxicity Nephrotoxicity Seizures Encephalopathy Pulmonary fibrosis	Nausea Vomiting Diarrhea Anemia
Hydroxychloroquine	Antimalarial	Candidiasis	Anemia Agranulocytosis Thrombocytopenia Seizures	Nausea Vomiting Diarrhea Weight loss Anemia
Topical, injectable steroids	Immunosuppressive	Candidiasis Mucosal atrophy progressive systemic sclerosis (scleroderma)	Minimal glucocorticoid effects	

Pernicious Anemia

Pathogenesis

Anemia is a decrease in oxygen-carrying capacity of red blood cells (RBC) and can result from RBC destruction, inadequate RBC production, or blood loss [1, 2]. PA results from vitamin B_{12} (cobalamine) deficiency, caused by absorption deficiency or a dietary deficiency [1–4]. Cobalamine is an essential compound in folate metabolism, and a lack of either folate or cobalamine results in a defect in DNA synthesis and the associated megaloblastic changes in cells with relatively high turnover such as hematopoietic precursors and gastrointestinal (GI) epithelium. Cytoplasmic development proceeds normally while cell division is slowed, resulting in large cells with an increased ratio of RNA to DNA. Megaloblastic anemia is present when the mean corpuscular volume exceeds 100 fL. Other conditions that can lead to cobalamine deficiency and megaloblastic anemia include gastrectomy, small-intestine bacterial overgrowth, diverticulosis, scleroderma, tapeworm, tropical sprue, alcoholism, and medications such as neomycin and colchicine.

Cobalamine cannot be synthesized; dietary sources are limited to animal protein foods (highest sources are seafood, meat, eggs, dairy), although many enriched and fortified grain products have added B_{12} [4, 5]. The recommended daily allowance for adults is 2.5 μg. With estimated body stores of 2–3 mg [6], the onset of symptoms of anemia usually occurs after several years of inadequate consumption or absorption.

Intrinsic factor (IF) produced in gastric parietal cells binds to cobalamine and protects it from degradation until it can be absorbed in the ileum. Anti-IF antibodies and antibodies directed against gastric parietal cells result in a lack of IF and subsequent poor absorption of cobalamine and potentially megaloblastic anemia. Correct identification of the underlying cause (i.e., folate vs. cobalamine deficiency) is important, rather than empirical folate therapy, which will improve only the anemia and not the neurological symptoms of a cobalamine deficiency (paresthesia, impaired neurocognitve function).

Clinical Features

General Features

Symptoms of PA may include weakness, light-headedness, shortness of breath, lowered energy levels, palpitations, and angina [6]. Physical findings in the patient with florid cobalamin deficiency include pale skin, with slightly icteric skin and eyes, and rapid pulse. There may be anorexia with varying degrees of weight loss. Megaloblastosis of the small intestine epithelium may result in diarrhea, which subsequently causes malabsorption and contributes to weight loss. A hallmark feature of PA is the neurological symptoms of peripheral paresthesia, weakness, ataxia, loss of concentration, memory loss, disorientation, and even dementia. Early demyelination can progress to axonal degeneration and neuronal death. These neurological symptoms are a direct result of the cobalamine deficiency (not the anemia) and can be permanent even after correction of both the cobalamine deficiency and the related anemia. Empirical treatment of undiagnosed PA using folate can correct the anemia but mask the underlying cobalamine deficiency, thus placing the patient at risk for worsening neurological symptoms [6]. Gastrointestinal manifestations beyond the oral features mentioned below include anorexia, flatulence, and constipation.

Oral Features

Oral findings can occur quite early in PA and include atrophic glossitis (red and smooth tongue), burning mouth, and aphthous stomatitis. Any patient over age 40 with unexplained weakness and these oral findings should have a complete blood count with RBC indices and serum levels of B_{12} and folate. A thorough diet, nutrition, and health history are important to detect other contributing factors.

Diagnosis

Diagnostic tests for pernicious anemia include the Shilling Test, which uses radio-labeled B_{12} to demonstrate inadequate absorption and urinary excretion of cobalamine, and anti-IF (60% of patients) or antiparietal cell (90% of patients) antibodies.

Treatment

There is no treatment directed at reducing the autoantibody production. Once the diagnosis of PA is established, replacement therapy with monthly parenteral B_{12} or oral daily doses of B_{12} leads to rapid correction of symptoms [2, 6–8]. Prognosis is excellent, although established neurological symptoms may remain. Continuous evaluation and monitoring are necessary because of the increased prevalence of gastric polyps and possibility of gastric carcinoma in later years [9].

Oral Health and Nutrition Complications and Management

Oral Complications and Management

The oral complications of PA (glossitis, burning mouth, aphthous stomatitis) generally improve with adequate cobalamine replacement. If burning persists and significantly impacts quality of life, adjuvant analgesic medications for neuropathic pain (clonazepam, low doses of tricyclic antidepressants, gabapentin, and others) may provide relief. Periodic aphthous lesions can be managed by early and brief treatment with moderate to potent topical steroid ointments or gels such as clobetasol or fluocinonide; patients with frequent or persistent lesions should be referred to an oral medicine specialist for additional care.

Nutritional Management

A comprehensive nutrition assessment (refer to Chapter 19 for a more detailed discussion) is the first step in determining nutrient needs and a tailored diet management approach. Although the OHCP may detect oral nutrition manifestations and difficulties in eating, the level of nutrition intervention required for individuals with PA requires referral to an RD.

Nutrition assessment includes a detailed diet history including the use of any dietary supplements or special diets that may impact vitamin B_{12} absorption, metabolism, or excretion. Other concurrent diseases or surgical histories (e.g., gastrectomy) that may affect B_{12} status should also be explored. A nutrition focused physical examination (NFPE) should be completed. The NFPE of the head/neck area should address patient reported symptoms of oral problems and their impact on oral function (biting, chewing, and swallowing) as well as possible signs of nutrient deficiencies or excesses. Use

of complementary and alternative medicine by individuals with autoimmune diseases is common and should be questioned in detail (see Chapter 9). Select dietary supplements can impact oral health and function as well as interact with medications. Individuals should be cautioned against the use of any supplements that can affect vitamin B nutriture and immune function.

Energy and nutrient needs should be based on goals for weight (gain, loss, and maintenance), prior intake, and estimated needs in light of current therapies. The diet education materials in the Appendix provide guidelines for diet management of oral sequellae. Nutritional management should be planned with the physician treating the PA to complement pharmacologic therapies. Diet management must address oral sensory and functional challenges, side effects of any medications, concurrent diseases, and cultural and personal preferences. Oral function, appetite, side effects of medications, clinical parameters, level of fatigue, nutrient intake, and weight should be monitored regularly by an RD. The OHCP should monitor patient weights; question patients regarding oral function, appetite, and intake; and refer accordingly.

Pemphigus Vulgaris

Pathogenesis

PV is an autoimmune, mucocutaneous bullous disease. Although there are several forms of pemphigus (vulgaris, foliaceous, vegetans, and paraneoplastic), 80% of all patients with pemphigus have PV [10, 11]. PV affects both sexes equally and is more common among Jews, particularly Ashkenazi Jews and in people originating from the Indian peninsula. Although rare, pediatric cases have been reported, PV most commonly develops during the fourth to sixth decades of life [10, 11]. It should be noted that PV is often diagnosed before the age of 40 in Indian patients, whereas Caucasian patients are more often diagnosed at later ages. PV is characterized by autoantibodies directed against desmosome-associated protein antigens (desmoglein 3 in 100% of cases, and desmoglein 1 in 50% of cases) found in epithelial and epidermal intercellular substance [12]. Because the desmosome is the primary attachment mechanism between keratinocytes, the inflammatory destruction of that attachment leads to epithelial separation, formation of characteristic fluid-filled bullae, and subsequent ulceration. When the epithelial attachment is compromised or destroyed, even minor mucosal trauma may result in epithelial separation (acantholysis) and bullae formation. The bullae quickly rupture, leaving relatively nonspecific, shallow ulcerations with an irregular border.

Clinical Features

General Features

The typical presentation of PV is multiple, chronic, shallow mucocutaneous ulcerations, preceeded by bullae. The lesions do not heal without treatment and often develop following minor trauma (referred to as the Nikolsky sign). Although the oral presentation of PV is by far the most common first site of lesions, and the exclusive site in approximately 25% of patients, it is not well recognized in the mouth, and, unfortunately, the oral presentation is often associated with significant diagnostic delays [13, 14].

Oral Features

Multiple, shallow, chronic oral mucosal ulcerations are the typical presentation of PV. Generalized desquamative gingivitis is another common presentation of oral PV, appearing as generalized gingival erosion and erythema. Other diseases to be considered in the differential diagnosis include mucous membrane pemphigoid (MMP) and erosive lichen planus; several other disorders may be considered but are exceptionally rare. Oral complications of PV include painful gingival and mucosal lesions that can prevent adequate oral hygiene and intake of food, resulting in risks for significant dental and nutritional difficulties, and complications related to immunosuppressant medications used in the treatment of PV (see relevant sections below).

Diagnosis

A perilesional biopsy must be performed and submitted for both routine (hematoxylin and eosin) and direct immunofluorescent (immunoglobulin G [IgG]) stains [10–12]. Additionally, circulating antibodies (IgG) are detectable in 80–90% of patients with PV and the titer is generally correlated with the level of clinical disease [15] and is therefore a useful measure of treatment effectiveness and disease activity.

Treatment

PV is a serious, chronic, incurable disease that can lead to death. The goal of treatment is elimination of lesions by reduction in autoantibody production using systemic therapy; local treatment can be utilized to manage local oral lesions if the only manifestation of disease or to manage oral lesions recalcitrant to systemic therapy. First-line therapy is usually prednisone in moderate to high doses (1–2 mg/kg) [16, 17]. Doses of prednisone can be reduced while maintaining therapeutic benefit with the use of adjuvant medications such as azathioprine, cyclophosphamide, methotrexate, or dapsone (see Table 15.2). Mycophenolate mofetil is a newer immunosuppressant medication with a more desirable side effect profile compared to prednisone and can be effective as first-line and adjuvant (steroid-sparing) therapy [18]. Recent reports indicate that novel and targeted immune modulatory agents such as rituximab (a monoclonal CD20 antibody) could also be successfully utilized to manage autoimmune bullous diseases such as PV or MMP. What is more, additional therapeutic strategies such as immunoadsorption aimed directly at the pathogenic autoreactive antibodies with agents such as protein A may represent an alternative to what remains the first-line steroid-based therapy [19].

With aggressive treatment, complete resolution of lesions is common, although many patients require maintenance doses of prednisone or the adjuvant medications due to the chronic nature of the illness life long.

Oral Health and Nutrition Complications and Management

Oral Complications and Management

The oral lesions of PV may be painful. Two-thirds of patients with PV find their oral lesions more problematic than the skin lesions [13]. It is therefore common for patients with PV on systemic treatment to receive an adjuvant oral mucosal topical regimen composed of high potency topical steroids or other immunosuppressive medications. Especially when there is a gingival component,

oral hygiene can be very difficult, and patients avoid cleaning their teeth near the gingivae and as a result, plaque accumulation can lead to significant caries and gingival and periodontal disease. Adequate management of the oral lesions of PV is essential so the patient can maintain a healthy oral environment; tooth loss can be problematic aggravate tissue inflammation, and because replacement by a removable prosthesis may not be possible in the presence of a blistering mucosal disease. Recalcitrant oral lesions may be managed with injectable and potent topical steroids; referral to an oral medicine specialist is indicated. The patient with oral PV should be on an aggressive health-promotion and disease-prevention plan with frequent recall and dental prophylaxis and dental disease prevention. Individuals experiencing difficulty eating, weight loss or gain, or changes in appetite should be referred to an RD for medical nutrition therapy (MNT). Immunosuppressant medications prescribed to treat PV increase the risk for several oral disorders such as candidiasis, stomatitis and erythema multiforme (see Table 15.3). Systemic antifungal therapy (fluconazole) is indicated when there is oral candidiasis (Table 15.4). Oral lesions (mucositis) that are a result of medications such as methotrexate and cyclophosphamide may require substitution with an alternative medication if available or management of oral lesions and related symptoms.

Table 15.4 Oral candidiasis treatment regimens

Treatment for oral candidiasis		
Topical		
Clotrimazole troches[a]	2 wk	Dissolve 1 10 mg troche in mouth 5 times/d
Nystatin vaginal suppositories[b]	2 wk	Dissolve 1 tablet (100,000 U) in mouth 6–8 times/d
Systemic		
Fluconazole	2 wk	100 mg/d
Ketoconazole[c]	2 wk	200 mg/d
Itraconazole[d]	2 wk	200 mg/d
Treatment for angular cheilitis		
Antifungal cream Clotrimazole 1% Miconazole 2% Ketoconazole 2%	2 wk	Apply to affected area 4 times/d
Combination Creams[e] Hydrocortisone–iodoquinol cream	2 wk	Apply to affected area 3 times/d

[a] Use with caution because of sugar content

[b] Although this preparation is not designed for oral use, clinicians have found it useful for the treatment of oral candidiasis when the sugar content of other topical anticandidal medications is of concern. A sugarless flavored lozenge maybe dissolved simultaneously in the mouth to mask the taste of nystatin

[c] Must use with caution; monitor for hepatotoxicity with liver function tests

[d] Should be used for resistant strains of *C. albicans*

[e] Some clinicians have found combinations creams more effective than antifungal medications alone in the treatment of angular cheilitis. These include combination preparations of topical hydrocortisone, antifungal agents, and hydrocortisone–iodoquinol cream, which combines an antifungal–antibacterial agent with an anti-inflammatory antipruritic

Nutritional Management

PV increases nutrition risk due to oral lesions secondary to disease or treatment (Table 15.3). There are no specific nutrient needs associated with the disease; in contrast, nutrient needs and diet modifications should be tailored for patients based on their oral manifestations of the PV and planned treatment as well as any other comorbid conditions. Oral pain may require palliative management in order to facilitate oral care and oral intake of foods and fluids. When diet alone

cannot meet energy and nutrient needs, oral supplements can be used to augment diet. Common symptoms include anorexia secondary to the associated pain, weight loss during acute phases of the disease process, and risk for dehydration. Dehydration may occur depending on the location and extent of oral lesions and their impact on ability to consume fluids; at times a percutaneous enteral gastrostomy (PEG) feeding tube is needed to provide for energy, nutrient, and fluid needs. Efforts to control weight loss and combat the unpleasant systemic side effects of medications should be initiated early with a referral to an RD for medical nutrition therapy (MNT). When steroid therapy is expected to be chronic, serum glucose and lipid values along with weight and weight change should be monitored regularly, and individuals should be evaluated for risk for or presence of osteoporosis. Initiation of calcium supplementation and Vitamin D early (see Chapter 15) may prevent subsequent development osteopenia or osteoporosis. The American College of Rheumatology evidence-based recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (2010) indicated "A" level evidence for use of calcium and vitamin D supplementation for such individuals [20]. Nutrition screening and assessment guidelines for OHCPs and RDs are detailed in Chapter 19. Diet guidelines for xerostomia and oral dysfunction are provided in the Appendix. In the diet management of PV, mucosal pain management prior to mealtimes and use of a straw may help facilitate oral intake. Coordinated follow-up by the healthcare team with experience in management of the unique needs of patients with PV is critical to optimal care of patients.

Mucous Membrane Pemphigoid

Pathogenesis

MMP, like PV, is an autoimmune disorder but in MMP the autoantibodies are directed against the basement membrane of the epithelium [10, 16, 17]. In contrast to PV, MMP is limited to the mucosa, with the target antigen (bullous pemphigoid antigen) being found at the basement membrane zone, where the inflammation results in a separation from the underlying connective tissue, bullae formation, and then nonspecific ulceration. MMP does not generally involve the skin surfaces, that variant of pemphigoid being termed bullous pemphigoid [18]. The clinical presentation is similar to that of a patient with PV: multiple, chronic oral ulcerations preceded by bullae commonly involving attached gingiva. Individuals with MMP are more likely to report spontaneous bleeding than individuals with PV because of the location of the autoimmune response in MMP. Biopsy with routine and direct immunofluorescence staining can distinguish between the two disorders and for definitive diagnosis.

Clinical Features

General Features

The presentation of MMP may be similar to that of PV, and severe cases of lichen planus. MMP may involve other mucosal surfaces including the ocular mucosa, genital mucosa, esophagus, and airway. Nikolsky sign (bulla and blister formation following minor trauma) occurs in MMP and PV; PV may involve skin. Unlike PV, healing of MMP lesions can be associated with cicatrix, or scar formation. This variant of MMP is called cicatricial pemphigoid. The scars can be significant, leading to oral, pharyngeal, esophageal, and ocular strictures that limit motility and function. MMP is a chronic, incurable disease that can be controlled with systemic, and at times local, potent anti-inflammatory medications.

Oral Features

Oral findings in MMP include erythematous lesions with multiple, shallow, chronic ulcers that are preceded by bullae. Generalized desquamative gingivitis is a common presentation of MMP. Cicatrix formation can limit oral opening and flexibility of oral mucosa. Differential diagnosis includes PV and erosive LP. The oral cavity is the predominant site of MMP. Oral complications of MMP include sometimes painful gingival and mucosal lesions that can prevent adequate oral hygiene and intake of food, resulting in risks for significant dental and nutritional complications. Patients may also experience complications related to immunosuppressant medications used in the treatment of MMP (see relevant subheadings below).

Diagnosis

Like PV, a definitive diagnosis of MMP requires a perilesional biopsy and subsequent routine and DIF staining to confirm the presence of subepithelial antibody.

Treatment

Patients diagnosed with MMP in the oral cavity should be referred to an ophthalmologist to rule out ocular manifestations. These present as erythema, ulceration, and partial or complete adhesion of the conjunctiva. These adhesions are referred to as *symblepharon* and can potentially result in blindness if untreated. Although prednisone is often a drug of choice to rapidly control the disease, it is not typically used in large doses for prolonged periods [10, 16, 17]. Dapsone, may be used in combination with prednisone allowing lower dose steroid for clinical control or may be used as a single agent in controlling MMP and has a more desirable side-effect profile than prednisone [21, 22]. It is important to determine whether the patient has a G6PD deficiency because these patients are at much greater risk for dapsone-induced hemolysis and methemoglobinemia. Adjuvant medications listed in Table 15.3 are helpful in refractory disease. MMP is more responsive than PV to local treatment using potent topical (clobetasol, halbetasol) or injectable steroid medications.

Oral Health and Nutrition Complications and Management

Oral Complications and Management

Oral MMP can be painful and can make it very difficult for patients to adequately clean their teeth near the gingivae leading to plaque accumulation can lead to significant caries risk and gingival and periodontal disease also aggravating MMP. Adequate management of the oral lesions of MMP is essential so the patient can maintain a healthy oral environment; tooth loss can be problematic because replacement by a removable prosthesis may not be possible in the presence of a blistering mucosal disease. When oral hygiene cannot be maintained, chlorhexidine rinses may be helpful in reducing plaque levels until oral hygiene can be improved. Recalcitrant oral lesions can be managed with injectable and potent topical steroids, and referral to an oral medicine specialist is indicated. The patient with MMP should be on an aggressive heath-promotion and disease-prevention plan with frequent recall and dental prophylaxis. Individuals with difficulty eating or drinking due to the MMP or those with changes in weight or appetite should be referred to an RD for MNT.

Immunosuppressant medications prescribed to treat MMP increase the risk for several oral disorders such as candidiasis, stomatitis and erythema multiforme (see Table 15.3). Systemic

antifungal therapy (fluconazole) is indicated when secondary oral candidiasis develops (Table 15.4). Oral lesions that are a result of medications such as methotrexate and cyclophosphamide may require substitution with an alternative medications when possible or pain management may be needed.

Nutritional Management

Nutrition management is similar to that described previously for PV. Elevated energy and nutrient needs are challenged by compromised ability to consume adequate nutrition, pain, and altered quality of life. Likewise, when seeing patients with MMP, it is incumbent on the RD to integrate oral hygiene instruction into counseling strategies and communicate regularly with the physician and OHCP.

Non-Organ-Specific Autoimmune Disorders

Systemic Lupus Erythematosus

Pathogenesis

SLE is an autoimmune disease that affects multiple tissues and organ systems. Approximately 90% of patients are female, generally of childbearing age. Multiple autoantibodies are found, the only disease-specific autoantibody being anti-Sm, a small protein associated with RNA; antibody to double-stranded DNA is also highly suggestive of SLE [23, 24]. The principal tissue damage in SLE comes from the deposition of immune complexes and small-vessel vasculitis in multiple organs: heart, lungs, kidneys, joints, skin, nervous system, and GI tract. The manifestations of the disease depend on the severity of the expression of the disease and the organ system affected, resulting in variable presentations.

Clinical Features

General Features

Any young woman presenting with multiorgan system symptoms should be evaluated for SLE. The more commonly encountered symptoms are briefly described here. The symptoms vary from mild and nonspecific to severe and may have periods of exacerbation and remission, and a patient may have periods of relatively inactive disease followed by a lupus "flare."

Arthralgia and myalgia are common and variable. The classical malar ("butterfly") rash may develop; it is a fixed, erythematous rash over the nose extending as far as the chin and ears. The rash is photosensitive, and damaging exposure to sun can also result in a generalized maculopapular rash. Immune complexes deposited in the glomeruli may result in glomerulonephritis in about one half of patients and can be rapidly progressive and result in renal failure. Neural involvement can lead to impaired cognition, headache, seizures, and a variety of other nonspecific neurological symptoms. Small-vessel vasculitis can result in thrombus formation and increased clotting. Libman-Sacks vegetations involving the heart valves can increase the risk for infective endocarditis. Hemolysis leading to anemia and thrombocytopenia can be severe. Pericarditis, pleurisy, and pneumonitis are not uncommon cardiopulmonary manifestations of SLE. Nausea, diarrhea, and vague abdominal

discomfort are common GI symptoms, and intestinal vasculitis can occur; this serious complication can lead to perforation of the GI tract.

Oral Features

SLE may affect several tissues in the orofacial region: oral mucosal inflammation and ulceration, glossitis, salivary gland inflammation and fibrosis resulting in hyposalivation (similar to SS), and temporomandibular joints arthralgia and masticatory muscle myalgia [25, 26]. When taking immunosuppressive medications to control SLE symptoms, the patient may also develop oral candidiasis and mucositis.

Diagnosis

Four of 11 findings are sufficient to establish a diagnosis of SLE: malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disease, neurological disease, hematologic disorder, immunologic disorder, or anti-Sm and anti-ds-DNA antibodies [23, 24]. For oral mucosal lesions, a biopsy showing vasculitis will assist in diagnosis.

Treatment

SLE is incurable, with variable progression; most patients experience continuous symptoms of varying intensity along with periods of disease flares. Mild disease activity is treated symptomatically, and those patients with life-threatening manifestations (renal, cardiopulmonary) require aggressive immunosuppressive therapy primarily with prednisone and in combination with adjuvant immunosuppressant and cytotoxic medications (Table 15.2). Symptomatic treatment includes the judicious use of nonsteroidal anti-inflammatory drugs (NSAIDs, acetaminophen) for myalgia and arthralgia, antimalarial agents such as hydroxychloroquine, and adjuvant analgesics for neuropathic burning pain (centrally acting pain medications such as gabapentin, tricyclic antidepressants, and others).

Oral Health and Nutrition Complications and Management

Oral Complications and Management

The oral complications of SLE include oral ulcers, xerostomia, glossitis, neuropathy, arthritis, and myalgia [25]. If systemic treatment is provided, oral findings may improve with treatment of the SLE. Xerostomia and immunosuppressants place the patient at increased risk for oral candidiasis, periodontal disease, and caries; frequent recall is important to minimize this risk. Xerostomia may improve with sialogogues and with treatment of the underlying salivary gland involvement. Oral candidiasis should be treated with systemic antifungal therapy (fluconazole) or topical antifungal therapy (Table 15.4). Dental sealants, topical calcium/phosphate and fluoride, and chlorhexidine affecting the oral flora may reduce the risk for caries. Topical steroid medications (clobetasol, fluocinonide) can be beneficial for focal oral ulcerations. Oral conditions that do not respond to therapy should be managed by referral to an oral medicine specialist. Referral to a registered dietitian is important when there are oral problems interfering with ability to eat and drink and when

there are GI symptoms or evidence of disease or treatment-related malabsorption to help prevent and manage weight loss, nutrient deficiencies, and malnutrition.

Approximately 20% of patients with SLE have Libman-Sacks vegetations on cardiac valves, placing them at increased risk for infective endocarditis [27]. The OHCP should consult with the physician to determine whether such lesions exist and follow the American Heart Association recommendations for endocarditis prophylaxis following the most current guidelines (www.heart.org). Patients with SLE may also have a coagulopathy (platelet and clotting factor antibodies) and should have a coagulation profile prior to extensive oral surgery, including management of the bleeding, following consultation with the physician.

Finally, it is possible that dental treatment or acute dental disease could trigger a lupus flare. Although there is little to be reasonably done to avoid this, patient education about the possibility is important so there is minimal delay in responding to the flare.

Nutritional Management

Given its systemic nature, SLE can affect the GI tract from entry to exit. The manifestations of the disease, organ systems and joints affected, and presentation as well as the medication management of the disease all impact nutrition and diet needs and goals. Expert consultation with an RD will include assessment functional and sensory factors impacting the ability to eat and drink (oral motor, cranial nerve, integrity of the oral cavity), along with body composition, clinical (signs and symptoms of nutrient deficiencies), and biochemical parameters (protein status, glucose, and cholesterol as well as liver, renal, and immune function tests) parameters, and determine nutrient needs and route(s) of feeding. The recommendations for nutrition screening, assessment, and management including diet described in earlier sections of this chapter and in Chapter 19 apply in cases of SLE as well. However, given the potential for multi-organ system involvement with SLE, additional modifications in macro and micronutrient content of the diet may be needed. For example, the patient with GI involvement may need modification in vitamin, mineral, and trace element as well as dietary fiber composition. Those with renal involvement may require a protein-modified diet.

Rheumatoid Arthritis

Pathogenesis

RA is an autoimmune disease affecting multiple organ systems, although the principal characteristic is persistent inflammatory synovitis. The synovitis and subsequent joint pain and destruction can vary widely among patients. The disease affects women three times more frequently than men, and the majority of patients are in the fourth or fifth decade at the time of diagnosis [24]. Although autoantibodies are detected in the majority of patients with RA (about 50% antinuclear antibody and 80% rheumatoid factor) not all patients will demonstrate autoantibodies. While it is unknown what events initiate the inflammatory response, the hallmark synovial inflammation is characterized by infiltration of T-lymphocytes, macrophages, and fibroblasts [28].

Clinical Features

General Features

The onset of painful peripheral joints in a symmetric fashion is the usual presentation of RA; it may be accompanied by nonspecific weakness and fatigue. Peripheral joint stiffness and swelling develop over time. The disease can be progressive and debilitating, leading to joint fibrosis and ankylosis.

Oral Features

Although oral signs of RA are not common, they do occur, and certainly there can be oral complications to RA treatment. Approximately 50% of individuals with RA will have involvement of the TMJ determined by a variety of imaging techniques. However, probably less than one half of these develop symptoms such as jaw stiffness, TMJ pain, and limited range of motion. Certainly, a small number of patients have aggressive and progressive destruction of the TMJ, potentially leading to fibrosis, ankylosis, and anterior open bite because of condylar destruction. When SS occurs with RA (not uncommon), hyposalivation can increase the risk for caries, periodontal disease, and candidiasis. Hyposalivation can lead to increased alveolar bone loss which, in addition, may cause complications of RA independent of xerostomia [29].

Diagnosis

The diagnosis of RA requires the presence of at least four out of seven criteria: morning stiffness, arthritis of three or more joints, arthritis of the hand joints, symmetric arthritis, rheumatoid nodules, serum rheumatoid factor, or radiographic changes consistent with RA [30, 31]. As discussed in the pathogenesis section, autoantibodies are not found in all patients with RA (Table 15.1).

Treatment

The objectives of RA treatment are relief of pain, reduction of inflammation, protection of articular structures, maintenance of function, and control of systemic involvement. There is no cure for RA. Physical therapy is a major part of management of RA to minimize pain and maximize function. Medical management of the disease generally first utilizes NSAIDs, although there is increasing evidence that low-dose glucocorticoids provide good disease control with minimal side effects [32, 33]. Intra-articular injection of anti-inflammatory medications may occasionally be considered. A class of medications referred to as disease-modifying antirheumatic drugs is used for patients not responding to other RA medications (Table 15.2) [34].

Oral Health and Nutrition Complications and Management

Oral Complications and Management

If signs of TMJ involvement are found (condylar erosion, pain, limited opening), consultation with the physician and an oral medicine specialist is useful for considering medication adjustment or intra-articular injection; rarely surgical intervention may be indicated from arthrocentesis, arthroscopy, and in rare instances where advanced TMJ destruction may require total joint replacement.

When manual dexterity of the hands is affected, the patient's ability to clean the teeth can be significantly impaired. Individualized assessment to identify strategies to improve the ability to clean the teeth is essential and includes customized toothbrush holders and irrigation and other devices to allow periodontal hygiene (i.e., floss holder). If hyposalivation is present, caries prevention should include diet counseling, fluoride, calcium supplementation, chlorhexidine rinses, and sealants where appropriate. If immunosuppressant medications are prescribed, there is increased risk for oral candidiasis and/or stomatitis (seen with some cytotoxic medications; see Table 15.3). Candidiasis treatment recommendations are summarized in Table 15.4. Severe TMJ ankylosis and/or destruction can significantly affect the ability to eat. In such instances, a referral to an RD for MNT to prevent weight loss or nutrient deficiencies is recommended.

Nutritional Management

Nutrition management of RA is similar to that cited for other autoimmune diseases, particularly SLE. Diet modifications may be needed depending upon on the degree of oral and joint function, dexterity, and range of motion of the head, arms, and hands. Nutrient and energy needs vary with the presence of comorbid conditions, weight status, the organ systems affected, and the pharmacologic management of the patient. Early intervention is critical to successful management. Frequent follow-up is important as changes in medications and exacerbations of disease may impact diet and subsequently nutrition status. The reader is referred to the other sections of this chapter and the Appendix for diet education materials and management strategies.

There have been numerous diets suggested for RA [35–37], many with substantial methodological differences and some limited scientific evidence to support their use; these include the "no-nightshade" diet, vegan or vegetarian diet, the Mediterranean diet, and elimination diets. The Mediterranean, vegetarian, and vegan diets are notably richer in antioxidants and omega 3 and 6 fatty acids hence support of their use is based upon potentially decreasing the inflammatory response of the individual [36]. The concept behind the elimination diet is that food may serve as disease aggravating factors and their elimination may reduce disease symptoms. The diet starts with gluten free grains, eliminating red meats, dairy, citrus, and some other fruits and vegetables for 7 days; after that foods are reintroduced one by one to see if they aggravate symptoms. The National Dysphagia Diet may provide guidance for those with joint impairment, dry mouth, and dysphagia.

Lahiri et al. [35] conducted a meta-synthesis of lifestyle risk factors for RA. They concluded that foods rich in antioxidants and oily fish (containing omega 3 and 6 fatty acids) may have a protective effect on risk of disease but data regarding vitamin D deficiency and red meat consumption were inconclusive. In contrast, Costenbader et al. [37] analyzed data from the two *Nurses Health Study* cohorts from 1980–2004 and found no association between antioxidant intake and risk of RA. A systematic review by Hagen et al. [35] evaluated dietary interventions for RA. Fourteen clinical trials were included in the review; 11 were clinical trials with patients that had RA that compared study diets with a usual diet. Three compared different diets. The primary findings of this review revealed that none of the diets studied in the trials (vegetarian, Mediterranean, elemental, or elimination diets) had sufficient evidence to support their claims in these patients; most studies were small, of short-term duration and had some risk of bias. The possible negative side effects including weight loss and nutrient deficiencies cannot be overlooked. Although this review included some older studies, the findings may be valuable to OHCPs and RDs when faced with patients asking about use of these diets for their RA.

Sjögren Syndrome

Pathogenesis

SS is a chronic, multiorgan systemic autoimmune disease [38] that affects most dramatically the exocrine lacrimal and salivary glands, that may result in profoundly dry eyes and mouth. It occurs in women about nine times more frequently than men, and most commonly begins between the ages of 30 and 40. It may occur alone (primary SS) or frequently in combination with another autoimmune or connective tissue disease (secondary SS) [39, 40]. Autoantibodies to Ro/SS-A and La/SS-B antigens are common and relatively disease specific but not necessary; ANA is very common but not disease specific (Table 15.1) [41]. The disease is characterized by a multifocal lymphocytic infiltration of the salivary and lacrimal glands, leading to acinar atrophy and parenchymal fibrosis; the condition, like other autoimmune conditions has variable severity and variable progression, end stage SS leads to no measurable tear and saliva production. Extraglandular involvement also occurs primarily due to immune complex vasculitis. A small number of patients with autoantibodies and multiorgan system manifestations are at risk for developing lymphoma [42].

Clinical Features

General Features

Symptoms of dry eyes and dry mouth are gradual in onset and variably progressive. Eye irritability and photosensitivity are common eye complaints and can lead to corneal injury. Inability to swallow food or the need to wash it down with fluids is a common oral complaint. Speech and oral health are affected and may lead to rampant caries, periodontal bone loss and other oral diseases, and affect oral intake of nutrients. Some patients develop enlarged parotid salivary glands.

Oral Features

Oral features of SS include diminished saliva pooling and dry oral mucosa. Smooth surface caries (sites of teeth uncommonly involved by cavities), dental demineralization and erosion, candidiasis, and mucosal irritation or injury occurs when the mouth is dry.

Diagnosis

Diagnostic criteria for SS have been the subject of considerable debate, with as many as five varying criteria sets [43–45]. Most practitioners agree that the diagnosis requires evidence of decreased gland function, autoantibodies, and occasionally a minor salivary gland biopsy demonstrating multifocal lymphocytic infiltration. Some have recommended diagnostic criteria based only on symptoms.

Treatment

There is no cure for SS; treatment focuses largely on minimizing the symptoms and, when severe, use of immunosuppressive medications. When there is evidence of remaining gland function,

sialagogue medications (pilocarpine, bethanechol, cevimeline) can be effective in stimulating saliva and tear production. "Artificial tears" and 'saliva substitutes' may provide short-term symptomatic relief (palliation) and tear production when exocrine function cannot be stimulated." Steroid and NSAIDs have not shown any benefit in saliva or tear production.

Oral Health and Nutrition Complications and Management

Oral Complications and Management

The oral complications of SS can be serious and can dramatically affect quality of life. Hyposalivation leading to rampant caries can be very difficult to treat and result in infection, pain, loss of teeth, and inability to chew properly. Prevention is key, prior to severe damage, as the process of loss of mineral leading to cavitation can be difficult to treat and maintain. The process of dental mineralization must be addressed early for effectiveness. Removable prostheses may not be tolerated because of the dry mucosa, irritation, and lack of retention. Candidiasis can occur because of hyposalivation (see Table 15.4 for treatment). Every effort should be made to prevent disease and promote health. Excellent oral hygiene, diet instruction and fluoride, remineralization of teeth with calcium and phosphate, and frequent evaluation are essential. Bacterial risk for caries and gingivitis may be affected by use of chlorhexidine. Diet evaluation and management are critical elements of comprehensive care to minimize caries risk and optimize nutritional value of foods when eating ability is impaired. Patients should have a thorough head and neck examination, particularly when salivary gland enlargement is present, to assess changes to facilitate early diagnosis of lymphoma that may arise in SS.

Nutritional Management

Nutrition management of the patient with SS is challenged by insufficient or total lack of saliva, which serves to moisten and facilitate mastication of foods, movement of foods in the oral cavity, and swallowing. Depending on the degree of salivary function remaining, eating ability is compromised. Dietary guidelines are primarily based on empirical evidence and are provided in the Appendix. Recommendations include instructions to always carry a water bottle, drink fluids with meals, increase fluidity of mealtime foods (gravies, sauces, soups), and avoid "coarse" foods that may irritate the mucosa such as hard bread crusts. Temperate foods with spices and seasonings adjusted to fit individual tolerances should be promoted. Small frequent meals are often preferable as eating time may be prolonged, however, attention must be given to simple carbohydrate exposure in the diet due to dental risk. Salty foods and snacks and added salt should be minimized to reduce the impact of salt on increasing thirst. When patients complain of altered taste, simple taste testing in the office to determine tolerable tastes (sweet, salt, bitter, sour, umami) can be done, and those tastes that are better tolerated can be emphasized. If dairy products are not tolerated, alternative calcium sources should be identified or a calcium supplement should be recommended. Use of sugarless gums and mints, particularly those rich in xylitol as an artificial sweetener following meals and snacks may help reduce caries risk and increase salivary production in individuals with residual capacity to produce saliva [38]. Furness et al. [46] reported that gum chewing can increase salivary production in individuals who have some salivary function but may not affect symptoms of dry mouth [46].

Table 15.5 Guidelines for practice

	Nutrition and diet	Oral health
Assessment	• Comprehensive nutrition assessment including nutrition focused physical exam, biochemical profile, and history	• Physical examination mucosal and periodontium teeth
	• Individualized diet based on symptoms, degree of oral compromise, other sequellae and acute and chronic diseases	• Saliva quantity and quality
	• Screen for osteoporosis risk	• Dry mouth
	• As-needed multivitamin and mineral supplements	• Oral burning
		• Impaired chewing
	• Referral to physician and/or oral healthcare professional as needed	
	• Frequent monitoring of assessment parameters	
Prevention	Referral to physician and/or oral healthcare professional as needed	• Frequent recall and dental prophylaxis
	Referral to physician and/or oral healthcare professional as needed	• Sialagogues, prescription fluoride, sealants for patients with xerostomia
		• Modified techniques for improved oral hygiene
		• Antibiotic prophylaxis based on immune status or cardiac risk
		• Medical consult regarding health status and management strategies
		• Referral to RD
	• Frequent monitoring of above assessment parameters	• Avoid situations that may precipitate disease flare-up
Intervention	• Referral to physician and/or dentist as needed	• Frequent recall and dental prophylaxis
	• Modify diet according to symptoms, changes in nutritional status, and oral pain and dysfunction	• Sialagogues, prescription fluoride, sealants for patients with xerostomia
	• Monitor drug—nutrient reactions or sequallae of drugs on diet and nutrition status, and adjust diet accordingly	• Modified techniques for improved oral hygiene
		• Medications that address specific oral components of autoimmune illness
		• Referral to oral medicine specialist and/or RD

Summary

Patients with autoimmune disorders present significant challenges to oral, systemic, and nutritional health. The disease itself and its medical management can impact oral health and nutrition status, biting, chewing and swallowing ability, diet, esthetics, and quality of life. Subsequent medical management may further challenge eating ability depending on the side effects of medications. Optimal patient management requires coordination and collaboration among physicians, OHCPs, and RDs as well as other healthcare team members to minimize risk for disease, manage active disease(s), and improve quality of life (Table 15.5).

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Chapter 16
Osteoporosis

Elizabeth Krall Kaye

Keypoints

- Osteoporosis is common beginning in middle-age in women and is less prevalent and occurs later in men
- There are associations between osteoporosis and risk of periodontal disease and tooth loss, however, there is no evidence of causality
- Alveolar bone loss is a key outcome of periodontal disease
- Osteoporosis treatment strategies including osteolytic inhibitors can affect the oral cavity and dental care
- Vitamin D, calcium, and exercise are essential to osteoporosis prevention

Keywords Osteoporosis · Periodontal disease · Tooth loss · Alveolar bone loss · Osteolytic inhibitors · Vitamin D · Calcium · Osteoporosis prevention · Periodontal diseases · Teeth · Dietary calcium

Introduction

Tooth loss and periodontal diseases become more prevalent with advancing age and result from the interaction of many factors, including intra-oral conditions, poor dental hygiene, lack of access to dental care, genetics, lifestyle, and systemic diseases. One such systemic disease, osteoporosis, is characterized by a decline in bone mineral density and bone quality that predisposes to fracture. It has been hypothesized that systemic osteoporosis impacts the jaw and alveolar processes and directly influences the risks of periodontal disease and tooth loss [1]. Periodontal disease and osteoporosis share risk factors and risk indicators, notably age [2, 3], smoking [2, 4], and diabetes [5, 6]. The evidence that osteoporosis causes oral disease is limited [7]. Nevertheless, a patient's systemic bone status is an important determinant of overall health and well-being. As dentists expand their activities to include healthcare screenings and lifestyle counseling aimed at ensuring optimal levels of both oral and general health [8], it is important to be aware of a patient's systemic bone status and risk factors for osteoporosis.

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Osteoporosis

Skeletal tissues are dynamic. Bone mineral is continuously being broken down (resorbed) by osteoclasts and reformed by osteoblasts in a series of coordinated, or coupled, actions. The resorptive phase of this remodeling process is estimated to last 2–3 weeks, while bone formation to replace the lost skeletal tissue continues for approximately 2–3 months [9]. In young healthy adults, the two phases are balanced so that the amount of bone mineral remains fairly constant. In middle-aged and older adults and in disease states such as osteoporosis, the phases tend to be uncoupled and dominated by mineral loss and resorption. The result is a net loss of bone mineral over time resulting in osteopenia (bone mineral density that is lower than normal) and osteoporosis.

The decline in bone mineral content and the structural deterioration in osteoporosis are evident microscopically and upon bone imaging. The compact cortical layer that forms the exterior shell becomes thin and the normally dense network of calcified trabeculae in the bone interior is thin and disconnected. The bone appears abnormally porous, giving the disease its name. These changes result in bone that is fragile and susceptible to fracture with a minimal degree of trauma such as a fall from standing height or less.

The density of remaining bone mineral in the total body or at specific skeletal sites (most commonly measured are the hip, wrist, and spine) is quantified by X-ray absorptiometry. Test results are expressed either as bone mineral density (BMD) or T-scores which relate an individual's BMD to a reference value derived from the mean BMD of healthy 20–29 year olds. T-scores above −1.0 (i.e., not lower than 1 standard deviation below the reference value) are considered normal, while T-scores between −2.5 and −1 define osteopenia, and those less than −2.5 define osteoporosis. Risk of fracture doubles with each standard deviation below normal [10].

It is estimated that at least 8 million women and 2 million men in the United States have osteoporosis, and another 34 million individuals have osteopenia that puts them at increased risk of fracture [11]. Although BMD alone is a good indicator of fracture risk, an individual's probability of fracture is more precisely estimated when BMD is used in combination with clinical risk factors or indicators. At age 50, a woman who has no clinical risk factors and a normal BMD has a 3–4% chance of any major fracture over the next 10 years [12]. With a BMD T-score of −2 and no clinical risk factors, her 10-year fracture risk is approximately 1.5 times higher, whereas low BMD plus multiple clinical risk factors increases fracture risk approximately tenfold.

As given in Table 16.1, clinical factors that increase the risk of fracture include age, low body mass index, female sex, personal and family history of fracture, use of certain medications, and medical conditions [13, 14].

Effects of Osteopenia and Osteoporosis on the Oral Cavity

It has been hypothesized that osteopenia and osteoporosis confer an increased risk of periodontal disease and tooth loss [7, 15]. While many published studies demonstrate statistically significant associations, the evidence is not strong enough to conclude that low BMD is a causal determinant of periodontal disease or a reflection of shared risk factors [7]. A major limitation to reaching a consensus on the nature of the osteoporosis-periodontitis link is the lack of cohort studies in the literature and abundance of those with a cross-sectional design. In the hierarchy of study designs for establishing causality, cross-sectional designs deliver lower quality evidence than do cohort studies for several reasons. Cross-sectional surveys and case-control designs do not clearly establish which condition preceded the other or how long each condition has been present. In addition, when the outcome is radiographic or clinical periodontal disease, one may not know the status of the teeth that

Table 16.1 Common risk factors and risk indicators for primary and secondary osteoporosis

Primary osteoporosis	Secondary osteoporosis
• Advanced age	• Hypogonadism (male and female)
• Female sex	• Use of glucocorticoid or anticonvulsant medication
• Postmenopause	• Excess thyroid hormone
• White or Asian ethnicity	• Rheumatoid arthritis
• Family history of osteoporosis or low-trauma fracture	• Alcoholism
• Low body weight	
• Low dietary intakes of calcium and vitamin D	
• Low physical activity level	
• Cigarette smoking	

have been lost. Teeth that remain are likely to be healthier than those that are missing, creating a false inverse relationship. Another limitation is the fact that many studies were conducted with small sample sizes. Given the complex causes of oral and systemic bone loss, associations between the two are likely to be moderate or weak, and large sample sizes are needed to ensure adequate statistical power. Most studies excluded men. An evaluation of the evidence for causality must also take into account whether analytic methods controlled for important confounders such as age, years since menopause, smoking, and hormone replacement use.

Periodontal Diseases: Alveolar Bone Loss

Alveolar bone loss (ABL) often precedes tooth loss and is a key outcome in periodontal disease, thus alveolar bone is labile and has a principal role in support of the dentition. In periodontal disease, bacteria lead to initiation of the host inflammatory response that leads to ABL. It has been speculated that osteoporosis reduces alveolar bone quantity and quality, thereby exacerbating the periodontal disease process. A 5-year cohort study of 1,025 women reported that women with osteoporosis at any site (forearm, spine, hip) experienced greater loss of alveolar crest height compared to women with normal systemic bone status [16]. Another cohort study found that concurrent 5- and 10-year changes in alveolar bone mass and trabecular pattern—a qualitative assessment of overall quality of jawbone structure [17]—were correlated with changes in BMD at the forearm and hip [18, 19]. These studies are consistent with a study by Payne et al. [20], who found that osteoporotic women exhibited significantly more sites with ABL than women with normal spine BMD.

Cross-sectional and case-control studies also report significant positive associations between systemic bone and alveolar bone level [15, 21–25]. However, limitations of several of those studies include lack of control for confounders [23, 25] and small sample size [23]. The largest cross-sectional studies of ABL describe results from over 1,200 participants in an ancillary component of the Women's Health Initiative Observational Study [15, 22]. Severe periodontal disease was defined as mean alveolar crest height (ACH) loss $\geq$3 mm, or $\geq$2 sites with $\geq$4 mm ACH loss, or tooth loss related to periodontal disease. The overall adjusted odds of severe periodontal disease were approximately doubled in women with osteoporosis relative to those with normal BMD (15), but this association was age dependent. Among women age 70 or older, the odds ratio was 3.6 while in women under 70, it was 1.6.

Clinical Measures of Periodontal Disease

In the absence of radiographs, periodontal disease status is defined on the basis of clinical parameters such as probing pocket depth (PPD), clinical attachment loss (CAL), gingival recession, gingival bleeding, and tooth mobility. The use of different indices and cut-offs to designate periodontal disease yields varying estimates of periodontal disease prevalence and makes it difficult to compare the outcome of studies relating it to systemic bone status. Two of the five prospective studies published between 2001 and 2013 found significant associations between systemic BMD and clinical measures of periodontal disease. In a study of 179 men and women aged 70 years old, those with osteoporosis exhibited more sites with progression of CAL (after 3 years, the site was at least 3 mm worse than the baseline value) than persons with normal BMD [26]. These results were adjusted for gender, baseline CAL, body mass index, serum albumin, total cholesterol, and hand grip strength. In a 7-year observational study, 34 periodontal disease patients of both sexes were characterized by their pattern of changes in CAL and PPD [27]. Active disease was defined as an increase in percent of sites with CAL $\geq$5 mm over 5 years and 5 or more teeth with PPD $\geq$5 mm after another 2 years of follow-up, while stable disease was defined as a decreasing percent of sites with CAL and <5 teeth with deep pockets. More than half of the active periodontitis group reported having osteoporosis compared to 8% of patients whose periodontal disease was stable [27].

In contrast to those findings, Famili et al. found no difference in baseline BMD nor 2-year rates of BMD loss [28] between women with periodontal disease at baseline (CAL >4 mm on 12 or more teeth, $n = 163$) and those who were disease-free ($n = 39$). However, it is not clear if periodontal disease status remained the same in both groups over the follow-up period. Following 1,210 men for an average of 2.7 years, Phipps et al. [29] found no differences in percent of sites with CAL $\geq$5 mm, PPD $\geq$6 mm, or progression of periodontal disease (2 or more teeth with incident loss of attachment $\geq$3 mm) among baseline quartiles of total femur BMD. Although the follow-up study of participants at in the Women's Health Initiative Observational Study reported more rapid loss of ACH in women with poor systemic bone status, it did not find that changes in CAL and PPD were related to baseline BMD [16].

Findings from cross-sectional and case-control studies of clinical periodontal measures are also mixed. Brennan et al. [22] studied 1,329 postmenopausal women and found that overall, mean CAL increased as BMD at several skeletal sites decreased. The relationship was evident only among women with no subgingival calculus and remained after adjustment for age, cigarette smoking, education, and time since last dental cleaning. These findings contradict an analysis of the third National Health and Nutrition Examination Survey (NHANES III) data in which women with low BMD of the total femur and high mean calculus index scores had up to 2.5 times as many sites with CAL greater than 7 mm as women with comparable calculus but normal BMD [30]. Differences in methodologies were cited in an effort reconcile these discrepant findings [22]. Numerous studies reported associations between worse clinical periodontal parameters and poor BMD status in women [21, 23, 25, 31–37] and men [38]. Once again, lack of control for confounders [23, 25] and small sample size [23, 33, 34] limit the interpretation and generalizability of some findings. After controlling for covariates, Jabbar et al. found that BMD was no longer a significant predictor of periodontal disease [39].

Tooth Loss

Periodontal disease is a common reason for tooth loss in older adults [40, 41]. This provides a rationale for using tooth loss as a surrogate measure of past periodontal disease activity. There are a limited number of prospective studies that examine change in BMD and loss of teeth. In a 5-year follow-up study, Iwasaki et al. [42] categorized the rates of BMD loss for 404 women into tertiles

and compared rates of tooth loss among them. Women with the fastest rate of systemic bone loss were at 1.27–1.38 greater risk (depending on the systemic site) of tooth loss than those with the slowest bone loss. These findings support a previous study which reported higher rates of bone loss at the hip, spine, and total body over a 7-year period in postmenopausal women who concurrently lost teeth relative to women who lost no teeth [43]. In a cohort of healthy men and women, all age 70 years and with at least 20 teeth remaining at baseline, there were no significant differences between persons with osteoporosis and a healthy group with regard to number of teeth present at baseline or number lost during 3 years of follow-up [26]. The requirement that 20 teeth be present at baseline may have resulted in selection of subjects with better oral health.

In general, cross-sectional studies with elderly subjects or a wide age range have found correlations between BMD and number of teeth remaining [44–47] or edentulism [48], while the association was not evident when fragility fracture was the measure of systemic bone quality [49].

Summary of the Evidence for an Association Between Osteoporosis and Periodontal Disease or Tooth Loss

The question of whether low BMD and osteoporosis independently increase the risk of periodontal disease onset or progression remains unanswered despite the large number of studies that have been conducted. Interpretation of the findings is complicated not only by study design features and various definitions of periodontal disease, but also the fact that, within a single study, statistically significant results may be observed for some skeletal sites and periodontal disease/tooth loss indices but not others [16, 22, 24, 33, 46], or for one sex [32] or age group [22] but not another. Such discrepancies have been attributed to variation in percentages of cortical and trabecular bone and in prevalence of either disease in the study populations.

Therefore, there is a lack of evidence for a causal association and lack of agreement as to clinical significance when associations are found. A weak association can still be meaningful if the conditions are highly prevalent in a population. In the US population age 50 and older, osteoporosis and osteopenia affect approximately 44 million people, while periodontal disease affects approximately half of US adults aged 30 and older [50]. Even if osteoporosis and osteopenia were to cause only a small increase in the risk of periodontal disease, a reduction in the incidence of these risk factors could potentially eliminate hundreds of thousands of cases of periodontal disease each year. Therefore, examination of the effects of osteoporosis therapies on periodontal disease and tooth loss is warranted.

Effects of Osteoporosis Prevention and Treatment Strategies on the Oral Cavity

Medications for the Treatment of Osteoporosis

Approved treatments for osteoporosis include hormone replacement therapy (HRT), the selective estrogen receptor modulator raloxifene, the hormone calcitonin, recombinant human parathyroid hormone (PTH), and antiresorptives such as bisphosphonate. Bisphosphonate has been shown to reduce CAL, PD and gingival bleeding, and distance between the alveolar bone crest and cemento-enamel junction [51–53]. However, incidents of osteonecrosis of the jaw (ONJ) after invasive dental procedures among women given high-potency intravenous bisphosphonate for cancer [54] raise concerns about its use. Among patients taking lower dose oral antiresorptive medications for

osteoporosis, the prevalence of ONJ is low [55]. New agents are becoming available for management of cancer involving bone and osteoporosis. Denosumab is a monoclonal antibody directed against the cell surface receptor (receptor activator of nuclear factor ligand; RANK-L) affecting osteoclast differentiation and function that is now FDA approved for bone cancer [56, 57]; other agents are in clinical trial and are expected to become available in the future. RANK-L inhibitor and bisphosphonate drugs increase the risk of osteonecrosis, primarily when used as part of cancer therapy but rarely in osteoporosis. ONJ risk is related to cumulative drug dose and the medical condition being treated. Oral Health Care Professionals (OHCPs) must be aware of the use, schedule and doses of these agents so that the patient's dental care is managed appropriately.

HRT studies utilized supplements of either estrogen alone or a combination of estrogen and progestin. A 3-year randomized controlled trial of HRT found a significant increase in alveolar bone mass in the treated group compared to a group given only calcium and vitamin D supplements [58]. Payne, Reinhardt, and colleagues reported that estrogen sufficiency is associated with preservation of alveolar bone density and less frequent CAL [20, 59–61]. Postmenopausal women who never used estrogen were twice as likely as premenopausal women to have periodontal disease ($\geq$30% teeth with at least one site with CAL $\geq$5 mm), whereas the odds of disease among postmenopausal estrogen users were not significantly elevated [62]. In NHANES III, postmenopausal women who used estrogen for at least 2 years had lower mean CAL values than women who never used it [30].

Several large population-based studies of postmenopausal women also concluded that women who have ever used HRT retain more teeth than nonusers and have a lower likelihood of being edentate [63–65] independent of age, smoking, and other factors. Duration of HRT use was also related to tooth retention. But a study of individuals seen in a dental school reported no association between HRT and number of teeth [49]. Long-term HRT also has significant adverse health effects which led to a decline in its use [66]. Thus, nutritional approaches to osteoporosis prevention appear to be safer alternatives.

Nutritional Approaches to Osteoporosis Prevention

Calcium and Vitamin D

Calcium is one of the major components of bone's hard tissue. It also has numerous other functions in the body. Vitamin D plays a critical role in calcium homeostasis by aiding calcium absorption from the gut, and along with PTH, is one of the primary hormones that regulates mineral deposition and release from bone and excretion via the kidney. Inadequate dietary calcium intake and/or vitamin D status result in a negative calcium balance and the body will then use calcium stored in the skeleton for its immediate needs. Eventually, this loss of mineral contributes to decreased BMD. Other factors such as smoking [67] and thyroid and kidney function [68] affect calcium homeostasis, but correction of calcium and vitamin D intakes is one of the more easily modifiable approaches to restore balance. Raising calcium and vitamin D intakes, typically with supplements, slows the rate of bone loss [69, 70], but there is inconsistent evidence of a benefit on fracture risk [71–73]. However, calcium and vitamin D supplements are important adjuncts to drug therapies for osteoporosis.

Few studies have examined the effect of calcium and vitamin D intakes or supplements on periodontal disease or tooth loss. Hildebolt et al. [74] reported a 0.74% per year increase in mandibular bone mass over a 3-year period with administration of 1,000 mg calcium and 400 IU vitamin D. The magnitude of the increase was similar to that seen in women given calcium and vitamin D plus estrogen; however, there was no true placebo group. In a study of 51 patients receiving periodontal maintenance, there were no significant differences in mean levels of mean PPD, CAL, and alveolar height loss among those who elected to use calcium and vitamin D

supplements and patients who did not [75]. After 6 months of follow-up, the supplement users displayed less periodontal disease but the benefit did not persist at 1 year [76]. In a randomized placebo-controlled trial to study the effects of 500 mg/day calcium and 700 IU/day vitamin D supplementation on systemic bone loss in elderly men and women, the supplemented group showed an approximate 50% reduction in the risk of tooth loss over 3 years [77].

Calcium Alone

A calcium intake that was below recommendations (1,000 mg/day for <50 years, 1,200 mg/day for age 50+) was associated with an increased incidence of tooth loss in men but not in women [78]. However, calcium intake from dairy foods was associated with fewer teeth with CAL ≥3 mm [79] and had a protective effect on tooth loss incidence in both men and women [80]. A prospective study of 552 older men suggested that calcium intakes above 1,000 mg/day may be beneficial in slowing ABL progression, independently of age, initial number of teeth, smoking status, vitamin D intake, caries status, and clinical periodontal disease status [81]. A calcium supplement trial conducted in men concluded that added calcium, either 600 or 1,200 mg/day, had no effect on tooth loss risk; however, only 2 men lost any teeth during the 2-year study [82]. Nishida et al. [83] analyzed dietary intake surveys and periodontal data in more than 12,000 adults from NHANES III. After controlling for age and smoking status, the odds of having periodontal disease (mean periodontal attachment loss ≥1.5 mm) were nearly double in younger men and women whose calcium intake was below 800 mg/day relative to ≥800.

Vitamin D Alone

Vitamin D status is determined by the level of serum 25-hydroxyvitamin D (25(OH)D), which reflects both the contribution from diet and from the conversion of 7-dehydrocholesterol in the skin into pre-vitamin D after exposure to the sun. Optimal serum levels are 25 ng/ml or higher. Mild to moderate vitamin D deficiency is indicated when levels are less than 25 ng/mL and severe deficiency when <10 ng/ml. Vitamin D deficiency is common in the US, affecting 42% of adults [84]. Persons at greater risk include nonwhites, the obese, and those in poor health, without a college education, or no daily milk consumption [84]. Daily supplementation with 800–1,000 IU/d of vitamin D or up to 50,000 IU monthly is considered safe and sufficient to maintain serum 25(OH)D at optimal levels [85]. Correction of vitamin D deficiency requires supplements at higher doses than typically found in over-the-counter preparations.

In NHANES III participants, low levels of serum 25(OH)D were associated with a greater extent of CAL in older individuals [86], and with gingival bleeding at sites without attachment loss [87]. Because many individuals do not routinely have serum 25(OH)D measured and do not know their vitamin D status, studies are needed of periodontal disease and dietary and supplemental vitamin D intake—sources of vitamin D that can readily be monitored.

Summary of the Evidence for an Association Between Osteoporosis Therapies and Periodontal Disease or Tooth Loss

HRT and antiresorptive agents may be effective in reducing periodontal disease and tooth loss, but have serious side effects. The studies using nutritional approaches to reduce periodontal disease have several limitations, including many with a cross-sectional design [75, 83, 86, 87], lack of data on

Table 16.2 Adult dietary reference intake values (recommended dietary allowances or adequate intake) of calcium and vitamin D in the United States [88]

Age	Calcium (mg/d)	Vitamin D	
		IU/d	μg/d
0–6 months	200[a]	400	10[a]
6–12 months	260[a]	400	10[a]
1–3 years	700	600	15
4–8 years	1,000	600	15
9–13 years	1,300	600	15
14–18 years	1,300	600	15
19–30 years	1,000	600	15
31–50 years	1,000	600	15
51–70 years (Males)	1,000	600	15
51–70 years (Females)	1,200	600	15
70 years and older	1,200	800	20

[a] Adequate intake

supplement use to complement dietary intake estimates [83], small sample size [75, 76], and secondary data analyses of randomized trials [77, 82]. There is a need for more prospective studies of the effects of calcium, vitamin D, and other nutrients on periodontal disease and tooth loss.

Professional and Practice Issues

The OHCP can increase a patient's knowledge of risk factors, especially poor nutrition and smoking, that affect both oral and systemic bone health. It is important to stress good nutrition and lifestyle habits in childhood and early adulthood before the signs of osteoporosis become evident.

Recommended intake levels for calcium and vitamin D in the United States [88] are given in Table 16.2 and major food sources of these nutrients are shown in Fig. 16.1. Nutritional guidance should emphasize a balanced overall diet and use of food as primary sources of calcium and vitamin D rather than supplements. Foods supply additional nutrients that are essential for bone health, including magnesium, phosphorus, selenium, B vitamins, and vitamin A. Quality of the total diet is important too because extreme intakes of nutrients such as protein, phosphorus, sodium, and caffeine can alter calcium absorption and excretion, particularly when calcium intake is marginal [68]. By obtaining nutrients from foods instead of supplements, one is less likely to take in extreme levels. Furthermore, the US Preventive Services Task Force concluded that the amounts of calcium and vitamin D in many over-the-counter supplements (400 IU vitamin D or less, 1,000 mg calcium or less) are not effective in preventing osteoporotic fractures [71]. Calcium supplements have been cautiously linked to adverse outcomes such as kidney stones [71] and myocardial infarction [89].

As previously noted, although HRT used in the treatment and prevention of osteoporosis appears to reduce ABL and the risk of tooth loss, its usage has begun to decline. However, because many women have used HRT in the past, documentation of its use should be part of the patient records. Use of any osteoporosis drug should be recorded for male and female patients.

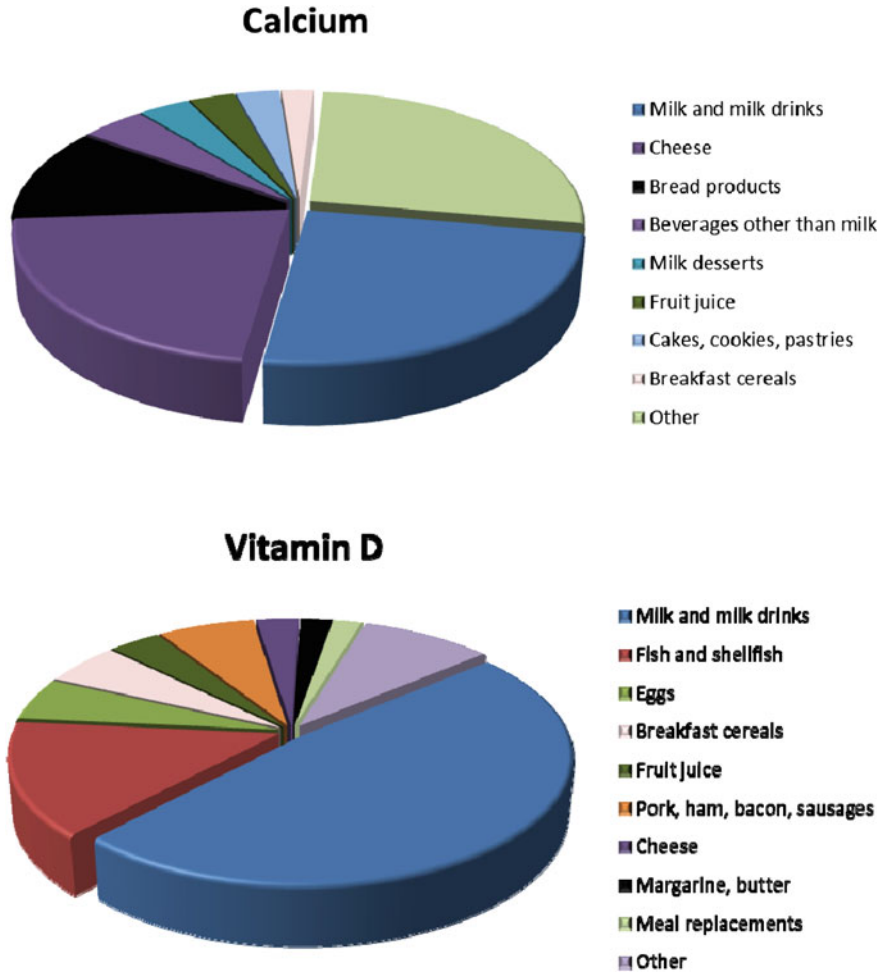

Fig. 16.1 Major dietary sources of calcium and vitamin D, US Adults age 19+, 2003–2006 [90]

Summary and Recommendations Based on Evidence to Date

More prospective studies are needed. Randomized controlled trials of nutritional supplements could also provide useful information on the relationship if measurements of oral bone and tooth counts are incorporated into the design of the trial. Even though the clinical relevance of the association between osteoporosis and oral health is not known, it remains prudent for dental patients to maintain good calcium and vitamin D nutrition for the benefit of systemic bone health at least, and possibly for oral health as well. Table 16.3 provides some practice-based guidelines for OHCPs and nutrition professionals. OHCP must recognize the impact of osteolytic inhibitors upon dental care.

Resources for the Practitioner

Knowledge of a patient's osteoporosis status is relevant to periodontal care, just as it is important to know whether the patient has heart disease or diabetes. But many people with osteoporosis are

Table 16.3 Guidelines for practice

Oral health and nutritional professionals	
Prevention	• Screen all patients for osteoporosis risk factors and risk indicators • Refer high-risk patients to physician for evaluation • Encourage calcium-rich diet and exercise In addition, for the nutrition professional—review calcium-rich food sources and use of calcium and vitamin D supplements only as needed
Intervention	• Include an osteoporosis item on all medical history forms for new patients and when updating health status of current patients. Although osteoporosis is most common in postmenopausal women, approximately 20% of cases of osteoporosis are older men. Premenopausal women with a history of abnormal absence of menstrual periods are also at increased risk • Document current and past use of osteoporosis drugs in the patient's medical and dental records. Currently approved medications include alendronate, risedronate, ibandronate, zoledronic acid, calcitonin, estrogen/hormone therapy, denosumab, teriparatide, and raloxifene • Have a brief osteoporosis risk questionnaire available for the patient to complete or take home • Encourage a balanced nutritional intake • Encourage smoking cessation

unaware that they have the disease. Accurate and cost-effective screening for osteoporosis requires bone densitometry equipment, but that is beyond the scope of a dental or nutritional practice. However, several brief, self-administered osteoporosis risk questionnaires have been developed that can not only be employed as a first step in a multistage screening but also serve to increase osteoporosis awareness. These questionnaires assign scores for the presence or absence of each of several major risk factors or indicators for osteoporosis such as age, race, underweight, estrogen therapy, rheumatoid arthritis, previous fracture, smoking, alcohol use, and physical exercise. It must be pointed out that although screening instruments by themselves do not provide a diagnosis; patients need to follow-up with an examination from their primary care physician and a bone density scan in order to make a diagnosis of osteoporosis or osteopenia. Examples of osteoporosis risk calculators can be found at the following websites: http://www.osteofound.org/iof-one-minute-osteoporosis-risk-test

http://www.askapharmacist.com/osteoform.htm

The following websites provide free information and educational materials about osteoporosis disease facts, risk factors and prevention, diagnosis, and treatments.

The National Osteoporosis Foundation, http://www.nof.org

International Osteoporosis Foundation, http://www.osteofound.org

National Institutes of Health Bone Diseases Center, http://www.niams.nih.gov/Health_Info/Bone/

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Chapter 17
Orofacial Pain

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Keypoints

- Chronic orofacial pain may be musculoskeletal, neuropathic, or neurovascular in origin and can impact diet intake and nutrition status
- Treatment of chronic orofacial pain requires diagnosis of the underlying cause and individualized treatment for each pain diagnosis

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- Primary aims of treatment focus on decreasing pain, restoring function, and maintaining high quality of life and activities of daily living
- Medications used to manage chronic orofacial pain may have associated systemic, oral, and nutritional sequallae which require management
- Motor and sensory function in patients with chronic orofacial pain conditions requires an interprofessional approach to support oral function, diet, and nutrition

Keywords Chronic orofacial pain · Musculoskeletal pain · Neuropathic pain · Neurovascular pain · Nutrition status · Diet · Nutrition · Dietary patterns

Introduction

Pain is defined by the International Association for the Study of Pain (IASP), as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. Pain can be classified as acute or chronic. Acute pain is often localizable and serves a biological purpose warning the individual of tissue damage. It is usually short in duration and can be managed by removing the offending stimulus, treating the condition and/or by using medications to treat the painful condition and/or by using medications for anesthesia or analgesia. However, when the pain persists long after the tissue heals or lasts more than 3 months and has no biological purpose in relation to host protection or damaging medical condition it is considered as a distinctive pathological condition designated as "chronic pain." Chronic pain can be further classified into chronic benign pain (not associated with chronic disease) and chronic malignant disease (such as associated with cancer). Pain may have peripheral and central origins and interactions that complicate pain presentation and must be considered in management, particularly in chronic pain.

In the orofacial region, acute pain is primarily related to dental or periodontal pathology (caries, pulpitis or dental infections), or sinus and ear infections. It resolves when the source of the pain is successfully treated. Chronic orofacial pain stands alone as a disease itself. Associations between chronic orofacial pain disorders and diet and nutrients are explored; approaches to dietary management of individuals with chronic orofacial pain disorders are discussed. The rich neurological innervation of the face and oral cavity, the unique sensory function of taste in the oral cavity, the central importance of the face and oral cavity in development, and in social interaction and important functions may magnify the impact of chronic pain in the region. This chapter addresses chronic orofacial pain disorders and their diagnosis and treatment approaches.

Chronic orofacial pain is often classified by the symptoms and organ systems involved into three major types: musculoskeletal, neuropathic, vascular pain, and psychogenic/psychological (Table 17.1). Unfortunately, many patients present with more than one of these chronic orofacial pain types at the same time. In these types of pain, overlap makes the diagnostic process and management more complex. In this chapter, the etiologies and existing treatments of each group are discussed separately.

Musculoskeletal Orofacial Pain

The most common musculoskeletal disorder causing orofacial pain is temporomandibular disorder (TMD). TMD is defined by the American Academy of Orofacial Pain as a "collective term embracing a number of clinical problems that involve the masticatory musculature, the temporomandibular joint

Table 17.1 Chronic orofacial pain conditions [45]

		Location	Characteristics	Symptoms	Duration
Musculoskeletal	Muscles	Muscles of mastication Jaws, teeth	Dull, diffuse, moderate–severe	Limited opening, aggravated during function	Weeks to years
	Joints	Temporomandibular disorders (TMJ), ears	Moderate-severe localized, deep	Limited opening, aggravated during function. Deviation during opening, joint sounds ("clicking", "popping", "crepitus")	Weeks to years
Neuropathic	Paroxysmal	Trigeminal nerve distribution	Severe, sharp electric like pain	Trigger zones, activating pain with light touch Does not awake from sleep	Up to minutes, several times a day
	Continuous	Related to trauma and to nerve distribution	Mild-severe, Burning, continuous	Allodynia, Does not awake from sleep	Continuous
Vascular	Migraine	Unilateral	Severe, throbbing	Nausea, vomiting, photophobia, phonophobia, aggravated with physical activity	Hours to days
	Cluster headache	Periorbital	Severe, active and non-active periods	Tearing, redness of eye ptosis, myosis, Rhinorrhea, awakes from sleep	Minutes to hours
	Paroxysmal hemicrania	Temporal	Sharp, excruciating, awakes from sleep	Conjunctival injection Tearing with nasal congestion and discharge Awakes from sleep	Minutes, many times a day
	Neurovascular Orofacial Pain (NVOP)	Oral and face	Severe, Episodic, throbbing, awakes from sleep	Nausea Photophobia Phonophobia Tearing Swelling Nasal congestion Awakes from sleep	Minutes to hours

(TMJ) and associated structures, or both" [2]. Although TMJ disorders and masticatory muscle pain (MMP) present unclear etiologies, the interaction between a peripheral nociceptive source in the muscle and a altered central nervous system component (central sensitization) seems to be the most likely underlying cause.

TMD related to the joint commonly presents as more localized pain. Deep pain may be associated with "clicking" and other joint sounds as, "popping," "grating," or "crepitus" that is aggravated during function. It has been suggested that joint pain accompanying TMD, known as TMD arthralgia involves the activation of an inflammatory process that may be caused by several pathologies such as internal derangements (changes within the joint structure and disharmonic joint function due to disk/condyle coordination), trauma, infection, or autoimmune disease. The pathologies may lead to degenerative TMJ changes and, in some cases, to a chronic inflammatory state. The role of inflammation in TMJ pathologies is supported by increased levels of cytokines, prostaglandins, and 5-HT assessed in the synovial fluid of affected TMJs [3–5]. Studies have shown that the altered pain modulation might play a role in TMD etiology [6–8].

MMP is a continuous, poorly localized dull, aching pain, variable in intensity, aggravated during function such as biting or chewing and accompanied by localized tender spots in muscles that reproduce pain on palpation known as "trigger points." Trigger points may be "active" or "latent." The "active" tender points present with a referred pain pattern to a distant site upon palpation. In contrast, "latent" trigger points, present with local tenderness without distant referral [9]. In the active trigger point although the origin of the pain is the muscle, patient complaints that may replicate the chief complaint can be reported [10]. For example, a localized tender point in the trapezius and masseter may refer pain to the mandibular molar and the temporalis muscle may refer pain in maxillary teeth [11]. Therefore, a careful physical exam and history are imperative in order to make the correct diagnosis.

The pathophysiology of MMP is unclear. It has been associated with muscle hyperactivity or parafunction, changes in motor function due to secondary chronic pain mediated at the spinal level and not the primary source of pain [12–14]. MMP may be a localized expression of widespread myofascial disorders (pain developed from fascia and muscles) such as fibromyalgia [7, 15].

In 2011, new terminology was suggested to better describe myogenic masticatory pain, "Persistent Orofacial Muscle Pain" (POMP) [16]. According to Benoliel et al., POMP involves the interaction between a peripheral nociceptive source in muscle, an altered central nervous system component and diminished coping ability by the patient.

Neuropathic Pain

Neuropathic pain is a central and/or peripheral nervous system disorder; it usually arises from injury or dysfunction of the nervous system [1]. It represents abnormal function of the nervous system itself in contrast to somatic pain that arises from noxious stimuli of normal tissue in the body, which is considered normal or physiological. Neuropathic pain can be divided into two main categories *Episodic* or *Continuous*. Episodic pain is characterized by paroxysmal, sharp, electrical shock-like pain quality felt in the area innervated by the involved nerve [2] (e.g., trigeminal neuralgia and glossopharyngeal neuralgia). Continuous pain is characterized by spontaneous, constant, dull, aching, burning pain (e.g., atypical odontalgia, burning mouth syndrome, traumatic neuromas, and traumatic trigeminal neuralgia). In this chapter the continuous neuropathic orofacial pain is discussed.

Pain resulting from a peripheral cause such as a nerve injury is termed peripheral neuropathic pain. In the orofacial area, peripheral neuropathic symptoms can occur after trauma such as surgery, accidents with/with out fractures of facial bones, and orthognathic surgery or minor trauma including intraoral innervations like root canal therapy, implant surgery, dental extraction, or periodontal surgery [17–20]. It can also occur due to neoplasia, treatment of the cancer, or vascular compression [21]. Positive symptoms such as allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (increased pain from a stimulus that normally provokes pain) can be present in the patient with chronic orofacial pain along with negative symptoms (e.g., numbness).

Advanced neurophysiological testing including brainstem reflexes and quantitative sensory testing (QST) can identify nerve damage [22–25]. However, such elaborate tests are not always available in the clinical setting, therefore simple clinical tools such as a pin, a blunt instrument, warm and cool stimuli and cotton wool can be used to assess sensory modalities [26].

Peripheral neuropathic pain usually involves trauma to the nerve; types of trauma include crushing, pressure or a cut, which results in an inflammatory response triggering several mechanisms that ultimately causes peripheral (increased response of nociceptive neurons in the periphery to the stimulation of their innervated area) or central sensitization (increased response to stimulation due to

amplification of signaling in the central nervous system). It is important to note that the sole presence of inflammation (followed by edema or their mediator secretion) can cause nerve damage inducing ectopic activity and spontaneous pain. Therefore the role of the immune system in neuropathic pain, and the role of proinflammatory cytokines, is increasingly recognized. Nerve injury may also trigger several mechanisms that activate the ascending pain pathways or maintain central sensitization including ectopic impulse generation (when the injury site acquires the abnormal capability of generating nerve impulses on its own). Additionally, neuroma formation may occur. A neuroma results when the nerve is severed and the severed ends fail to reconnect forming a mass of knotted disorganized tissue. Up-regulation of sodium channels at the site of neuroma may induce hyperactivity, which may act as the neuropathic originator [27].

Normally, the sympathetic nervous system is not involved in nociceptive transmission and sympathetic fibers are able to release norepinephrine (NE) into tissues without inducing pain. However, in some nerve injuries, changes can occur in primary afferent receptors causing them to become sensitive to these adrenergic substances and consequently sympathetic stimulation results in pain. The increase in circulating catecholamines may also explain the increased pain during periods of stress or anxiety frequently reported by individuals with chronic pain [28]. Subsequent nerve damage neuropeptide expression is altered in the trigeminal ganglion and indicates functional changes. Phenotypic changes in the primary afferents nerve and spinal dorsal horn and V subnucleus caudalis neurons also occurs [29].

The role of glia cells in chronic neuropathic pain has been demonstrated. Studies have shown that in response to neuronal signals, glia can release excitatory molecules as proinflammatory cytokines, glutamate, nitric oxide and prostaglandins, which enhance the dorsal horn neurons' hyperexcitability and neurotransmitter release from primary afferents [30]. Bacteria and viruses also stimulate glia cells which may explain why pain and allodynia are frequently associated with some systemic conditions. (e.g., Herpes Simplex, Herpes Zoster and Human Immunodeficiency Virus (HIV)) [30, 31].

Neurovascular Orofacial Pain

The International Headache Society, classifies headaches as Primary or Secondary [32]. The *primary* headache is not associated with any other illness or pathology. Included in this category are migraine (with and without aura), tension-type, and cluster headaches. In contrast, a *secondary* headache is a headache that is secondary to a well defined, primary organic condition that include some acute and critical diagnoses (e.g., brain tumors, brain hemorrhage) or as well as some benign conditions such as sinus infections and allergies.

The most recognized form of vascular pain is migraine that is mainly characterized by unilateral, moderate to severe throbbing pain aggravating by or causing avoidance of routine physical activity. It may be accompanied by nausea, with or without vomiting and phono and photophobia [33]. Although the pain is not associated with mastication, it can be followed by muscle tenderness and typically awakens the patient from sleep [16]. The strong familial association suggests that genetic factors may be involved [2].

Triggers of a migraine attack can be endogenous factors such as hormonal changes, psychosocial stress, sleep deficit or hunger, or exogenous factors as certain types of food (see Section "Treatment of Neurovascular Orofacial Pain") or stimulation of several sensory pathway modalities [34]. The mechanisms involving migraines are not fully understood; however, the source of the pain in this syndrome seems to involve the activation of the trigeminovascular pathway resulting in the release of neurotransmitters and modulators including serotonin, calcitonin gene-related peptide (CGRP), nitric oxide, dopamine, and glutamate [34–36]. Vasoactive and neuroactive neuropeptides such as substance P, CGRP, and nitric oxide, are released at the nerve endings nearby to the blood vessels

[37, 38] inducing vasodilatation, plasma extravasation, and sensitization of the nerve endings initiating the migraine attack. Increased craniofacial muscle tenderness is also present in patients with migraine. In such cases allodynia and hyperalgesia are present; possibly related to central sensitization. Trigeminal afferent information from intracranial and extracranial sites is combined in the trigeminal nucleus caudalis and modified by the pain modulatory system modifying pain input (pain level enhanced or decreased). In vascular pain, simultaneously, input from pericranial or masticatory muscle afferents may add to the development of suprathreshold stimulation/pain and the intense neural input induces central sensitization. This may also explain the efficiency of migraine interventions aimed at the craniofacial muscles. Further research is necessary to better understand the mechanisms underlying migraine [39].

Although the most common presentation of migraine involves the frontal, temporal, or parietal areas, cases occurring in the orofacial region have been reported and named "facial migraines" [40–42]. Individuals with facial migraines usually experience throbbing pain in the maxillary teeth and occasionally in the mandibular teeth. The pain may even be felt in an edentulous area. The presence of these symptoms often results in a misdiagnosis since the pain resembles intraoral dental conditions like toothache and frequently results in unnecessary and inappropriate dental procedures. Benoliel suggested that a primary neurovascular pain may occur in the perioral and intraoral structures; termed "neurovascular orofacial pain" (NVOP) [43]. Patients suffering from NVOP complain of throbbing, as well as episodic toothaches, often accompanied by lacrimation, rhinorrhea, and mild symptoms of photophobia or phonophobia [44]. The pain is resistant to dental interventions but responds to abortive and prophylactic drugs typically used for migraine attacks. A careful history and lack of a positive dental cause for the pain should alert the clinician to the possibility of other non-dental causes of pain including NVOP.

Treatment of Chronic Orofacial Pain

Management of chronic orofacial pain requires complete diagnosis of underlying mechanisms of pain and on selective treatment for each pain diagnosis. However, medication uses may overlap between different pain categories, and, in many cases the treatment that ultimately relieves the patient's pain is somewhat empirical. Table 17.2 provides an overview of treatment approaches for chronic orofacial pain conditions. Diet modification may be included in the treatment strategies used since mechanical and sensory oral function may be altered by the disorder and because oral intake and swallowing may trigger painful symptoms. Sections in this chapter "Diet, Nutrition and Chronic Orofacial Pain" and "Changes in Diet and Dietary Patterns Associated with Chronic Orofacial Pain" address research and clinical practice findings relevant to chronic orofacial pain disorders.

Treatment for Musculoskeletal Orofacial Pain

The management of TMDs includes identification and control of causal/perpetuating factors. Primary aims include decreasing any overloading, restoring function and continuation of normal daily activities [2]. These aims can be achieved using physical, pharmacological and/or psychological approaches. Prior research has reported that 75% of the population has experienced a sign or symptom of TMD during their lifetime, however less than 5% need therapeutic treatment [9]. The success of conservative approaches such as physical therapy, including muscle exercises, thermal packs, and an oral splint has been demonstrated in clinical settings. Despite the clinically empiric evidence of the benefits of splints, there is a paucity of research published that demonstrates the effectiveness of splints in controlled clinical trials.

Table 17.2 Chronic orofacial pain treatment approaches [45]

		Abortive treatment	Prophylactic treatment	Nutrition/Diet
Musculoskeletal	Muscles	NSAIDs[a]	Physical therapy Muscle relaxants Tricyclic antidepressants	Manage side effects of medications; moisten and modify food consistency as needed; peel (as needed) and cut/chop fruits and vegetables
	Joints	NSAIDs	Oral appliance Physical therapy Tricyclic antidepressants	As above
Neuropathic	Paroxysmal (Trigeminal neuralgia)		Anti convulsants	Manage side effects of medications
	Continuous	Opioids	Anti convulsants, Tricyclic antidepressants	Manage side effects of medications
Vascular	Migraine	NSAIDs, triptans, Opioids	β blockers Tricyclic antidepressants. Anti convulsants	Avoid individual 'trigger' foods such as alcohol (particularly red wine), caffeine containing foods such as coffee, teas, chocolate, and caffeinated beverages (such as soda), tyramine containing foods (aged cheese, smoked fishes, cured meats), monosodium glutamate, and foods containing aspartame (an artificial sweetener) [71] Manage side effects of medications
	Cluster Headache	Oxygen Triptans	Steroids Lithium β blockers	Manage side effects of medications
	Paroxysmal hemicrania	Indomethacin	Indomethacin	
	Neurovascular orofacial pain (NVOP)	NSAIDs	β blockers Tricyclic antidepressants	Manage side effects of medications Modify food consistency if opening the mouth, biting and or chewing exacerbate pain

[a] *NSAIDs* Nonsteroidal anti-inflammatory drugs

Although the importance of occlusion in TMD etiology has not been demonstrated, occlusion has led to extensive use of oral splints. Oral splints are removable intraoral devices used to raise vertical dimension and reduce joint and muscle stress [45]. While their use seems to be beneficial in TMJ arthralgia however, a meta-analysis demonstrated only minor benefits of splints in management of TMDs [46, 47]. Although splints are the most popular treatment for TMD management in the clinical setting, the mechanism(s) of action of remains unknown therefore they are referred as adjunctive therapy [48–50].

Controlling a patient's pain is essential while contributing factors are being identified and managed. Nonsteroidal anti-inflammatory drugs (NSAIDs), are commonly used in the management of pain and disability associated with joint disease. Various other oral medications can be used to control muscle pain including analgesics, muscle relaxants, anxiolytics, antidepressants, and sleep promoters. These drugs are most effective when combined with physical medicine and rest.

Although selective COX-2 inhibitors may reduce undesirable gastrointestinal side effects related to the use of earlier generation NSAIDs, they have potentially serious renal and cardiovascular system side effects. Therefore, patients taking NSAIDs should be carefully monitored [45]. In patients with myofascial pain, NSAIDs can be combined with a muscle relaxant or benzodiazepine medications to provide greater pain relief than when used alone. Most muscle relaxants (e.g. cyclobenzaprine, carisoprodol) exert their effects by diminishing the flow of impulses to skeletal muscles. However due to their sedative effect, they should be taken at bedtime. Amitriptyline at low doses (10 mg/day to 30 mg/day) has also been reported to be beneficial for patients with craniofacial myofascial pain, including muscular TMDs and chronic tension-type headaches [51]. Clonazepam, a long-acting benzodiazepine with anticonvulsant properties also has been proved helpful [52–54]. Future research is needed with a focus on drug trials with scientifically sound study designs for myofascial and arthralgia pain since treatment for these conditions remains somewhat empirical [55]. In the presence of muscle trigger points, trigger point injections in addition to other physical and medical modalities may be beneficial.

The goal of physical therapy is to decrease pain and concurrently improve joint movement, reduce inflammation, and promote strengthening muscle activity to allow regeneration of tissues. These measures include exercise, joint mobilization, posture training, and the use of physical agents and modalities [56].

Cognitive behavioral therapy treatment may play an important role in TMD management as its intent focuses on behavioral modification of maladaptive habits altering negative thoughts or feeling while decreasing distress and suffering. These aims are achieved by simple exercises or a personalized program that teaches relaxation, goal-setting, problem-solving, communication, counseling, and how to alter emotional responses to pain. Whether separately or combined with other pain treatments, cognitive-behavioral therapy has been shown to produce significantly decreased pain, emotional distress, and disability [57]. The evaluation and treatment plan for individuals with chronic OFP should include both the physical and emotional dimensions of chronic pain.

Treatment of Neuropathic Pain

The management of neuropathic pain (NP) is a challenge for researchers and clinicians. Prevention is always the primary goal in health care. Pre-emptive analgesia is a approach to attempt to "prevent" central sensitization by using preoperative anesthetic blocks in dental procedures. The mechanism behind this approach is to attenuate the impact of the peripheral nociceptive barrage associated with noxious stimuli preoperatively, intraoperatively, and/or postoperatively [58]. Studies have shown that preoperative anesthetic blocks may result in less postoperative pain when compared with dental procedures without local anesthesia [59].

Management of neuropathic pain includes pharmacologic agents with long-term prescription that present considerable side effects. Early intervention may result in a better prognosis. As in any other chronic pain condition, psychological support is frequently indicated as NP and has a significant impact on patient's quality of life. Although neuropathic pain is not a life threatening condition, it may be a lifetime condition. Treatment approaches should therefore include addressing coping strategies with the patients so that they can maximize their quality of life.

The basis of NP pharmacotherapy lies in use of antiepileptic drugs (AED) and tricyclic antidepressants (TCA) [60, 61]. TCAS and AED analgesic mechanisms are based on the regulation of neuronal excitability in the central nervous system, either increasing inhibition or reducing excitation. They are commonly used for treatment of a several chronic pain entities of neuropathic, vascular, and musculoskeletal origins.

TCAS were originally prescribed for the treatment of depression. These antidepressant drugs have been used increasingly as analgesics for the management of chronic pain. The actions of TCAs are related to the inhibition of synaptic reuptake of serotonin and norepinephrine. TCAs also block sodium channels preventing neurons from "firing" and may act as NMDA antagonists preventing central sensitization. TCAs are contraindiciated in elderly patients and patients with cardiovascular or coronary diseases; side effects include dry mouth, weight gain and sedation [62].

The most effective TCAs that block reuptake of norepinephrine and serotonin are amitriptyline, nortriptyline, and imipramine. Among them, nortryptline presents the least side effects. Drugs such as duloxetine that are tricyclic norepinephrine and serotonin reuptake inhibitors (SNRIs) have increasing support in management of neuropathic pain [63, 64].

Anticonvulsants were developed to control epilepsy; however, both epilepsy and neuropathic pain are associated with functional changes in the subunits of sodium and calcium channels [65]. They enhance neuronal stability through several mechanisms ultimately resulting in pain relief. The mechanisms include blockage of sodium and calcium channels as well as inhibition of glutamate release. Anticonvulsants also facilitate γ-aminobutyric acid GABA-receptor function: therefore inhibitory pathways are increased [66].

Gabapentin and pregabalin are the most widely used AEDs and have shown to be effective for the management of peripheral neuropathy [67]. The recent generation of anticonvulsants is very safe and has a favorable side effect profile; their primary side effects are dizziness, sedation, and fatigue [59, 68].

Topical medications represent an alternative treatment and avoid potential systemic side effects and may have utility for peripheral neuropathic pain. Their intent is to induce peripheral analgesia with a high local concentration of the active drug applied at the affected site with minimal systemic dosing. These drugs are different from transdermal analgesics that require effective systemic concentrations associated with an increased risk of side effects. Clinical studies have shown that a combination of topical drugs has been successfully used in the management of oral neuropathies [69]. Moreover, Heir et al. suggest that topical medications as a single treatment or in combination with systemic medications can reduce the severity of orofacial NP [70].

Treatment of Neurovascular Orofacial Pain

It is important to note that the patients can contribute to their treatment by learning to identify and avoid migraine triggers; this may involve lifestyle changes to adapt to a healthy lifestyle. For example, dietary triggers should be identified and eliminated as much as possible, sleep patterns should be modified as needed to ensure an adequate number of hours of sleep nightly, and regular physical activity and exercise encouraged. Dietary triggers tend to vary with the individual; common reported triggers include alcohol, particularly red wine, caffeine containing foods such as coffee, tea,

chocolate, and carbonated beverages (such as soda), tyramine containing foods (aged cheese, smoked fishes, cured meats), monosodium glutamate, and foods containing aspartame (an artificial sweetener) [71]. Involving the patient in his/her therapy helps to gives them a sense of control and participation. It can often help the patient cope with the disorder as well [72]. Non-pharmacologic methods including biofeedback, acupuncture, and relaxation techniques, can be used as an complementary therapies [73, 74].

Pharmacologic management of vascular-type pain is either abortive or prophylactic. The choice of treatment should be based on the frequency of attacks. However if the attacks are infrequent but are associated with significant disability, prophylactic therapy should also be considered [75]. Prophylactic medications include Beta-blockers (e.g., metoprolol, propranolol, timolol) and anti-convulsants (e.g., divalproex, topiramate) as the most effective of migraine prevention [76–78]. Several medications are used as abortive agents for migraine attacks. These medications should have a rapid onset of action, high overall efficacy with complete relief of the headache and associated symptoms. Nonsteroidal anti-inflammatory drugs (NSAIDs) act through peripheral and central mechanisms. Peripherally they block neurogenic inflammation following trigeminal nerve activation. Centrally they restrain prostaglandin synthesis, prevent sensitization, and prolong 5-HT and noradrenalin action in brain neurons activating inhibitory pathways.

Triptans are a class of related chemical agents that have selective agonist activity at 5-HT1b/1d receptors. They are thought to abort migraine headaches through several mechanisms including reduction of neurogenic inflammation by inhibiting the release of vasoactive neuropeptides (e.g., CGRP, SP) at the margin between trigeminal afferents and meningeal and dural blood vessels, inhibition of neural transmission centrally at the level of trigeminal nucleus caudalis and by causing vasoconstriction of painful dilated intracranial arteries (e.g., dural, meningeal and cerebral). The triptans represent a marked improvement over previous abortive medications, but they are associated with some undesirable adverse effects, including chest tightness. Although the majority of individuals who take triptans do not show any changes on an electrocardiogram, a small decrease in the diameter of the coronary arteries can occur. Therefore, these drugs should not be used in patients who have or are at high risk of developing ischemic heart disease.

In case studies, investigators have shown that if the pain is not blocked within 60–120 minutes, molecular changes occur in neurons located at spinal trigeminal nucleus making them generate the pain themselves [79]. Therefore, successful treatment of migraine increases significantly if the medication is given as soon the migraine attack begin, before the establishment of cutaneous allodynia and central sensitization.

Complementary and Alternative Medicine

Traditional chronic pain therapies are challenging and present several limitations leading to only partial success. Therefore, patient interest in and inquiry about complementary and alternative medicine (CAM) is increasing. Lopez et al. [80] explored use of CAM therapies in a sample of 82 patients with Burning Mouth Syndrome; of these, 40% included CAM in their treatment plans and 39% of these individuals perceived the CAM as effective in managing their pain. The literature supports the value of acupuncture for the management of idiopathic headaches [81], and has shown promise in the management of TMDs and Burning Mouth Syndrome [82–84].

The absence of the undesirable side effects that medications provide along with the fact that CAM is an increasingly popular method to treat pain as a complement to traditional medical approaches deserves attention. Further studies are necessary to establish safety, efficacy, and mechanisms of actions of CAM therapies for facial pain. Please refer to Chapter 9 for a more extensive discussion of CAM therapies.

Pain Modulation

The role of pain modulatory system, which have the ability to enhance or decrease pain perception, has been investigated in chronic pain. Pain perception is the result of peripherally generated data that is transmitted centrally, and modulated in the central nervous system before its arrival in the cortex, and awareness of pain. The same external stimulus can evoke different perceptions responses among different people, depending on their pain modulatory system.

Two tests are available that can provide information on the individual modulation systems status; Temporal Summation (TS) and Conditioned Pain Modulation (CPM) [85]. TS assesses the hyperexcitability of the central nervous system and is believed to be the psychophysical correlate of windup of second/third order neurons reflecting central sensitization. The mechanism underlying TS is excessive activation of N-methyl-D-aspartate (NMDA) receptors in response to high levels of repetitive input, clinically manifested by allodynia and hyperalgesia [86]. The relevance of TS has been confirmed in studies reporting that enhanced TS is present in several idiopathic chronic pain disorders including fibromyalgia, low back pain, and tension-type headache [6, 87–92]. In patients with chronic orofacial pain, it has been used to assesses TMD central sensitization after a third molar surgery, chronic tension-type headache, and trigeminal neuropathic pain [93–98].

CPM (former known as Diffuse Noxious Inhibitory control (DNIC)) represents the endogenous analgesia system, where descending pathways exert modulatory effects on incoming spinal nociceptive data representing a key mechanism for pain modulation [99]. Reduced efficiency of the CPM effect (less efficient descending pain inhibitory system) has been demonstrated in patients with idiopathic pain disorders, such as TMD, fibromyalgia, tension headache, migraine, and irritable bowel syndrome, suggesting that altered CPM has a role in the pathogenesis of chronic pain conditions [100–104]. The individual's pain modulatory system can define susceptibility to develop chronic pain disorders [105–108].

Gender and Orofacial Pain

Differences in gender associated with pain syndromes and pain thresholds have been extensively reported in the literature. Studies have shown that women report more severe, frequent, and longer duration of pain compared to men [109]. Women suffer significantly more from migraines [110], tension-type headaches [111], and fibromyalgia [7] then men and have a higher prevalence of TMDs, Atypical Odontalgia, and Burning Mouth Syndrome [112–115].

Differences in pain between the genders vary with biological maturity and consumption of exogenous sex hormones. For example, sex differences in orofacial pain seem to have onset at puberty, reach a peak during the reproductive years, and start to decline at menopause [116]. Studies have shown that the increased prevalence of TMDs is linked with the use of oral contraceptives, hormone replacement therapy [117], and the effect of exogenous hormones including oral contraceptives. The role of gonadal hormones in pain mechanisms has also been demonstrated [118, 119]. Several neuroactive agents involved in inflammation and pain as nerve grow factor, γ-aminobutyric acid, and neurotransmitters as serotonin, dopamine, and epinephrine have shown changes along oscillations with changes in plasma levels of estrogen [120]. Gender may also influence when and where individuals seek treatment delivery of treatment, and treatment effectiveness [121, 122].

The association between gender and pain modulation is controversial [123, 124]. Differences in anatomy, neural and hormonal, environmental factors, cultural and previous experiences can influence the way that nervous system modulates pain perception [125]. A 2010 review of the literature reported that gender differences in CPM responses were found in about 50% of the studies published

[106]. Prior research studies have reported that CPM is less efficient in females [123, 126, 127] than in males; however, other authors found no significant differences regarding CPM effect and gender [128, 129]. In summary, the differences between men and women regarding to pain are very clear and clinicians should take these differences into account to maximize treatment outcomes [130, 131].

Diet, Nutrition, and Chronic Orofacial Pain

The associations between nutrition, diet, and chronic orofacial pain conditions are multifaceted. The nature of the disorder (musculoskeletal, neuropathic, or neurovascular) as well as its treatments can influence appetite and mechanical as well as sensory factors involved with eating, drinking, and swallowing thus affecting dietary intake and subsequently nutritional status. Single nutrients or dietary components may influence the development of the condition as well as have pharmacokinetic impacts [132]. Unfortunately, there is a paucity of published research on any of these associations. This section will summarize published research and reviews on diet, nutrition, and chronic OFP and provide empirically derived recommendations for management of chronic orofacial pain disorders. Diet recommendations are also in Table 17.2. Diet and nutrition side effects of medications used with chronic OFP are discussed in Chapter 6.

The impact of chronic OFP on diet and nutrition status is related to sensory and motor functions of the oral cavity as well as emotions. Oral functional challenges along with the depression, fatigue, and compromised quality of life are common in patients with these conditions and can affect food choices as well as diet quality and composition. The associations between pain, mood, and food choices are outside the scope of this chapter and text.

Changes in Diet and Dietary Patterns Associated with Chronic Orofacial Pain

Individuals with chronic orofacial pain that is musculoskeletal in origin such as TMD may have motor limitations on their ability to open their mouth, bite, and chew which are associated with pain and discomfort. Anecdotal evidence and pilot studies [133–135] suggest that OFP disorders may influence eating related quality of life [136] (OFP-ERQoL), dietary intake and, if experienced over a long period of time may negatively impact nutritional status. Raphael et al. explored dietary fiber intake in women with myofascial pain seen in a university-based clinic [133]. Nutrient intake was compared to age and gender matched data from the *US Continuing Survey of Food Intake* (USCSFI) for a similar geographic region. Food diaries and daily pain scores were collected and analyzed. The majority of subjects reported difficulty chewing and eating self identified "hard" and "soft" foods; there were no significant between group differences for calories, dietary fiber, or macronutrients between the patients with myofascial pain and those in the USCSFI database. However using linear regression, the authors found that increased pain was associated with reduced dietary fiber intake and those with higher pain scores consumed less dietary fiber than their age matched healthy controls. This study was one of the first to identify that classification of food as "hard" or "soft" varies with the patient. In a pilot study, Kharti et al. explored VAS data of patients with temporomandibular disorders (TMD) and myofascial pain as well as neuropathic and neurovascular disorders [137]. Those with musculoskeletal disorders had significantly higher pain VAS scores with mouth opening, biting, and chewing then those with neuropathic or neurovascular disorders. Patients with neuropathic and neurovascular conditions had less pain with the mechanical functions of food

consumption (biting, chewing, and opening their mouths) than those with OFP conditions that were musculoskeletal in origin.

Durham et al. have proposed a TMD-specific *Oral Health Impact Profile* tool that has some questions related to eating related quality of life [136]. The *Manchester Disability Scale* and Kurita's Score of Chewing Ability can be used to identify difficulties with mouth opening, biting, and chewing in individuals with TMD [138, 139]. However, none of these patient assessment tools address the scope of the eating and beverage consumption issues patients with chronic OFP disorders face. Being able to eat and drink comfortably in social situations is of concern for patients with chronic OFP conditions. To date, there are no validated measures for clinicians to assess diet and nutritional status or eating related quality of life in these patients.

Common complaints of patients with POMP regarding eating are due to pain with mouth opening, biting, and chewing. Oral healthcare professionals (OHCPs) may recommend a "soft" diet for TMD disorders without any definition of what compromises a soft diet. It is likely that the real intent here is for a mechanically altered diet to minimize masticatory efforts. However, "soft rolls" require more jaw movement to bite, chew, and swallow then popcorn kernels or a chopped tomato, both of which have more fiber than a "soft roll." In this example, the soft roll may really be "hard" for the patient to eat as the masticatory effort may be greater than that needed for the chopped tomato. Prudent approaches for OHCPs or any health professional seeing a patient with a chronic orofacial pain disorder would be asking patients open-ended questions about whether and how their condition has impacted their ability to eat and drink at home or socially and probe for problems. Guidance on modifications to reduce associated discomfort and pain and enhance the eating experience is important. Simply cutting foods well, using moist or moistened foods (via gravies or sauces) may be adequate for some patients. Peeling fruits and vegetables with tough skins and chopping whole foods to consistencies that can be tolerated may allow patients to consume their preferred foods and enjoy meal times at home or when eaten out. The national dysphagia diet may provide some useful approaches for individual patients.

There are no published dietary guidelines for patients with neuropathic or neurovascular disorders except for avoidance of specific trigger foods. Hence patients are left with no evidence-based guidelines on approaches to optimizing their ability to eat or quality of their diet. As described above, open-ended questioning may reveal food related triggers or patient perceived barriers to eating with their disorder. Appendices 2D–G of this text has dietary guidelines for texture modification which may be helpful to patients. OHCPs should have general knowledge of approaches to supplement energy and nutrient intake in order to provide initial recommendations to patients, and should note the need for oral hygiene and caries prevention in order to reduce caries risk in patients requiring additional calories or small, frequent meals. Individuals having difficulty meeting energy and nutrient needs, with poor appetite or exhibiting unintentional weight changes should be referred to a registered dietitian (RD) for medical nutrition therapy.

Role of Nutrients in the Etiology and Management of Chronic Orofacial Pain Disorders

Roles for Vitamin D, omega 3 and 6 fatty acids, antioxidants, and soy have been postulated in the etiology and management of chronic OFP disorders [45, 132, 140]. In neurovascular disorders such as migraine, select food components such as caffeine, cheeses, chocolate, and red wine [141] are known triggers of a headache. Vitamin D has been a topic of debate in the etiology and management of many diseases and disorders including chronic pain. In the U.S. and globally, the prevalence of vitamin D inadequacy and deficiency has been identified [142]. Vitamin D sources include diet,

sunlight, and supplements. Turner et al. studied vitamin D status of patients with chronic pain in Minnesota and concluded that although vitamin D inadequacy may represent a source of pain, prospective, randomized clinical trials are needed to determine the effects of vitamin D repletion on pain incidence and severity [143]. Straube et al. conducted a systematic review of vitamin D and chronic orofacial pain [132]. Many of the studies reviewed were nonblinded or observational in nature; the results demonstrated that there was a lack of definitive evidence for a vitamin D—chronic orofacial pain relationship.

Bell et al. [140] has proposed that selected dietary components including omega 3 and 6 fatty acids, vitamin D, and flavonoids be studied in patients with chronic OFP conditions to explore their possible antihyperalgesic roles. They proposed that the ratio of omega 3 to omega 6 may influence inflammatory pain and medications used to manage the pain. Goldberg and Katz conducted a meta-analysis to explore the analgesic effects of omega-3 fatty acid supplementation for inflammatory joint pain [144]. Although studies included did not include orofacial pain disorders, the author did point out that the omega-6 fatty acid metabolism has a proinflammatory effect whereas omega-3 fatty acids can have an anti-inflammatory effect. Hence the ratio of the two fatty acids may be worthy of further study in patients with chronic OFP. There is a lack of clinical trial evidence to support the role of supplementation of single nutrients for the prevention or treatment of any chronic orofacial pain disorders. Clearly, it is an area for future research. Nutrients in foods and supplements when consumed in recommended amounts are needed to support health; excessive doses should be avoided.

Burning mouth syndrome (BMS) or symptoms many be primary or secondary in nature. Although it is a known consequence of diabetes, in patients with primary BMS there are no associated nutrient deficiencies or known laboratory findings. Sardella et al. explored the role of nutrients as causative agents in BMS in a case controlled trial in Milan [145]. They found no significant differences in serum iron, ferritin, folic aid, or vitamin B12 between the control and BMS groups.

Management of Medication Related Side Effects

Chapter 6 covers food and medication interactions extensively. Among the medications used to manage chronic OFP disorders, the related side effects can impact the oral cavity causing hyposalivation, affect appetite and subsequently dietary intake and weight gain as an outcome of the increased appetite. These are summarized in Table 17.2.

Summary

Chronic orofacial pain can be classified as musculoskeletal, neuropathic, and vascular disorders. Different from acute pain, chronic pain is the disease itself and not a symptom accompanying other diseases. An accurate diagnosis is the key to more effective management of these challenging conditions. Treatment strategies are multifaceted and often involve pharmacologic, physical, and diet therapies. A coordinated interprofessional team approach helps to provide comprehensive patient care. Associations between diet, nutrients, and chronic oral facial pain disorders are “ripe” for further research.

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Chapter 18
Oral Surgery, Diet, and Nutrition

Hani Braidy, Vincent B. Ziccardi, Wendy Phillips and Kate Willcutts

Keypoints

- Dento-alveolar surgeries can have short-term impacts on oral function and ability to eat and drink depending on the location and extent of surgery
- Maxillofacial trauma results in increased energy and nutrient needs for wound healing; depending on the location and extent of trauma, nutrition support may be needed
- Treatment following orthognathic surgery typically requires diet consistency modification and additional calories and nutrients for wound healing
- Patients with cleft lip and palate require modified feeding strategies preoperatively and initially postoperatively
- Nutrition support following oral surgery is typically achieved using oral liquid nutrition supplements or an enteral tube feeding

Keywords Oral maxillofacial surgery · Nutrition · Dentoalveolar surgeries · Oral function · Maxillofacial trauma · Orthognathic surgery · Diet consistency modification · Liquid nutrition supplements · Enteral tube feeding

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Introduction

Interactions between diet, nutrition, and oral surgery are multidirectional as they impact each other on multiple levels depending on the nature and extent of the oral condition, the oral and maxillofacial surgery and preexisting nutritional status of the patient. The nutritional status of a patient can profoundly affect healing of many tissues such as skin, mucosa, cartilage, and bone, all of which may be disrupted by traumatic events such as fractures or reconstructive maxillofacial surgical procedures. Without adequate energy, micro, and macronutrients patients may be at risk for compromised immune function, delays in wound healing and postoperative infections requiring additional treatments. Conversely, the treatments of many oral and maxillofacial conditions may adversely affect food and fluid intake, further compromising patient's nutritional status. Many head and neck cancers and their management will severely compromise the functional ability to eat as well as appetite due to the disruption of the oropharynx, which may require perioperative nutritional enteral or parenteral support (see Chapter 13 on Management of Head and Neck Cancers).

Approaches to diet and feeding patients undergoing oral and maxillofacial surgical procedures including dentoalveolar, maxillofacial trauma, and orthognathic surgical procedures as well as cleft lip and palate surgery are discussed in this chapter. The first part of this chapter focuses on oral surgeries and known and postulated impacts on diet and nutrition. There is a paucity of published research on oral maxillofacial surgeries and diet/nutrition hence some of the literature cited appears dated. Given that the basic surgical techniques have not changed substantially over this time, the diet and nutrition concerns raised continue to be relevant. The second part of the chapter addresses approaches to nutritional support for individuals undergoing oral and dental surgeries.

Dentoalveolar Surgery and Nutrition

There are many types of dentoalveolar surgeries that include extraction of unsalvageable teeth or impacted third molars, treatment of oral pathology, preprosthetic surgery, and surgical placement of dental implants. Since these procedures are voluntary and not usually emergent, the oral health care professional (OHCP) can partner with the patient to ensure that they are not at nutrition risk and prepare them for any short-term shifts in diet that may be necessary in the immediate post-operative period. These surgical procedures generate a variable amount of swelling and discomfort which may have a short-term impact on oral function including mastication, swallowing, speech and tongue, lip, soft palate, and mandibular range of motion. Chaushu et al. studied health-related quality of life in patients undergoing orthodontic premolar extractions and found that 80% of patients experienced significant eating difficulty during the first postoperative day [1]. The ability to eat without difficulty required an average of 3 days to return [1]. The elective removal of impacted third molars, which is generally more invasive, can disturb food ingestion for several days. In a study of 249 patients undergoing third molar surgery, Conrad et al. found that 85% of patients experienced substantial difficulty chewing, which improved by postoperative day six [2]. Eating was found to be the last health-related quality of life measurement to normalize in this investigation. Factors noted to be implicated with prolonged recovery included female gender, length of surgery more than 30 minutes, and impaction level [2]. The degree of surgical difficulty in relation to postoperative chewing impairment was evaluated in a study of 86 patients undergoing third molar extractions [4]. Patients suffered greater disability when the impacted third molar was rated as "difficult" by the examiners [3]. Despite the profound short-term impact on chewing and dietary intake, third molar surgery does not usually necessitate perioperative nutritional supplementation due to the brief period of compromised oral function and the relative health patients undergoing these elective surgeries.

In order to facilitate food intake, a liquid or mechanical soft diet is recommended immediately postoperatively following dentoalveolar surgery. This includes a variety of full liquids, blenderized, and pureed foods: soups, milkshakes, juices, applesauce, or other fruit/vegetable puree, gelatin desserts, ice cream, and puddings. The meaning of a "soft diet" here can be interpreted as foods that are liquid or semi-liquid and do not require opening the jaw wide or chewing. Patients are instructed to progressively advance their diet over a few days with gradual increases in food texture and particle size advancing to foods such as mashed potatoes, pasta, cereals, peeled and chopped fruits and vegetables without skins and seeds as well as moist, cut protein foods (meats, poultry, fish, and meat alternatives). Rice or other small particulate foods such as seeds, peanuts, or popcorn, which can get lodged in surgical sites, are generally avoided until soft tissue healing is complete. Adequate fluid intake is important; patients should be encouraged to consume 2 liters a day of liquids.

Individuals with diabetes may have difficulty controlling their blood glucose postoperatively as the immediate postoperative diet is high in simple carbohydrates. Dosages of insulin and oral hypoglycemic agents may need to be adjusted under the supervision of the patient's diabetes care providers to prevent large glycemic fluctuations. Chapter 11 on diabetes addresses dietary management for patients with diabetes in greater depth.

Patients undergoing extensive maxillofacial reconstructive surgery may not be able to wear a removable temporary denture due to inflammation and discomfort [4] or to allow for graft consolidation and prevention of soft tissue dehiscence. Careful removable prosthesis relining and adjustments by the restorative dentist can increase postoperative patient comfort and masticatory ability. Diet and nutrition management following this surgery is similar to the diet and feeding progression outlined above for dentoalveolar surgery. However, in cases where patients cannot meet their energy and protein needs via the liquid diet alone, meal replacement formulas, like instant breakfast may be used; this is addressed in more detail in the section on "Oral Diets and Nutrition Supplementation" of this chapter. Appendix 2E includes diet guidelines postoral surgery for individuals with and without diabetes.

Maxillofacial Trauma and Nutrition

Patients sustaining maxillofacial trauma usually experience significant and unique nutritional challenges. Energy, protein, and other macro and micronutrient needs are greatly increased in trauma patients, especially if their injuries are multisystemic or complicated by sepsis. Isolated maxillofacial trauma does not usually trigger a significant catabolic state in healthy patients, unless malnutrition or substance abuse precedes the traumatic event. Mandible or midface fractures increase basal metabolism by approximately 10%, which, if the patient is able to return to their regular diet within a few days, is not likely to impair wound healing or nutritional status provided the patient consumes a nutritionally balanced full liquid diet during this time period [5]. A prolonged period of full liquid diet intake may be necessary in patients requiring maxillomandibular fixation (MMF) (see Fig. 18.1). The immobilization of the jaws optimizes the fracture healing in the same way a cast provides complete motion restriction of a broken extremity. MMF is usually indicated in fractures of the maxilla, mandible, and alveolar process either as a sole therapy or in combination with open reduction and internal fixation methods (see Fig. 18.2). Due to the immobilization of the jaws, the patient is unable to chew, and is therefore restricted to a strained, full liquid diet that can go through a wide straw during the length of the recovery. Spaces between the teeth cusps and behind the dental arches allow liquids to be conveyed to the oropharynx. A liquid blenderized diet should provide all the necessary nutrients including adequate calories, protein, other macro, and micro nutrients, as well as dietary fiber [5]. Commercial nutritional supplements such as Instant Breakfast®, Boost® (Société des Produits, Nestlé S.A., Vevey, Switzerland), or Ensure® (Abbott

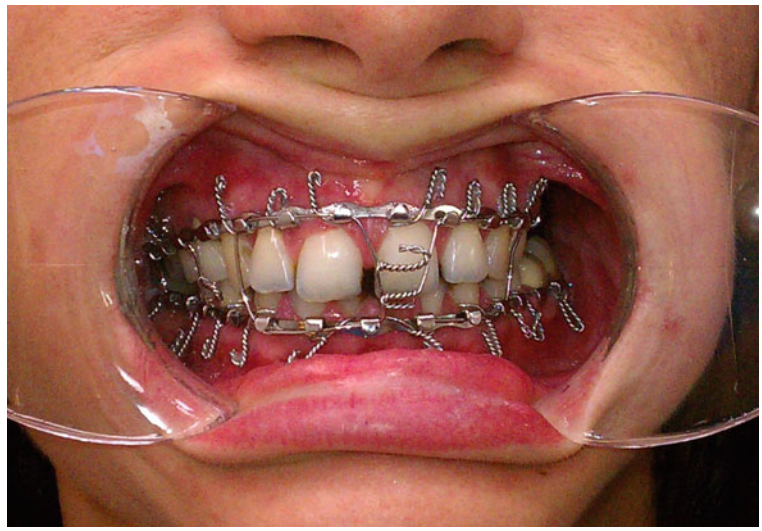

Fig. 18.1 Patient with mandible fractures treated with MMF

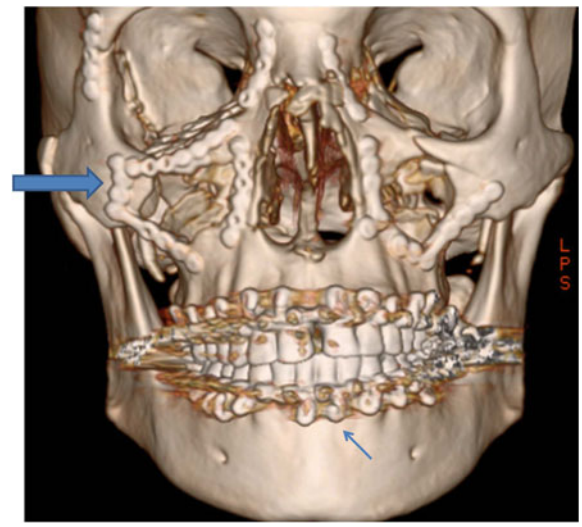

Fig. 18.2 Patient with extensive panfacial fractures. Titanium plates and screws (*large arrow*) and MMF (*small arrow*) can be appreciated

Laboratories, Chicago, IL) may be necessary to support the liquid diet. Due to catabolic nature of the stress response to the fracture, energy and protein needs are increased. Referral to a registered dietitian (RD) is recommended to determine energy and nutrient needs for wound healing postoperatively and design a full liquid diet plan for the patient.

Orthognathic Surgery and Nutrition

Orthognathic surgery is usually electively performed to establish optimal form and function in patients presenting with dental and skeletal deformities resulting in facial distortions and dental malocclusions. As a result of their malocclusion, patients often have severe difficulty biting and chewing (Fig. 18.3). In conjunction with orthodontic therapy, maxillary and mandibular osteotomies

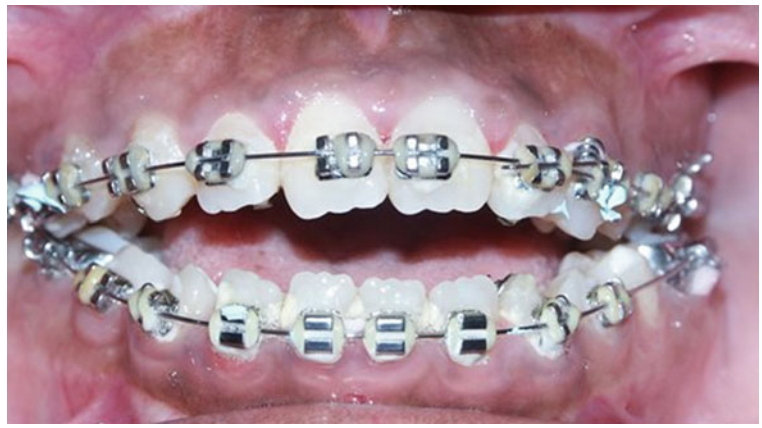

Fig. 18.3 Patient with severe dentofacial deformity and anterior open bite. This type of malocclusion is associated with difficulty masticating

can address these facial anomalies. Surgery is typically performed in an operating room setting under general anesthesia, requiring 2–6 hours of operative treatment and may result in substantial blood loss. In addition to a possible period of postoperative MMF ranging from 2–6 weeks, significant discomfort and swelling may impede dietary intake for a prolonged period.

Following surgery, a clear liquid diet for one meal is followed by progression to a full liquid diet that can be consumed through a straw for the first several days postoperatively. The progression of the diet consistency from liquid to solids is determined by the oral surgeon [6]. Adequate calories and nutrients are critical for wound healing and to maintain nutritional well-being. Oral nutritional supplements addressed in Section "Oral Diets and Nutrition Supplementation" and Table 18.2 of this chapter can be used to help patients meet energy and nutrient needs while on a consistency modified diet (the Appendix has a sample consistency modified diet). Within a week, patients usually progress to a mechanical soft diet using foods of a puree-like or finely chopped consistency such as mashed potatoes, soft pastas, chopped and moistened grains, meats, fish, poultry, beans along dairy products, and peeled and chopped or pureed fruits and vegetables [6].

Kendell reviewed patients' (aged 4–14 years old) nutritional status and conducted dietary analyses following orthognathic surgery accompanied by 6 weeks of MMF [7]. Patients taking a liquid nutritional supplement (Ensure Plus®, Abbott Laboratories, Chicago, IL) in addition to a blenderized diet were able to maintain a caloric intake similar to preoperative levels as opposed to the control group. In addition, the oral supplementation resulted in decreased weight loss postoperatively [7]. Patients undergoing orthognathic surgery and a prolonged course of MMF (6 weeks) also lost approximately 9.7% of their body weight [8]. Similar results were noted in a 2009 study by Kim, and all that showed an average body postoperative weight loss of 6.4% (5–10 lbs.) [9]. Kim et al. found that it took 5–10 weeks postoperatively for patients' weight to return to preoperative levels; the postoperative weight gain was facilitated by the improved masticatory function that the majority of patients experienced (84.1%). The application of titanium miniplates and screws to fixate osteotomies or fractures has shown to reduce the dependence on MMF to provide proper immobilization for bone healing. This technique may allow for an earlier return to the patient's regular diet which helps decrease postoperative weight loss [10].

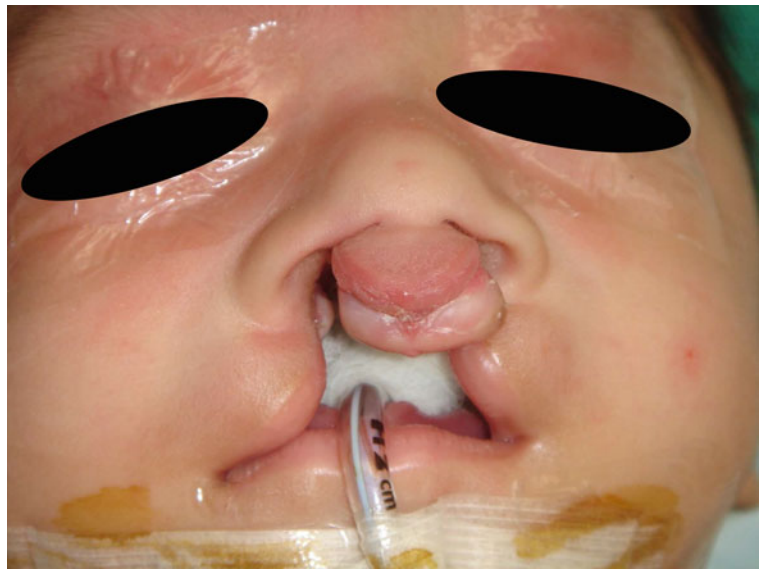

Fig. 18.4 Infant with unrepaired bilateral cleft lip

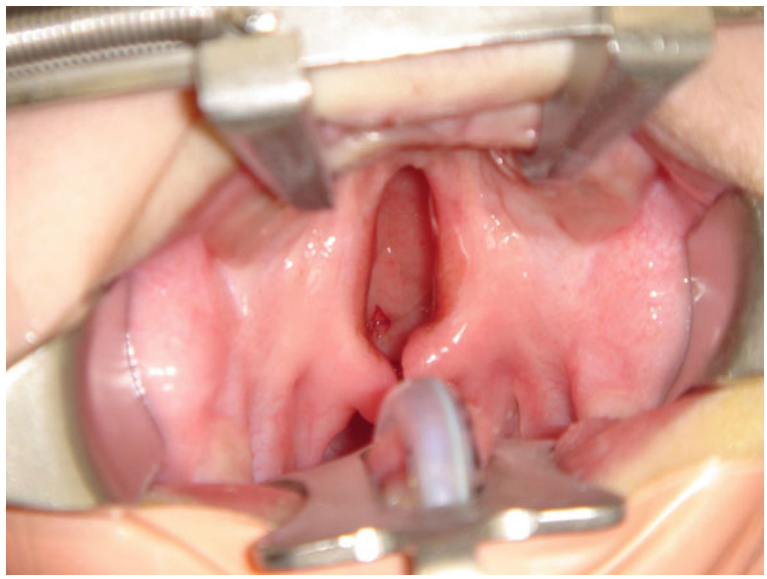

Fig. 18.5 Toddler with large hard and soft palate cleft. The nasal cavity can be seen through the cleft

Feeding Issues in Patients with Cleft Lip and Palate

Patients with cleft lip and palate may have difficulties feeding due to their inability to efficiently seal the oropharynx during sucking [11] (Figs. 18.4 and 18.5). This usually results in nasopharyngeal regurgitation and air ingestion, which can lead to inefficient feedings [12] and significant growth disturbances during the first 12 months. In newborns with these craniofacial anomalies, proper nutrition is critical as cleft lip surgical repair is usually delayed until the infant is at least 10 weeks

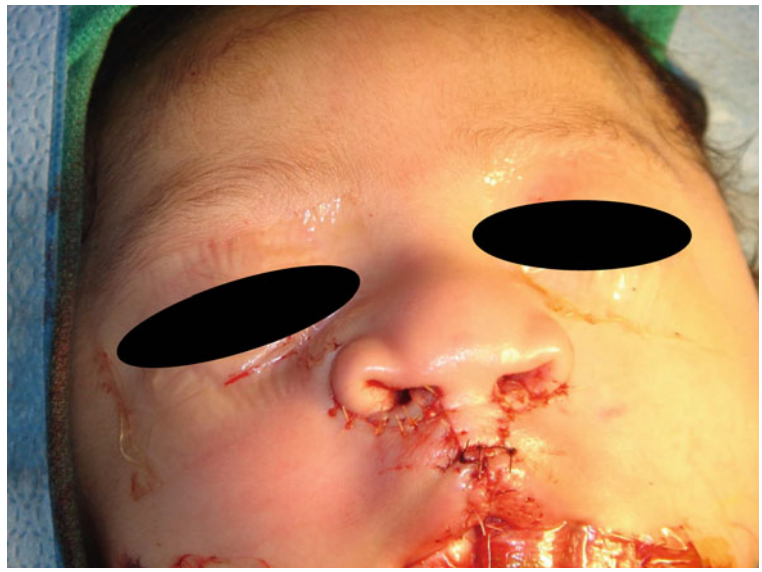

Fig. 18.6 Patient in Fig. 18.4, following repair of the cleft lip

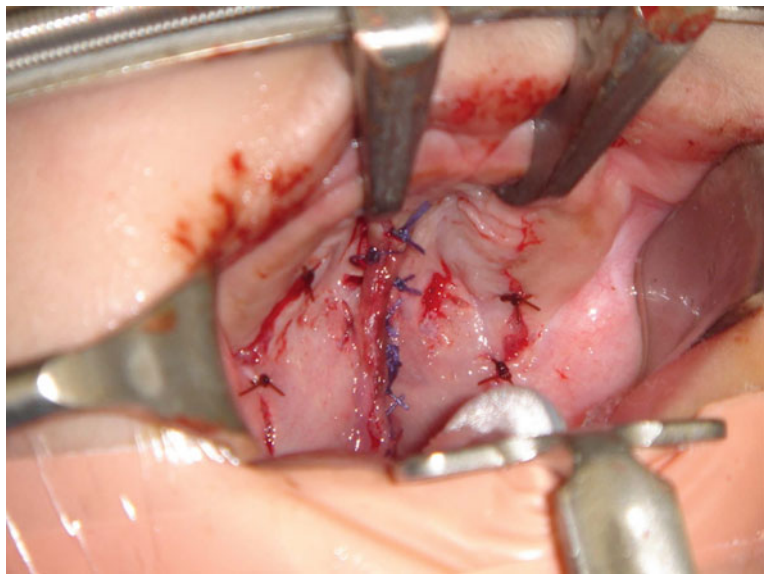

Fig. 18.7 Patient in Fig. 18.5 following cleft palate repair

old, 10 lbs., and have a hemoglobin of 10 g/dL ("rule of 10"). Modified nipples (i.e., Haberman Feeder®) and a compressible bottle have been recommended to facilitate feedings. In addition, holding the infant more erect may decrease nasal regurgitation [12]. Following cleft lip repair, the infant is encouraged to suckle as much as possible to strengthen the newly reapproximated orbicularis oris muscle of the lip (Fig. 18.6). Following cleft palate, palate repair at the age of 10–12 months is usually recommended to feed the toddler with a spoon or a syringe for approximately 4-weeks to decrease trauma to the sutures (Figs. 18.6 and 18.7).

Table 18.1 General indications for nutrition support [16, 22]

Little to no nutrition × 5 days or more and expected to not eat well for 5 or more days
Unintentional weight loss >10% in ≤6 months
BMI < 18.5
BMI < 20 and unintentional weight loss of >5% in ≤6 months
Not expected to meet nutritional needs orally due to high nutrient losses, hypermetabolism, or hypercatabolism

Nutrition Support

Nutrition is an important component of the healing process. The National Institute for Health and Care Excellence (NICE) guidelines recommend implementation of nutrition support for individuals with malnutrition, as defined by a BMI of less than 18.5, weight loss of at least 10% in the last 3–6 months, or a BMI of less than 20 with a 5% unintentional weight loss in the last 3–6 months [13]. General indications for nutrition support are addressed in Table 18.1. Nutrition support therapies include diet with oral nutritional supplements, enteral nutrition (tube feedings), and parenteral nutrition (PN). In individuals undergoing oral maxillofacial surgery, the oral and tube feeding routes are most often used for nutrition support when needed. Tube feedings should be reserved for those individuals who cannot meet energy and nutrient needs by diet alone with or without malnutrition. Oral nutrition supplements either as a liquid or a powder that must be reconstituted are defined as medical foods [14]. Most of these products are available to consumers in pharmacies and supermarkets without a Licensed Independent Practitioner (LIP) prescription. Selection of the appropriate formula for either oral or tube feeding use though should be done under the direction of a RD and LIP who will help ensure that the patient receives appropriate, cost-effective, and practical nutrition support.

Figure 18.8 is a decision tree that can be used to determine whether patients need nutrition support and the ideal route of administration. A tube feeding is indicated in individuals following oral or dental surgery who cannot meet their energy and nutrient needs orally to promote wound healing and prevent malnutrition and in those with malnutrition to promote healing and restore nutritional well-being. Preoperative nutrition support may be indicated in patients with preexisting malnutrition; during the immediate postoperative period, these patients may also need oral supplementation and/or enteral tube feeding to maintain their nutrition status [15, 16]. OHCPs can refer patients who are unable to meet their nutrient needs orally to a RD for medical nutrition therapy (MNT). As part of the MNT, the RD will conduct a comprehensive nutrition assessment, determine nutrition diagnoses, energy and nutrient needs along with a route of feeding. In consultation with the oral healthcare professional and patient, the RD will set diet and nutrition goals. Feeding progression is determined by the oral surgeon.

The gastrointestinal (GI) tract is the preferred site for nutrient delivery. An oral diet with or without oral nutrition supplements is the preferred route of feeding. PN is only indicated when the GI tract cannot be used [15, 16]. This may be due to a bowel obstruction, prolonged ileus, inability to achieve enteral access [17]. Referral to an RD and physician with nutrition support expertise is recommended to ensure clinically appropriate, safe, cost-effective methods of nutrition support are delivered.

Oral Diets and Nutrition Supplementation

Oral surgery may impact motor and sensory functions of the oral cavity. The location and extent of surgery tend to dictate the individual's ability to open their mouth, bite, chew, and swallow and

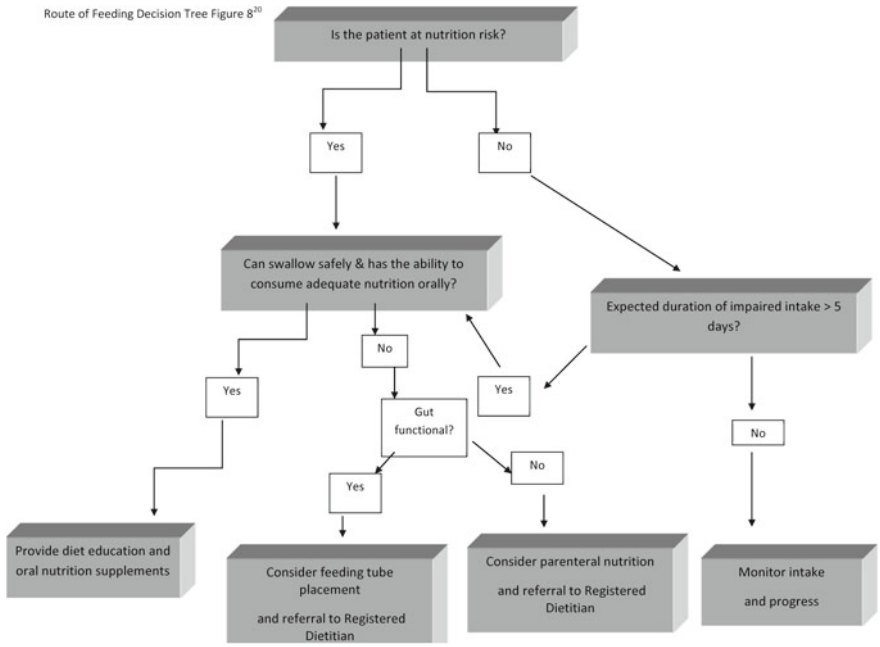

Fig. 18.8 Route of feeding decision tree [20]

subsequent diet form (whole, cut, chopped, puree or liquid) and nutrient intake. Individuals with limited oral opening or difficulty biting and chewing should first try a consistency modified diet. Depending on the extent of the limitations, cut or chopped fruits (and peeled) and vegetables, moistened and cut/chopped protein foods, and other harder to bite/chew foods may be tolerated. When necessary, broths, gravies, and sauces can be used to moisten foods. Use of mechanically chopped or pureed foods should be reserved for those who cannot tolerate any of the previously mentioned approaches. Visual appeal as well as taste and smell are important components of food preparation and presentation that can influence appetite and subsequently intake. Small, frequent meals and consistency modified diets can be helpful to maintain adequate calorie, protein, and total nutrient intake. When nutrition supplementation or support is warranted based on the algorithm in Fig. 18.7, liquid oral nutrition supplements should be considered in patients who can safely swallow [13]. The goal for supplementation should include a balanced mixture of protein, energy, fiber, electrolytes, vitamins and minerals to meet individual energy and nutrient needs and maximize wound healing.

Table 18.2 describes oral supplements and tube feeding products available commercially. Choice of formula usually depends on the patient's taste preferences, cost, and whether a complete meal replacement is needed. Most oral liquid nutritional supplements are meal replacement formulas, meaning their energy and nutrient composition mimics that of a meal; the volume of formula however depends on the individual's nutritional needs. Many of these products are available in several forms, typically regular (1 kcal/mL), high protein and high calorie (1.5–2.0 kcal/mL). They can be used to supplement total calories and protein for patients who are otherwise eating a variety of foods and/or can be considered total meal replacements for those who are unable to meet 100% of energy and nutrient needs without supplementation. Specialized liquid oral supplements marketed toward patients with diabetes or other health conditions are available, but consultation should be made with a RD prior to recommending these supplements.

Table 18.2 A list of common types tube feeding formulas

Company	Fiber-containing	Nonfiber containing	Calorically dense	Semi-elemental or elemental	For renal failure with need for electrolyte restriction	For gastric feeding or oral only—not intestinal	Low carbohydrate
Nestle[a]	Nutren with fiber, Replete with fiber	Nutren Replete Boost	Nutren 1.5, Nutren 2.0 Boost Plus Boost high protein	Peptamen	Renalcal Novasource renal	Boost, Boost Plus Carnation Instant Breakfast[a] Boost Pudding	Diabetisource AC
Abbott[b]	Jevity Promote with fiber	Osmolite Promote Ensure	Osmolite 1.5, Jevity 1.5, TwoCal HN, Nepro, Ensure Plus Ensure High Protein	Vital 1.5 Vivonex	Nepro	Ensure Ensure Plus Ensure Pudding	Glucerna
Other						Muscle Milk,[a] Scandishake	

[a] Contains lactose http://www.nestlehealthscience.us/products Accessed May 31, 2013

[b] http://abbottnutrition.com/categories/adult/adult-tube-feeding-products Accessed May 31, 2013

Homemade products such as milkshakes or double strength milk (mixing one quart of liquid milk with the amount of nonfat dry milk powder required to reconstitute a quart) may also be prepared by patients who are able to care themselves or have support systems. Home-made products that combine favorite foods and flavors are often preferred.

Enteral Nutrition

Enteral nutrition refers to feeding via a tube that delivers nutrients into the stomach or small intestine [18]. It is not needed for most individuals following surgical procedures of the oral cavity. However prior to or following extensive reconstructive procedures, head and neck cancer surgery (See Chapter 13) or surgery related to trauma, enteral nutrition may be indicated. If a prolonged recovery time is expected or there is preexisting malnutrition and it is anticipated that the surgical procedure itself will compromise the patient's ability to meet their energy and nutrient needs orally, placement of a feeding tube prior to or at the time of the surgery for enteral nutrition support merits consideration (see Figs. 18.8 and 18.9). Postoperatively, if it becomes apparent that safe oral intake will not occur for a prolonged period of time, a feeding tube is indicated to prevent malnutrition and meet energy needs for wound healing. Tube feedings can be administered to individuals in the hospital, another healthcare facility or at home. However, a coordinated interprofessional team approach is needed including the OHCP, RD, physician, and nurse to monitor the patient's well-being, tolerance and systemic, oral, and nutritional health.

Choosing the Route of Administration

Tube feedings can be administered into the stomach, duodenum, or jejunum [19]. Table 18.3 provides an overview of routes of delivery of feeding tubes. If the feeding tube is projected to be needed

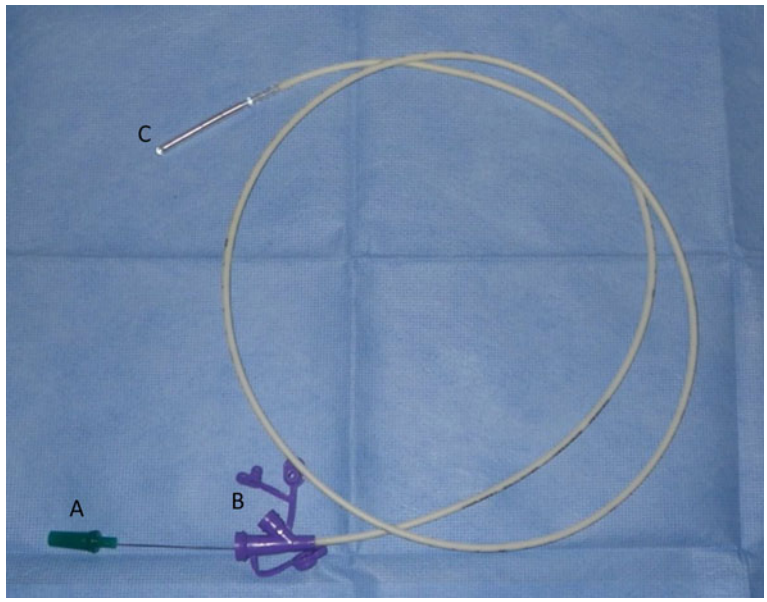

Fig. 18.9 Enteral feeding tube with metal stylet (*A*), ports (*B*), and radiopaque tip (*C*)

for less than 4 weeks, a nasally placed tube into the stomach is the primary choice (Fig. 18.10) [19]. For tubes that are needed longer term, a more permanent feeding access such as a percutaneous endoscopic gastrostomy (PEG) tube can be placed. PEGs may also be used for patients who have suffered a trauma or have another condition that does not allow access to the nose or oro-facial region for access. If intestinal access is needed for longer term, a surgically placed jejunostomy tube or PEG tube with a jejunal extension is used.

Table 18.3 Type of feeding tube, indications, length of time needed, possible methods of feeding [22, 24]

	Indications	<4 wks	>4 wks	Bolus/ intermittent	Gravity drip	Continuous (with pump)
Nasogastric	Functioning stomach, inability to take adequate oral diet	Yes	No	Yes	Yes	Yes
Gastrostomy		No	Yes	Yes	Yes	Yes
Nasojejunal	Gastroparesis, Obstruction, Pancreatitis, Intolerance of gastric feeding	Yes	No	No	Yes	Yes
Jejunostomy		No	Yes	No	Yes	Yes

Choosing the Tube Feeding Formula

Many enteral nutrition formulas are available on the market (see Table 18.2). They are broadly classified as polymeric (whole protein), semi-elemental (hydrolyzed proteins), and elemental (amino acids) [5, 20, 21]. These formulas are available in various concentrations from 1.0 to 2.0 cal/mL. The higher calorie, concentrated formulas are well suited for individuals on fluid-controlled diets such as patients with congestive heart failure or for those with high energy needs such as a trauma patient requiring oral and dental surgery. The semi-elemental and elemental types of enteral feedings are reserved for patients with malabsorption [22]. In addition there are tailored products such as those that are fiber enriched, disease-specific (e.g., diabetes), and immune-enhanced products [15]. Many of these specialized products lack scientifically sound evidence supporting their use over the standard polymeric formulas. An RD, OHCP, and physician should review available evidence and individual patients' needs when determining the appropriate formula.

Method of Administration

Enteral nutrition can be delivered through the feeding tube either continuously via a feeding pump or intermittently via bolus feeding depending on the route of feeding (see Table 18.3). Equipment necessary for continuous feeding can be expensive and insurance companies such as Medicare only cover these costs under certain conditions [23]. One of the conditions that necessitates a feeding pump is the need for a tube into the small intestine (see Table 18.3) [24]. For individuals fed into the stomach either via a nasogastric or gastrostomy feeding tube, a feeding pump allows for continuous administration of a controlled volume which can reduce the risk of feeling full or bloated. Patients who cannot tolerate large volumes of fluids at one time as evidenced by gastric distension, gastroesophageal reflux, vomiting, or intractable diarrhea also may benefit from using a feeding pump for continuous administration [22]. In order to minimize the amount of time the patient must be

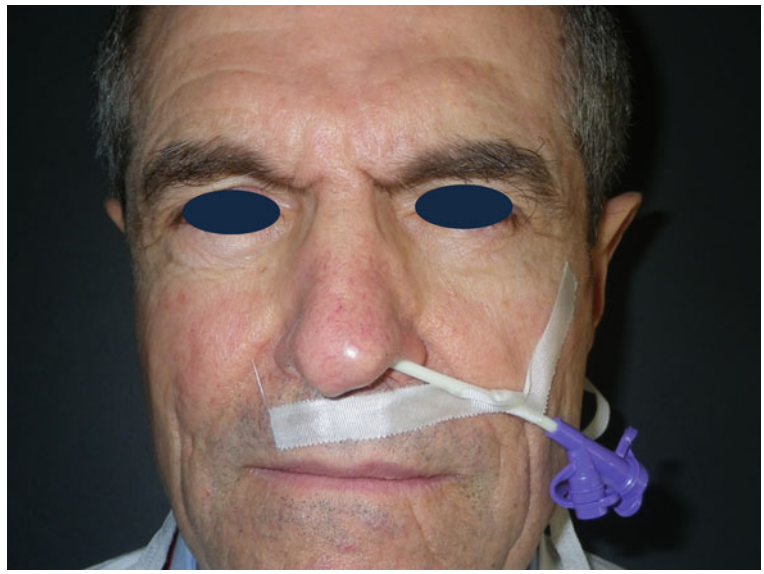

Fig. 18.10 Patient with nasogastric enteral feeding tube in place

connected to the feeding pump, clinicians generally calculate pump flow rates based on a portion of a 24 hours period.

Patients with a nasogastric or gastrostomy feeding tube who do not have access to or prefer to be not connected to pump and, can usually tolerate relatively large fluid intakes at one time, can use bolus (or intermittent) feedings. The amount of formula administered at each bolus feeding is based on individual energy and nutrient needs and tolerance. Provided the daily goal volume of tube feeding is met, patients who are awake and alert can decide when to administer their tube feeding. Some prefer to join their families during mealtime to keep the psychosocial nature of feeding intact, while others may vary this throughout the day [25]. A general recommendation is to use one 8 ounce can per feeding [24].

Regardless of the method of feeding administration, water flushes are important to avoid the tube from clogging and to adequately hydrate the patient [26]. Water flush volumes and frequency will depend on the patient's fluid needs and the amount of free water present in the tube feeding formula.

Monitoring Tolerance

Monitoring tube feeding tolerance requires an abdominal assessment that includes asking patients about nausea, vomiting, and bowel movements and assessing for presence of abdominal distention [16]. For patients fed into the stomach, the residual volume of the stomach is sometimes checked. A gastric residual volume of more than 250 mL may prompt the use of a pro-motility agent [27]. If the gastric residual volume is greater than 250 mL, it should be reported to the health professional monitoring tube feeding administration, typically the home health RD, nurse or the patient's physician [16].

Complications of Tube Feeding

Complications of tube feeding include nausea, vomiting, diarrhea, and clogged tubes. Tube occlusions may occur as a result of coagulation of the protein in the tube feeding or by medications. They can be prevented by regular flushing with water [20]. Diarrhea may triggered by a variety of causes: hyperosmolar or sorbitol containing medications (including liquid acetaminophen) [24, 28], *Clostridium difficile* infection, other infections, bacterial overgrowth, pancreatic insufficiency, or other GI causes of malabsorption [16]. The cause of the diarrhea must be determined. Once other causes have been ruled out, switching to a fiber-containing formula or initiating pharmacologic management of the diarrhea may be done. Conversely, constipation may occur. Treatment approaches to reduce constipation include adequate hydration, physical activity, if possible, stool softeners and/or laxatives. Once poor bowel motility has been ruled out as the cause of constipation, adding fiber as a modular (such as Benefiber) or switching to a fiber-containing formula may be helpful in improving bowel regularity [29].

Nausea and vomiting may be caused by too rapid infusion of tube feeding, bowel obstruction, constipation, slow GI motility due to side effects of pain medications, or other causes. Initially, tube feeding should be held and the potential for bowel obstruction was addressed. If constipation and slow GI motility are potential causes, the patient may benefit from stool softeners, laxatives, and/or pro-kinetic agents. Reducing the rate of tube feeding infusion temporarily and/or changing to a more calorically dense formula (see Table 18.2) may help improve tolerance.

Summary

Interactions between diet, nutrition, and oral surgery are multidirectional as they impact each other on several levels depending on the nature and extent of the oral and maxillofacial surgery, presence of other comorbid conditions and preexisting nutritional status of the patient. Proper diet is paramount for wound healing, as energy, protein, and other macro and micronutrients each play a critical role. Nutritional support can be used when patients cannot consume adequate energy or macronutrients via diet alone. When nutrition support is indicated, OHCPs working in collaboration with RDs and other health professionals can optimize patient care.

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Part V
Nutrition and Oral Medicine: Education and Practice

Chapter 19
Approaches to Oral Nutrition Health Risk Screening and Assessment

Riva Touger-Decker

Keypoints

- The primary aim of nutrition risk screening is to identify patients who are or may be at nutrition risk and in need of diet intervention by an OHCP and/or referral to an RD or other health professional for further assessment and intervention
- Health and nutrition risk screening in the dental setting includes a combination of subjective questions relative to diet, oral health status, biting and chewing ability, and body weight history as well as objective assessment of height, weight, and the condition of the oral cavity
- Determination of nutrition risk depends on the extent and number of non-normal responses to risk factor items for subjective questions, oral screening exams, anthropometric measures, and specific disease-related risk factors

Keywords Diet intervention · Nutrition risk screening · Risk determination · Oral screening exams

Introduction

The synergistic relationships between diet/nutrition and oral and systemic health support the need for health and nutrition risk screening as a routine part of dental care [1–4]. Nutrition and oral health can have a significant impact on general health [1, 2, 5–8]. Compromised diet intake can lead to decreased intake of essential nutrients and subsequent malnutrition, which increases the risk for systemic and oral diseases. Screening is the first step in disease risk detection, prevention, and management. Figure 19.1 includes definitions relative to screening and assessment of nutrition status. The primary focus of this chapter is to describe approaches to oral nutrition and diet risk evaluation for the oral health care professional (OHCP) and dental students. For the purposes of the screening processes discussed herein, all references to the OHCP include dental and as appropriate dental hygiene students. Approaches for the dietetics professional are also addressed and noted where appropriate.

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Malnutrition
"an acute, sub acute or chronic state of nutrition… with or without inflammatory activity have led to a change in body composition and diminished function" (35).

Medical nutrition therapy
Medical nutrition therapy refers to care provided by a registered dietitian that includes performance of a comprehensive nutrition assessment including determination of nutrition diagnosis(es), planning and provision of diet and nutrition care based on evidence-based guidelines and monitoring and evaluation of the client/patient's response to treatment and nutrition status (http://www.eatright.org/healthprofessionals/content.aspx?id=6877#.UQlFOeiNvfc).

Nutrition Screening
"A process to identify an individual who is malnourished or who is at risk for malnutrition to determine if a detailed nutrition assessment is indicated" (35)

Nutrition focused physical exam
"Measurement of vital signs and body composition, inspection for clinical manifestations of nutrient deficiencies, and abdominal, dermatologic, head, neck, oral cavity & cranial nerve screening" (34)

Screening
Defined first in 1957 by the U.S. Commission on Chronic Illness, it is "identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly"(1957) (36). In 1998, a U.K. Commission defined it as "the systematic application of test or inquiry to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventive action among persons who have not sought medical attention on account of symptoms of that disorder" (NSC 1998) (37).

Fig. 19.1 Definitions

The nature and extent of associations and relationships between nutrition, oral and systemic health have expanded; approaches to systemic health screening have been identified for OHCPs [9–14]. Several of these screening approaches include nutrition and diet parameters. Likewise strategies for nutrition risk and diet screening have been described for dental practices. For health and nutrition risk screening, the outcomes include identification of risk for disease, malnutrition, or presence of dietary factors associated with disease. Following screening, the OHCP can determine risk, oral or dental diagnosis(es) requiring intervention and provide appropriate baseline nutrition education and referral to other healthcare professionals for further assessment and management as indicated.

Global Goals for Oral Health 2020 proposed by representatives of Foreign Direct Investment (FDI), the World Health Organization (WHO), and the International Association of Dental Research (IADR) [8] and the 2012 American Dental Association (ADA) "Call to Action for Oral Health" [15] support expansion of the OHCP's role in health screening to improve oral, systemic and nutritional well-being. The oral-systemic-nutrition health risk screening, basic intervention, and referral processes can be used to detect risk for malnutrition and nutrition related oral health risk factors requiring diet/nutrition education and or referral to a registered dietitian (RD) (Fig. 19.1). The goal of nutrition and health risk screening is early detection and intervention to reduce the incidence and severity of nutrition risk and maximize response to treatment. The screen can be completed at the patient's initial and periodic reassessment appointments, taking less than 10 minutes. The amount of time that may be saved secondary to screening and subsequent care or referral, is not quantifiable. The outcomes of health and nutrition risk screening provide the OHCP with indication of weight status, food and nutrition access problems, dietary factors influencing oral health, oral integrity problems influencing diet intake, and any factors related to diet or nutrition that indicate risk for malnutrition or related chronic diseases (if such risk factors are assessed). The next steps to be taken should be based on individual needs. This may include diet assessment and education by the OHCP, referrals to social services for food and supplement resources in the community, a physician referral for systemic health issues or referral to a registered dietitian (RD) for medical nutrition therapy (MNT) (see Fig. 19.1 for definitions).

Table 19.1 describes possible risk factors associated with compromised nutrition and oral health for both OHCPs and RDs. This list is not all inclusive. The risk screen for OHCPs and RDs differs primarily in focus; nutrition first versus oral health first; however, the outcomes and goals should be similar. Possible interventions may include referral to the appropriate provider, either the RD or OHCP, the provision of baseline education, and a plan for future follow-up.

Determining Nutrition Risk: The Role of the Oral Health Care Professional

The primary aim of a nutrition risk screening tool is to identify patients who are at or may be at nutrition risk and in need of referral to a RD or other health professional for further assessment and intervention. Figure 19.2 is a sample of an oral health and nutrition risk screening tool used in an urban, northeastern U.S. dental school's adult clinics. The parameters included on this tool were derived from a 2004 study by Radler in the dental clinic [16].

Health and nutrition risk screening in the dental setting includes subjective questions (Table 19.2) relative to diet, oral health status, biting and chewing ability, and body weight history as well as objective assessment of height, weight, and the condition of the oral cavity. The extent to which these questions as well as laboratory data and other assessment components are used depends, in part, on the type of dental practice and the overall health and disease history of the patient. Practices that include diabetes screening may include a finger stick Hemoglobin A1C or use approaches previously validated in the dental literature [11, 12]. Patients with complex medical histories and/or who take multiple medications or dietary supplements may require more extensive physical and laboratory screening approaches and the OHCP may wish to use all of the questions in Table 19.2.

Nutrition risk factors are defined as "characteristics that are associated with an increased likelihood of poor nutritional status" [17]. Risk for malnutrition is based on the type and extent of risk factors present [18]. The elderly patient who lives alone, has lost more than 10 pounds in 6 months and has difficulty chewing is at risk for weight loss and malnutrition, as is the 35-year-old woman who presents with an unintentional 10 pound weight loss and candidiasis, complains of burning mouth, and on appropriate testing has a 2 hours post prandial blood glucose of 180 mg/dl.

History

The patient history reveals information about acute, chronic, and terminal diseases that may impact oral and nutritional well-being. In addition to asking patients about their medical, surgical, and drug history, diet and nutrition history questions may also be asked as outlined in Table 19.2.

Unintentional weight change may signal potential nutrition deficits, lack of money for food, or evidence of systemic disease. Weight screening is an inexpensive, noninvasive, rapid health risk assessment measure. Weight loss is characterized by loss of body-fat stores and lean body mass. Patients should be weighed during initial visits and subsequent checkups. The initial-visit weight provides a baseline for comparison for future reference. Although the weight history will be based on self-report, it is valuable to establish an objective 'first visit' weight as a basis for comparison on future visits. Weight change is typically associated with either a change in eating habits or evidence of a possible systemic disease. Eating habit changes may be intentional with a goal of weight loss or gain or caused by oral or systemic health issues influencing appetite or functional ability to eat. In either case, the result is a change in nutrient intake. Percent weight change can be calculated using actual and usual weight (Table 19.3). OHCPs should question patients as to whether the weight

Table 19.1 Medical and physical risk factors for compromised nutritional and oral health status

Alterations in taste
Autoimmune disorders
Cardiovascular disease
Craniofacial anomalies
Cranial nerve dysfunction
Crohns disease
Deficiencies of vitamins, minerals, trace elements
Dental procedures altering ability to eat a usual diet
Developmental disorders
Diabetes
Disorders of taste and smell
Eating disorders
Early childhood caries
End-stage renal disease
Erosion
Extensive dental caries
Fad dieting/nutrition quackery
Gastroesophageal reflux disease
Hypertension
Immunocompromising conditions (e.g., cancer, HIV infection, AIDS)
Infectious diseases
Multiple sclerosis
Musculoskeletal disorders
Neoplastic disease
Physical/mental handicaps
Polypharmacy
Poor dentition/edentulism
Poverty
Protein-energy malnutrition/wasting
Spinal cord injury
Radiation therapy
Salivary dysfunction
Substance abuse (alcohol and/or drugs)
Transplant surgery
Ulcerations/lesions
Unhealthy body weight
Unintentional weight loss
Vesiculobullous diseases
Xerostomia

change was intentional or unintentional. An unintentional weight loss of 5% or more in 3 months or less or of 10% or more in 6 months or less indicates risk for malnutrition. Body mass index (BMI) represents body weight in proportion to height; weight classifications based on BMI are underweight, normal, overweight, obesity (class I or II) and extreme obesity (class III). A BMI below 18.5 reflects underweight, 18.8–24.99 reflects normal weight; 25–29.99 represents overweight and a BMI value of 30 or greater indicates obesity. BMI is used to identify chronic disease and mortality risk due to overweight and or obesity in adults; an online BMI calculator is available at "www.nhlbisupport.com/bmi/bmi-m.htm". It should be interpreted with caution since it does not measure body fat distribution or variation in fatness due to race, age or fitness level. Once measurements are completed, OHCPs may wish to use one of several web-based programs available to calculate

Rutgers School of Dental Medicine Diet and Nutrition Risk Evaluation

Directions: Complete the questions below. ***Any*** ' Yes' answers to the questions below indicate that diet intervention (D1310)should be added to the patient's treatment plan. Also consider the patient's age, past medical history and dental/oral treatment plan in determining level of nutrition risk and need for diet intervention.

	YES	NO
1. Height: _____ Weight: _____ Body Mass Index (BMI): _____ Has there been an unintentional weight change (gain or loss, circle one) of =>10% in the past 6 months?		
2. Does the patient report having or present with an eating disorder? Anorexia Bulimia (circle one)		
3. Does the patient have any untreated smooth surface or interproximal lesions? (circle one or both)		
4. Does the patient have one or more RPDs? Mandibular or Maxillary (circle one or both)		
5. Does the patient have a full denture? Mandibular or Maxillary (circle one or both)		
6. If the patient has a denture, is it removed when eating?		
7. Does the patient report difficulty or pain in tasting, biting, chewing or swallowing foods? (circle all that apply)		
8. Does the patient have periodontal disease, soft tissue lesions or oral infections that interfere with eating? (e.g. ulcers, angular cheilitis, candidiasis)		
9. Does the patient consume sugar - containing drinks (soda, iced tea, juice, sports drinks/gels), gum or candy > 4 times a day?		
10. Does the patient consume sugar - containing drinks (soda, iced tea, juice, sports drinks/gels), gum or candy between meals?		
11. Does the patient consume < 3 servings of milk, yogurt, or cheese daily?		
12. Does the patient take any vitamin, mineral, herbal or other dietary supplements? If yes, list type(s) and dosage:		

Fig. 19.2 Sample dental school clinic nutrition risk screening tool

weight change and BMI [19] (http://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm, http://www.cdc.gov/healthyweight/assessing/bmi/). Equations for calculating and interpreting anthropometric data are in Table 19.3.

Medical History

The medical history reveals information about acute or chronic diseases that are risk factors for individuals with concurrent oral or dental problems that affect their ability to consume their usual diet. The medical history, when combined with questions noted in Table 19.2 provides the OHCP with insights into disease control and the need for diet intervention. This intervention, if focused solely on dietary strategies as a result of masticatory or soft tissue problems, can be done by the OHCP. Patients who need more in-depth nutrition assessment and diet counseling related to their systemic disease should be referred to an RD for medical nutrition therapy (MNT). Diabetes is associated with oral manifestations.

These manifestations vary and may include periodontal disease, dysgeusia, increased caries risk, candidiasis, burning tongue, xerostomia, and poor wound healing which may in turn impact appetite, eating ability, and, finally, oral intake [10, 20]. Neuropathies and opportunistic microbial infections in the oral cavity affect oral health, nutrition status, and inevitably diabetes control. Chapter 11 provides further information on screening, risk factors and management of patients presenting with risk for diabetes or with a diagnosis of diabetes.

Table 19.2 Nutrition risk questions to ask patients about common symptoms/conditions

Weight

- Has your weight changed at all in the past 6 months?
  - If yes, how?
  - If weight loss, was it intentional?
  - If weight loss was intentional, what type of diet were you following and for how long?
  - If weight gain, what are possible reasons you can attribute to weight gain?
- Do your clothes fit differently now than they did 6 months ago (1 clothing size = ~10 lbs.)?

Diabetes

- How do you manage your diabetes in terms of any special diet, medications, monitoring?
- If you take insulin, what is the type, quantity, and dose schedule?
- Do you follow any special diet?

Hyposalivation / Xerostomia

- Do you have any difficulty chewing or swallowing?
  - If yes, with liquids, thin or thick solids, semisolids, or both?
    - Has this difficulty been progressive: in degree of difficulty and types of foods?
    - Is swallowing painful? If yes, when? Can you eat a meal or snack without needing liquids?
  - If no, how many cups of liquids do you need to consume?
    - Have there been any changes in your medications or nutrient/herbal supplement use? If yes, describe changes.

Taste

- Describe any changes in taste that have occurred; what types of food, beverage?
- Has medication (Rx or OTC) changed at all during this time?
- Is your sense of taste different or missing or does everything taste bad/metallic? How does it taste?
- Do you have any difficulties chewing or swallowing food?
  - If yes, what?
  - Do you take any vitamin, mineral, herbal, or other nutrition supplements?
  - If yes, what, how much, what form, what frequency?
  - Do you follow any special diet?

Activities of daily living

- Do you do your own food shopping and preparation?
- If no, what help do you have/need?
- Do you ever run out of money for food during the month?

Oral function risk factors

- Do you have any difficulty opening your mouth, biting, chewing, or swallowing foods or fluids (swallowing)?
  - If yes, detail what foods/fluids cause difficulty and how.
- How often during the day do you eat, including meals and snacks?
- How many times a day do you drink sweetened coffees, teas, soda, juices, or other sweet beverages?
- When in the course of the day do you brush your teeth?

Questions to ask about osteoporosis risk

- How many servings of dairy products do you have on a typical day? (1 serving = 1 oz. cheese or 1 c yogurt or milk)
- Do you take a calcium and/or vitamin D supplement?
  - If yes, what is the name and how much do you take in 1 day?
- Do you get any physical activity or exercise in the course of a day or week?
  - If yes, how many times a week and for how long?
- If a woman, are you peri- or postmenopausal?
- Have you or a first-degree relative broken one or more bones?

Table 19.3 Formulas for weight and body mass index and other anthropometric calculations

Wt change is calculated based on usual body wt:
$\frac{\text{today's wt}}{\text{usual wt}} \times 100 = \%$ weight change
Current (today's) wt < usual wt = negative wt change
Current (today's) wt > usual wt = positive wt change
Ranges of desirable height and weight for adults: rule of thumb
Men = 106 ilbs for the first 5 ft + 6 lbs/in
Ex: 5′6″ man = 106 + (6 inches × 6 lbs/in) = 106 + 36 = 142 lbs ± 10% desirable wt
Women = 100 lbs for the first 5 ft + 6 lbs/in
Ex: 5′2″ woman = 100 + (2 inches × 5 lbs/in) = 100 +10 = 110 lbs ± 10% desirable wt
Note: ±10% = based on frame size; weight range may be 10% greater or less than the calculated wt
Body mass index
Body wt in kilograms (kg) (height in meters)^2 or Wt (in lbs) × 703 divided by (height in inches)^2
If patient does not know his usual weight, desirable weight can be used to calculate % desirable weight. This will also give an indication of body stores. Weight alone does not differentiate between body fat versus muscle mass

Autoimmune diseases such as pemphigus vulgaris increase nutrition risk by virtue of the oral and systemic sequellae of the disease and the medications used to manage the disease [1, 2]. Inflammatory arthritides have associated medication side effects, and joint pain or mechanical limitations may compromise eating ability. Steroid medications often used to manage these diseases increase risk of diabetes and nitrogen (protein) and calcium losses, thus increasing protein and calcium needs. The xerostomia associated with Sjögren's syndrome increases risk for dental caries, periodontitis, and oral mucosal injury or pain, which may make eating difficult or painful. Temporomandibular joint pain may result in limited opening of the mouth and compromised masticatory ability. Chapter 15 on autoimmune disorders provides further information on detection, systemic and nutritional issues and management.

Head and neck and oral cancers affect nutrition and oral health status. Surgery to remove tumors in the oral cavity may have severe functional effects on eating ability. Radiation to the oral cavity can destroy taste as well as the quality and quantity of saliva. Chemotherapy can cause anorexia, stomatitis, nausea, and vomiting, ultimately compromising nutrition status [21]. Chapters 12 and 13 provide further information on screening, risk factors and management.

Individuals with HIV infection or acquired immunodeficiency syndrome (AIDS) are at increased risk of oral infections and disease manifestations that alter functional and sensory functions of the oral cavity. Oral complications and malnutrition may occur secondary to the disease process and associated gastrointestinal, metabolic, immune, pharmacological, and psychosocial sequellae. Altered micronutrient metabolism may contribute to oral manifestations and subsequent malnutrition, further compromising oral integrity and the ability to combat infections. A referral to an RD for MNT is routine in this population. Chapter 14 provides further information on screening, risk factors, and management.

Medications

Patients should be carefully questioned about use of prescription and over the counter (OTC) drugs, as well as use of herbs, minerals, vitamins, and other dietary supplements. Select medications, both prescription and OTC can affect gingival tissue, saliva and oral integrity. It is up to the provider to review the potential drug–drug, drug–nutrient, and drug–symptom interactions with patients and

Component	Nutrition risk symptoms	Nutrient implications
Face	Malar pigmentation (dark skin over cheeks and under eyes)	Niacin, B vitamins, riboflavin, vitamin B_6
	Bitemporal wasting	Protein deficiency
	Pale	Inadequate iron
Lips	Cheilosis (red/swelling)	Inadequate niacin, riboflavin
	Angular fissures	Inadequate niacin, vitamin B_6, riboflavin, iron
Gingiva	Spongy, bleeding, abnormal redness	Inadequate vitamin C
Tongue	a. Glossitis (red, raw, fissured)	Inadequate folate, niacin, riboflavin, iron, zinc vitamins B_6 and B_{12}
	b. Pale, atrophic, smooth/slick (filiform papillary atrophy)	
	c. Magenta color	

Fig. 19.3 Identification of nutrient deficits in the oral cavity

guide them appropriately. Chapter 6 addresses the challenges and approaches to detection and management of drug, diet, and nutrition interactions. As part of any patient screen or assessment, the potential role of drugs, over the counter (OTC) or prescription, and or interactions within and between agents in both these categories in causing the findings merit consideration.

Dietary Supplements

Chapter 9 in this text is dedicated to this topic. Select dietary supplements in oral, tablet, suspension or powder form may alter the integrity of the oral cavity, interfere with action of prescription or OTC medications, and/or alter response to a select therapy. Supplements impacting the immune system, such as Echinacea, may interfere with the actions of immunosuppressing medications secondary to its immune enhancing effects. Part of a routine history and even follow-up appointments should include questions about use of dietary supplements, form, dosage, and frequency.

Oral Exam Findings

Although the oral exam is a routine component of the initial workup in the dental office, the focus of this section is consideration of the diet and nutrition implications of the exam findings. Figure 19.3 addresses nutrient specific implications of non-normal oral findings whereas Table 19.4 provides the OHCP and RD with recommended diet and nutrition strategies based on the oral physical exam findings. As part of the OHCP's comprehensive oral exam, they may detect non-normal findings or symptoms relative to diet and nutrition such as edentulism, inability to fully open the mouth or hyposalivation, all of which may compromise the patient's ability to consume foods. In such instances, questions about the client/patient's ability to consume foods and fluids should be asked

Table 19.4 Functional oral nutrition risk evaluation

Structure	Finding	Management
Lips	Dryness; sensation; cracking or fissuring, swelling; history of blisters or ulcers	Alter diet texture and consistency
	Angular Cheilitis	Screen for etiology (diabetes, drooling, B vitamin deficiency, dehydration)
Gingiva and oral mucosa	Soreness/pain; bleeding spontaneously, change in appearance; swelling, growths, discharge; bad taste; halitosis	Alter diet texture, temperature, and consistency
	Red or white patches/lesions; erosion/ulceration; focal pigmentation; erythema	Adjust diet texture and consistency; evaluate for nutrient deficiencies; screen for oral cancer
Teeth	Toothache/pain; looseness and mobility; dental prosthesis (removable or fixed); edentulism	Adjust diet, consistency; evaluate caries risk and diet adequacy—ability to bite, chew, swallow
Tongue	Soreness/pain; burning; rough patches; dryness; cracking or fissuring; growths; changes in taste; ulcers	Alter diet texture; screen for anemias, systemic disease; evaluate for nutrient deficiencies
Temporomandibular joint muscles of mastication	Difficulty or painful mouth opening; grinding sounds on joint opening, biting or chewing difficulty or pain, range of motion difficulty	Alter diet consistency, food 'hardness' and limit 'chewy foods'; Evaluate cranial nerve function
Salivary glands	Mucosal dryness; too little or too much saliva; drooling; change in color, consistency, difficulty swallowing dry food, altered taste, dry eyes; gland pain or swelling	Increase fluids (if dry mouth); limit spices, "hard" foods; review changes in medications; evaluate for dysgeusia, dysphagia; evaluate zinc status and blood sugar, minimize dietary caries risk

For each section, ask about patient complaints, duration of symptoms, and any changes in appearance, size, acuity, frequency, and pain

(see Table 19.2). Use of educational materials such as those Appendices 2 A–G are guidelines for diet modifications to meet functional challenges; patients/clients who cannot meet their nutritional needs with their usual diet due to oral dysfunction should be referred to an RD for more comprehensive MNT. In contrast, the RD detecting non-normal oral findings should provide the patient with interventions aimed at increasing their ability to consume a normal diet but refer the patient to the appropriate OHCP.

Patients with biting, chewing, or swallowing difficulties may be at nutrition risk depending on the presence of other risk factors and duration and severity of the problem. Simple guidelines on modification of food form and consistency may be adequate for individuals without other nutrition risk factors. Denture wearers or individuals who will be getting dentures for the first time need education on diet modification during the initial fitting and adjustment phases. However, if other risk factors or comorbid conditions such as diabetes or end stage renal/liver disease are present, individualized counseling may be indicated. The sample tool in Fig. 19.4 includes questions related to diet and caries risk that the OHCP may include in their caries risk assessment processes. The results of these questions provide insight into eating habits that may impact caries risk. Individuals with soft-tissue lesions, oral pathologies, orofacial pain or disorders that interfere with the ability to eat, or exam findings suggestive of nutrition deficits should be referred to an RD for MNT.

Eating Disorders

The OHCP may be the first health professional to note physical signs of eating disorders, most notably with bulimia, thus have a distinct role in detecting eating disorders. As the health professional who routinely assesses the head, neck, and oral cavity, the OHCP can detect bitemporal

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Note: This is to be completed by student doctors on patients who are treatment planned for diet intervention relative to oral health.Please be sure to explain the purpose of this diet assessment to the patient ***prior*** to any questions.

Patient Name: _____ Chart # _____ Date: _____

Complete the following based on your clinical exam and information from patient's chart:

1. Patient's current weight _____ Weight 6 months ago _____ % change _____

If % weight change greater than 10%, was the weight change unintentional? _____No _____ Yes

Height____BMI_____BMI Category: (Circle one: Underweight, Normal Weight, Overweight, Obese)

Significant medical history: _____

Medications: _____

Oral health: Caries risk category: LOW MODERATE HIGH

Soft tissue pathology: _____

Other dental pathology that may affect ability to eat: _____

Current prosthesis _____No _____ Yes

If Yes, what _____ Does patient use when eating? _____No _____ Yes

Prosthesis planned _____No _____ YesIf Yes, circle type: Full denture(s), RPD(s), Implant(s); & location: maxilla, mandible

Complete the following during your interview with the patient:

2. Are you on a special diet? _____ No _____ Yes
   If Yes, What type(s) of diet do you follow? _____
3. Do you take any vitamin, mineral, herbal or dietary supplements? _____ No _____ Yes
   If Yes, what type(s), how much, and how often do you take each

_____

_____

4. What food restrictions or allergies do you have? _____

_____

5. Do you avoid any foods / beverages because of the condition of your mouth (missing teeth, dentures, mouth sores)? _____ No _____ Yes If Yes, what _____

6. How many times a day do you eat (including meals and snacks)? _____

7. How many times a day do you drink the following between meals or with snacks:
   Sugar sweetened beverage (eg: tea, coffee, iced tea, fruit drink, juice, soda) _____ Diet soda _____

8. How many times a day do you chew regular gum or eat candy (including breath mints, hard candy)? _____

9. How often and when do you brush your teeth? _____

10. Please tell me everything you eat and drink on a typical day. If yesterday was typical you can tell me everything you had yesterday, beginning from when you get up; please be sure to include all meals, snacks, and beverages, and all portion sizes. This will help me evaluate your eating patterns and make recommendations for your oral and overall health. Please tell me approximate amounts and methods of preparation.

After completing the diet recall, ask when the patient does any oral hygiene so you can identify when the patient has exposure to fermentable carbohydrates during the day.

Example: *7am: 1 cup coffee, black with 1 packet sugar*

10am: 12 ounces OJ, 1 large bagel (4 inches in diameter) with 2 tsp cream cheese

Diet Recall:

Fig. 19.4 Sample diet recall and evaluation form for OHCPs

ASSESSMENT:

11. Assess the patient's diet using https://www.choosemyplate.gov/SuperTracker/default.aspx.

View 'Daily Food Group Targets' and then complete the following:

Daily Food Group Targets					
	Grains	Vegetables	Fruits	Dairy	Protein Foods
Target					
Eaten					
Status					
Daily Limits					
Total Calories Eaten:	Empty Calories Eaten:		Empty Calorie Limit:	Total Calorie Limit:	

DIET AND ORAL HEALTH EDUCATION NEEDS:

12. If applicable, determine the fermentable carbohydrate exposures the patient has without any preventive intervention. For each exposure, indicate a corrective action. Determine your diet education priorities, especially as it related to oral health.

Example

Exposure	*Recommended Intervention*
7am 1 cup oatmeal and 1 banana	*brush after breakfast*

Exposure	**Recommended Intervention**
1.	
2.	
3.	
4.	
5.	

Based on the diet evaluation and patient's eating habits, what are your recommendations for food group modification? (be sure to individualize to the patient preferences and lifestyle). Integrate caries risk reduction strategies and diet recommendations where possible. *For example, patient consumes excessive carbohydrate from fruit punch at dinner, and patient's diet lacks dairy foods. Suggest patient consume 8 ounces lowfat milk at dinner instead of fruit punch.*

1. _____
2. _____
3. _____
4. _____

Help patient determine measurable goals, based on your counseling session, that he/she thinks are achievable by the follow-up appointment.

Indicate date for follow-up appointment (if needed): _____

1. _____
2. _____
3. _____
4. _____

Is referral to an RD needed? ____No ____ Yes: indicate rationale and state referral procedure:

_____

Fig. 19.4 continued

wasting, thinning hair, and boney prominences that are symptomatic of anorexia nervosa as well as swelling of the salivary glands, redness in the back of the throat, lingual erosion, and symptoms of frequent regurgitation, which are common in bulimia [22, 23]. Approaches to teaching dental students about eating disorders have been tested with dental student populations in the U.S. [24] and Europe [25] in an effort to increase screening by OHCPs in clinical practice. Several validated screening tools exist, including the validated SCOFF questionnaire [27]. The U.S. version of this tool includes five simple questions: "Do you make yourself vomit because you feel uncomfortably full? Do you worry you have lost control over how much you eat? Have you recently lost more than 15 pounds in a 3-month period? Do you believe that you are fat when others say you are too thin? Would you say that food dominates your life?" [28]. If patient indicates "yes" to two or more questions then according to the tool they have an eating disorder and merit further evaluation and management for the eating disorder. Hague [26] provides approaches for the OHCP to use in screening for and referring patients with eating disorders for care. Oral manifestations for these disorders are grouped into three distinct categories, oral, systemic, and psychosocial [26] addressing the systemic nature of these disorders.

Osteoporosis

Osteoporosis is increasingly common in women (one in two women) and men (one in eight men) [29]. Associations between osteoporosis and oral health have been documented [30], particularly in reference to periodontal disease and implant surgery. Chapter 16 provides a detailed insight into oral and nutrition health and osteoporosis.

Dietary Habits

There are several approaches to diet assessment including dietary recalls, food frequency questionnaires, and food diaries. As G. Beaton wrote in 1994, "dietary intake cannot now be estimated without error, it never will be" [31, p. 259S]. He also stated "the nature and the magnitude of the error depends on both the data collection methodology and the subjects being studied" [31, p. 259S]. Amongst all the methods, the potential for over and underreporting exists resulting in error. The choice in method depends on the desired outcomes. In oral health care, the ideal dietary assessment strategy is one that includes a snapshot of the patient/client's typical eating patterns, frequency of eating, and one to two 24-hours recalls of typical foods and beverages consumed. A 24-hours recall, or recall of a typical day's diet starts with asking a patient to recall everything he or she had to eat and drink on a previous or typical day and recording approximate times, specific foods, and portion sizes. It refers to a recall of the prior 24 hours so if the preceding day weren't a 'typical' day then it may not be a true picture of the person's intake. A more comprehensive approach would be to include a typical weekday and weekend day recall. Figure 19.4 includes a sample dietary recall tool with instructions on how to guide the patient to provide the recall. Using nonleading questions such as "tell me everything you had to eat yesterday "instead of leading questions "what did you have for breakfast yesterday" helps to achieve more honest responses. The dietary recall is combined with asking questions about food group intake when these may not be mentioned in the recall. For example, if the patient doesn't mention any dairy products in their recall, one may ask "you didn't mention dairy products, do you ever have any milk, yogurt or cheese in the course of a day?". The same line of questioning may be repeated for the other food groups. In the USA, this would include fruits, vegetables, protein foods, dairy products, and added fats, sugars and oils. The U.S. Department of Agriculture's multiple-pass dietary recall approach (http://www.ars.usda.gov/is/ar/archive/jun04/recall0604.htm) has been shown to help provide a comprehensive view of dietary patterns,

nutritional adequacy, and factors influencing food and fluid intake. It is assumed that the RD will approach this section of patient assessment in a more detailed manner than the OHCP and provide more targeted nutrition and diet recommendations. However, it is incumbent on the OHCP to ask questions regarding oral function and diet as well as specific questions about diet intake and provide dietary guidelines in light of the patient's oral problems and planned treatment and refer patients accordingly to an RD.

The dietary intake information obtained via a dietary recall can be analyzed in one of two ways. For a general assessment of dietary adequacy, the foods and fluids consumed can be analyzed for calories, food group distribution and nutrients using the U.S. http://www.choosemyplate.gov/. Those outside the USA should consult programs available and dietary guidelines of their respective countries. Choosemyplate.gov provides an efficient and accurate (based on the U.S. Department of Agriculture's nutrient analysis database) approach to dietary analysis of calories and nutrients based on the individual's gender, age, and body size. Alternatively, the provider looking for a more comprehensive assessment of intake can do a nutrient analysis using these same tools to obtain calories, macro and micronutrient intake and the comparison of actual to recommended intakes of nutrients. Accuracy and attention to detail in the input of data is crucial for quality results.

The outcome of the dietary recall provides the OHCP with the information needed to assess diet related caries risk as well as food group distribution, total energy intake and nutrient intake. Depending on the extent of the food group and or nutrient analysis completed, the outcome could be a comparison of the 24 hours recall to the food group recommendations of the USDA with tailored suggestions to the patient on modifications to meet needs. As relevant the recall assessment may address the number of cariogenic exposures in the recall along with individualized suggestions on how to modify the diet (See Appendix 3E). Those who do a nutrient analysis using one of the programs identified above will have a comparison of the patient's energy and nutrient intake to federal recommendations so they can tailor suggestions to help patients meet their nutrient needs.

Food diaries are similar to a dietary recall but are completed independently by the patient for several days (typically 3–5) and then returned to the provider. Food diaries are more subject to reporting error than the dietary recall as patients may forget to complete them throughout the day. Individuals are typically asked to write down everything they have to eat and drink including timing and location and portion sizes over the course of several days. In research settings when a diary is used, the study team often calls the patient daily to review the diary to help ensure completeness of their recording. Analysis is done similarly to the recall but total intakes are then divided by the number of days of diary keeping to arrive at mean intakes for selected food groups or nutrients. Given the time required for daily follow-up with patients and the greater number of days for analyses, diaries are not very practical for the clinical setting.

Food frequency questionnaires (FFQ) are typically a list of foods and beverages arranged by food group with options for selecting from a few portion sizes and frequency of consumption (typically daily, weekly, monthly, or less than monthly); they do not include when foods are eaten, meals or snack breakdown or meal patterns. FFQs are designed for cross-sectional epidemiological studies wherein researchers want to collect data on specific food items or nutrients consumed. Their use in the clinical setting is limited by the type of data they provide. FFQ forms tend to have a nutrient analysis program designed for each specific form.

Final Steps for the Oral Health Care Professional

Once the OHCP has completed the health and nutrition screen, the determination of nutrition and oral health risk and needs for intervention must occur. Determination of risk depends on the extent and number of non-normal responses to risk factor items for subjective questions, oral screening exams, anthropometric measures, and specific disease-related risk factors. Figure 19.2 provides a

screening tool used with an adult dental clinic population; any positive response reflects risk and need for further evaluation by the OHCP. Findings should be reviewed with the patient and appropriate intervention and education along with any necessary recommendations for referrals should be discussed. Risk assessment is not a diagnostic tool; it provides the OHCP with an assessment of oral/dental factors that indicate the need for diet modifications and or referral to an RD for further assessment, diagnosis and management.

Determining Oral Health Nutrition Risk: The Role of the RD

Nutrition focused physical exam (NPFE) including the oral screen by the RD is a part of the nutrition assessment process. In the USA, the Academy of Nutrition and Dietetics, *Standards of Professional Performance and the Standards of Practice for Dietetics Practice* [32] indicate that RDs in clinical practice use the International Dietetics and Nutrition Terminology [33] which include nutrition diagnostic terms related to oral health conditions. The RD can distinguish between normal and non-normal oral conditions but cannot diagnose dental or medical conditions [34]. For example, they may note a patient is edentulous, has no anterior occlusion and has a white coating on their tongue; they cannot diagnose what may be candida but can provide the patient with MNT to help them achieve a balanced diet and refer them to an OHCP for diagnosis and treatment for the non-normal finding on their tongue. If for example, they detected angular cheilitis, it is their role to determine if perhaps it's due to a riboflavin deficiency and, if not, refer the patient/client to an OHCP or physician for further evaluation. The outcome of the oral screen conducted by the RD as part of NFPE is the identification of non-normal conditions that may impact the patient/client's nutritional status, reflect nutritional conditions and or impair dietary intake [34]. Subsequently the RD can use the nutrition diagnosis codes to determine the nutrition diagnosis(es), provide baseline guidance relative to oral health and nutrition and refer patients as appropriate to OHCPs or physicians. Figure 19.3 addresses nutrient specific implications of non-normal oral findings whereas Table 19.4 provides NFPE exam findings and suggested dietary management strategies. Tables 19.2 and 19.4 and Fig. 19.5 address a NFPE stepwise approach for oral screening for use by RDs in general clinical practice during the conduct of their nutrition focused physical exam. The interprofessional care and referral process ensures that patient/client receives comprehensive care from the healthcare disciplines best suited to their needs.

Summary

Although the rationale for nutrition risk screening in dental practice is logical and can be considered part of comprehensive oral health care, there is a paucity of published research and validated oral health screening tools. Figure 19.4 is a tool based on research conducted by Radler [16]. Radler studied patients seen for dental treatment planning in an urban, academic dental clinic to determine a model of factors predictive of nutrition risk. The model was developed based on correlation and regression analyses which were used to calculate sensitivity, specificity, and predictive value of a screening tool concept (Fig. 19.4) [16]. In dental school clinic settings, OHPCs, dental students, and RD faculty are likely to view a positive response to any item (Fig. 19.4) as an indicator of risk that can be evaluated more fully by the appropriate care provider. In other words, if the patient is obese and has no other positive responses, the dental student encourages the patient to consume a healthy diet and advises them of the risk factors associated with being obese. If a patient has extensive caries and consumes four or more fermentable carbohydrate containing snacks daily, they are treatment

STEP 1: Interview your patient. Important points to cover in your oral health interview…

Polypharmacy: use of medications associated with risk of dysphagia; chronic use of several medications (3 or more).

Xerostomia: Dry mouth. ***Questions for patients:***

- Do you ever feel your mouth is dry? If so, when? Can you consume a meal without a drink? Can you consume a snack without a drink?
- Has there been any change in your medication(s) both prescription and over the counter?

Dysgeusia: distorted taste***OR*** **Ageusia**: loss of/absent taste ***OR*** **Hypogeusia**: diminished taste

Oral Pain: where / when / how often? Does anything relieve this pain? If so, what?

Eating and drinking patterns: When during the day and what do you typically eat and drink. Are you on a special diet?

STEP 2: Extra-Oral Exam - Look at the face and overall appearance of your patient.

Face: positioning, profile, symmetry, and facial expressions; observe color and texture of the skin.

Temporomandibular Joint and Muscles of Mastication: focus on sounds, tenderness, movement, and assess 3-finger opening.

STEP 3: Cranial Nerves: Test key cranial nerves related to oral health.

Trigeminal Nerve V:
- Assess jaw movement and strength; sensation to the face (sharp, dull and light touch to three branches)

Facial Nerve VII:
- Assess facial expressions - raise eyebrows, frown/smile, purse lips, nasolabial fold; changes in taste

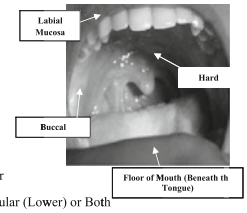
Glossopharyngeal / Vagus Nerve IX, X:
- Taste (changes) and swallow

Hypoglossal Nerve XII:
- Test tongue range of motion, strength (push against finger or tongue blade)

STEP 4: Intra-Oral: After your extra-oral exam is complete, inspect the intra-oral cavity.

Labial &Buccal Mucosa/Floor of Mouth/Gingiva/Hard Palate –

lookat color, texture, moisture, normal vs. nonnormal



- **Buccal mucosa:**Stenson's duct; saliva production
- **Floor of mouth:** Wharton's duct; saliva production

Soft Palate: say "ah", is uvula midline, does soft palate elevate?

Dentition: observe missing teeth, obvious caries, fractures

- **Edentulism**: Assess for tooth loss (where?)
- **Occlusion**: Assess the pattern in which teeth come together
- **Denture use?** Partial / Full / Maxillary (Upper) or Mandibular (Lower) or Both
- **Any complaints of difficulty chewing food? Difficulty with only certain type or textures of foods?**

Tongue: inspect color, appearance: dorsal (back), ventral (front), lateral (left/right) borders and movement.

STEP 5: Look for signs and symptoms of micronutrient deficiencies.

- Deficiencies with oral manifestations: Riboflavin, Niacin, Folic Acid, B6, and B12, Vitamins A & K, Iron
- If you suspect a nutrient deficiency, refer the patient to a physician.

	Clinical Manifestation	Risk for Deficit / Altered function
Gingiva	Spongy, bleeding, redness, lesions, ulcerations	Vitamin C, Vitamin K; systemic disease; impaired eating
Tongue	Glossitis; Pale, atrophic, smooth/slick Decreased taste	Folate, B6, B12, iron, Riboflavin, Iron, Folate, Zinc, Vitamin A
Teeth	Missing, broken, lack of occlusion	Ability to bite & chew food
Salivary glands	Enlarged, Tender to palpation	Bulimia, sialolothiasis ('salivary calculi')

STEP 6: Assess for difficulty swallowing.

Dysphagia Screen: Cognition (alert and oriented), Position (able to maintain upright position during meal), Cranial nerve exam (V, VI, IX, X, XII), Swallow, Cough Reflex

- Is the patient pocketing food? Does the patient have a wet cough or a hoarse voice?

Fig. 19.5 Rutgers—SHRP Graduate Programs in Clinical Nutrition 2013 (c March 2013). Stepwise approach to the conduct of the nutrition focused physical exam: head, neck and oral screen

planned for diet counseling by the dental student. If a patient has newly diagnosed diabetes and is getting new dentures, they are treatment planned for diet counseling on eating with dentures by the dental student under the supervision of the RD and encouraged to see an RD outside the school clinic for MNT for their diabetes. Nutrition risk is more accurately based on the type and extent of risk factors and their impact on oral function. Examples of conditions or diseases associated with nutrition risk are in each of the chapters of this text.

In clinical practice, OHCPs may adapt any of the tools in this chapter for use. The actual screening may be done by the provider or by a dental hygienist or assistant trained in the screening process. The Academy of Nutrition and Dietetics has a national provider network; in the USA (http://www.eatright.org/iframe/findrd.aspx) where individuals can use to identify referrals for patients as needed. Additionally local and state dietetic associations may have referral systems as well.

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Chapter 20
Approaches to Curriculum Development in Nutrition and Dental Education

Riva Touger-Decker and Connie Mobley

Keypoints

- Nutrition education as a component of interprofessional pre- and postdoctoral dental education and continuing dental education is important in order to translate theory into practice
- Nutrition education and training in dental schools in the twenty-first century includes diet and nutrition in relation to health promotion, chronic disease risk screening, control, and referral
- Competencies for nutrition and dietetics as part of dental education, considering the interprofessional approach should address: measurement of height and weight and calculation of body mass index, communication of the findings of such measurements to the patient/care giver, diet assessment and education as appropriate for health promotion, dental caries and dental procedures such as dentures (partial or full), oral surgery, trauma, head/neck cancer therapies, and referral approaches

Keywords Nutrition and dental education · Curriculum development · Nutrition competencies · Dietetics competencies · Dental education

Introduction

Since the release of the first edition of this book, the concept of interprofessional education and training across all of health care has expanded in part driven by the social, health and economic realities of the healthcare environment [1]. The 2011 Institute of Medicine (IOM) report, *Improving*

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Access to Oral HealthCare for Vulnerable and Underserved Populations [2] emphasizes the importance of interprofessional core competencies in training and education for health including oral health, nutrition, and diet. The report included four core competencies: recognition of oral disease risk as part of assessments, provision of educational information on oral health, integration of oral health with diet counseling, and referrals as appropriate to Oral Health Care Providers (OHCPs) [2]. Dental education, like dietetics education has been shifting its focus to prevention, patient-centered evidenced-based care, and interprofessional education while keeping pace with advances in technology, genetics, and genomics [1, 3]. In a 2012 review titled the *Evolution of Dental Education*, DePaola [4], encouraged banishing the silos that are pervasive in dental and health professions education and working across disciplines; concepts consistent with the IOM Report and Lancet Commission [1, 2]. The continued survival and integration of nutrition within dental education and training depends to some degree upon innovative and forward thinking approaches and attitudes by educators, administrators, and clinicians as they breakdown these silos and create interprofessional approaches to dental education and training. As dentists learn to integrate comprehensive patient care in practice, participate in interprofessional clinical teams and further their understanding and application of the "oral-systemic bi-directional linkages" [4], nutrition can be infused into the curriculum.

However, in order to ensure the integration of nutrition and oral health education (and vice versa) [1, 5, 6], it is essential that a body of knowledge for both dietetics and dentistry be delineated. Nutrition education as a component of pre and postdoctoral dental education and continuing dental education is important in order to translate theory into practice. Likewise, oral health and disease education, as a component of preprofessional and graduate dietetic education and continuing professional education, is necessary. This chapter addresses both dental and dietetics professional education and training.

Nutrition and Oral Health Education of Health Professionals

In the practice setting, collaborative efforts between dental and dietetics professionals to promote interprofessional healthcare teams have the potential to improve learning as well as patient outcomes [1]. Table 20.1 represents a paradigm for role modeling, collaboration, and referral between dietetics and oral health care professionals to address oral health and nutrition issues in practice.

Various approaches to achieve this paradigm have been advocated by the IOM [2], Pew Health Professions Commission [7], Lancet Commissions [1] and the World Health Organization (WHO) [8] for almost two decades. The 1998 Pew Health Professions Commission Report recommended that relationships between dentists and allied health professionals be developed and expanded and that interdisciplinary competence be required of all health professionals [7]. The 2010 Lancet Commissions report on *Education of Health Professionals for the twenty-first century: A global independent commission* promoted a "redesign of professional health education" (p5) that addresses the shifting economic, health, environmental, and behavioral environments that challenged "the tribalism of the professions—i.e., the tendency of the various professions to act in isolation from or even in competition with each other" (p5) which is similar to the call in the late 1990s to breakdown the 'silos' of health professions and practice and promote team-based care [1]. Fostering the core knowledge starting on the preprofessional level is a critical first step to finalize the recommendations made by these groups. Basic levels of care skills, including screening and risk identification and referral for intervention, are essential for health professionals [2] as clients seek comprehensive health care. Consistent with this approach, the IOM supports comprehensive training of dental professionals to ensure that they can "assess and treat the whole patient, not just the mouth" [2] as well as training non-OHCPs with a core of competencies in oral screening and referral [2]. The 2011 IOM report

Table 20.1 Dietetics and dental professional role modeling to achieve effective integration of oral health and nutrition service in health promotion and disease prevention and intervention

1. Registered Dietitian (RD)
Clinical setting
• Conduct intra-/extraoral screening and cranial nerve screening as part of nutrition-focused physical exams (NFPE)
• Integrate oral health screening as a component of NFPE (i.e., cranial nerve function, occlusion, edentulism, masticatory ability, swallowing, salivary adequacy)
• Recognize oral manifestations of systemic diseases and provide patients with guidelines to maximize oral intake
• Confer with and refer patients (via consults) to oral health care professionals (OHCP) for management of oral symptoms of diseases and/or risk factors for oral diseases
• Consult with OHCPs in interpretation of oral screen findings and planning in the long-term care setting
Community setting
• Establish partnerships with OHCPs in community and private practice settings
• Develop and implement collaborative oral health and nutrition screening/education programs in schools, worksites, and health maintenance organizations
• Promote collaborative education on nutrition and oral health among dietetics and OHCPs
• Develop nutrition education messages that encourage oral health
• Promote oral health in school and community nutrition programs
Research setting
• Promote collaborative nutrition and oral health research initiatives
• Design and conduct nutrition/diet components of oral health research initiatives
• Identify and support integration of oral health issues (e.g., screening, disease, management, education) as a component of nutrition research
2. Oral health care professionals
Clinical setting
• Include diet and nutrition screening, education, and referral for oral infectious disease prevention/control, optimal masticatory function, and management of other oral diseases/treatments as a component of comprehensive dental care
• Collaborate with RDs in delivery of MNT and provision of oral healthcare in long-term care settings
• Provide diet and nutrition guidelines for health promotion and disease prevention to patients and provide guidelines for diet to maximize oral intake
• Consult with and refer patients (via consult) to RDs for management of nutrition risk caused by compromised oral health (e.g., caries, immunosuppressive disorders, xerostomia, diabetes, oral surgery, cancer)
Community setting
• Establish partnerships with RDs in community and private practice settings to promote nutrition/diet screening and education in dental practice
• Develop and implement collaborative oral health and nutrition screening/education initiatives in schools, worksites, and healthcare organizations
• Promote collaborative education on nutrition and oral health among RDs and OHCPs
• Develop oral health messages that integrate nutrition and diet education
• Promote diet and nutrition as a component of school and community oral health programs
Research setting
• Promote collaborative oral health and nutrition research initiatives
• Design and conduct oral health component of nutrition/diet research initiatives
• Identify and support integration of nutrition topics as a component of oral health research as appropriate

Adapted from ref [29]

recommends that accrediting agencies for health professions education integrate these competencies into accreditation standards and require compliance [2]. The 2011 WHO Report, *Transforming Health Professions* Education addresses three distinct "dimensions of the challenge" (p4), quantity, quality, and relevance that are at core components of the transformation of health professions education which includes dentistry [2]. Change and transformation have been very slow [4]; this chapter addresses feasible approaches to integrating interprofessional education and training.

Nutrition in Dental Education

Dental accreditation standards and the *2010 Competencies for the New General Dentist (ADEA)* do not specify predoctoral nutrition education competencies [9]. Although the 1990 standards for nutrition in dental education specifically addressed knowledge of basic nutrition, the role of diet and nutrients in health and oral diseases, and nutrition counseling as it relates to oral health, standards since the late 1990s have focused on broad-based competency statements and emphasized technical skills. Throughout several areas of the competencies and standards, diet and nutrition content is implied in risk assessment and patient treatment planning functions. The biomedical sciences standards do not address specific sciences; rather, they must "ensure an in-depth understanding of basic biological principles, consisting of a core of information on fundamental structures, functions and interrelationships of the body systems" [10]. Similarly, "in-depth information" must be provided to develop understanding of oral health, oral disease, oral epidemiology, and the role of diet and nutrition in the etiology, diagnosis, prevention, and treatment of oral disease. Knowledge of principles of nutrition and diet and their clinical application in practice is implied throughout the document [9] because it provides the underpinning for achievement of several of the competencies. The accreditation standards for the majority of advanced specialty postdoctoral education programs vary in the specificity with which they address nutrition. The specialty postdoctoral program in periodontics does address knowledge of "principles of nutrition, especially as they relate to patient evaluation, disease processes, and wound healing" [11]. The effects of proper diet nutrition, fluoride therapy, and sealants in the prevention of oral disease is specifically addressed in the pediatric dentistry postdoctoral specialty program, along with practices that include patient management of children with metabolic disorders and with special needs [10]. Other postdoctoral programs include competencies focusing on management of medically compromised patients, those with chronic and terminal diseases, and those who have undergone surgical interventions. Implied in these required competencies is knowledge of diet and nutrition as they relate to comprehensive dental management [11, 12]. Interprofessional competencies are likewise supported by the Commission and Institute reports cited in this chapter. The Commission on Dental Education Standards published in 2010 includes a greater focus on humanitarian and technological issues and an increased emphasis on community service, interprofessional education, and student research opportunities [13]. Nutrition is integral to each of these areas.

Historically, the focus on nutrition education in dental schools was on oral infectious disease management. Although there is a lack of published research on the number of hours of nutrition and dietetics in the dental curriculum for the twenty-first century, nutrition topics in dental school in this century are increasingly addressing diet and nutrition in regards to health promotion, weight screening and chronic disease screening, control and referral in part in response to shifts in the practice arena. The 2013 American Dental Association "Call to Action for Oral Health" [14] calls for OHCPs to be advocates for disease prevention and health lifestyles inclusive of providing nutrition guidelines.

The absence of sufficient published data on how nutrition and diet are addressed in dental education in the USA and globally merits attention [15]. While individual school data known to these authors are described herein, quantifiable data are needed. Some dental schools include nutrition as a separate course whereas others integrate lectures, assignments, and seminars into existing courses in biochemistry, prevention, infectious diseases, clinical dentistry, health promotion, oral medicine, and oral surgery. Others, notably the Rutgers School of Dental Medicine, University of Nevada at Las Vegas Dental School, University of Iowa Dental School, and New York University's College of Dentistry also include clinical competency requirements in screening, diet assessment, and counseling. These combined didactic and clinical requirements provide students with the opportunity to transfer knowledge learned in the didactic courses into practice applications

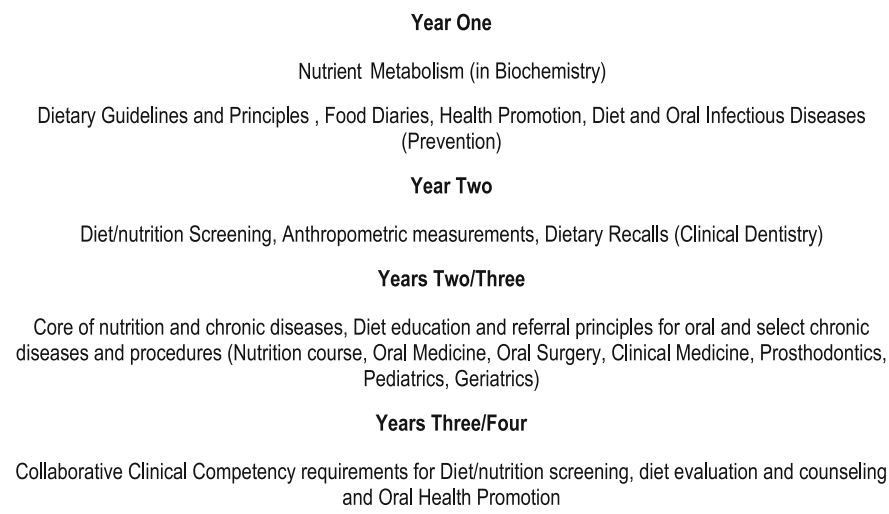

Fig. 20.1 Model for integration of nutrition into didactic and clinical courses in dental school

[16]. Figure 20.1 provides a model of how dental schools can integrate nutrition topics addressed in Table 20.2 into their didactic and clinical curricula.

This shift in curricular content is consistent with the aforementioned transitions in roles of OHCPs with a focus on interprofessional practice, health screening, and promotion and intervention roles of dentists that include diet and nutrition [17–19]. Lalla et al. and Barasch et al. explored diabetes screening and basic education practices of dentists [17, 18]. Their findings supported the role of dentists in measuring patient's height and weight, addressing blood sugar and referral of patients to appropriate care providers, which include dietetics professionals. Greenberg and Glick have explored the role of dentists doing weight, blood sugar, and blood pressure screening both from the provider's and patient's perspectives [19]. DeBate and others have studied eating disorder screening practices of dentists and hygienists and devised an approach to train dental students on eating disorder prevention [20]. These topics are all linked to diet and nutrition and infer the need for dental students to have core knowledge of anthropometric measurements and their interpretation [19], chronic disease screening and risk assessment, basic diet guidelines, and referral strategies to appropriate health professionals. Content areas recommended are outlined in Table 20.2; basic guidelines education should address those by WHO, the US Department of Agriculture, the American Heart Association, National Cancer Institute, and American Diabetes Association. Content knowledge on measurement, calculation, and interpretation of height, weight, body mass index, growth parameters, waist circumference, and screening parameters for chronic disease (blood glucose, Total, HDL and LDL cholesterol, Hemoglobin A1C, and blood pressure) should be taught so that they can be measured in performance competencies in clinical situations.

Nutrition topics are delineated in the Accreditation Standards for Dental Hygiene Education Programs [22] biomedical science component of the curriculum. Clinical dental sciences instruction competencies indirectly address the ability to evaluate an individual's diet and provide diet education relative to oral health. Dental hygiene science content must include oral health education and preventive counseling, and health promotion experiences that would include nutrition content. In the practice setting, it may be the dental hygienist who completes the patient's health assessment and any diet or nutrition evaluation, subsequently providing oral hygiene and health promotion instruction including diet.

Table 20.2 Didactic and Practice Components of a Curriculum Model for Dietetics and Dental Education Programs to Promote Collaboration and Interprofessional Experiences in Nutrition and Oral Health

Dietetics Education

1. Baccalaureate Program

a. Didactic topics

- Oral anatomy and physiology
- Oral manifestations of systemic diseases
- Oral sequellae of medications, chemo and radiation therapies
- Diseases of the oral cavity and their effects on taste, smell and mastication

b. Clinical Experiences

- Field visits to dental schools/clinics
- Work with dental& dental hygiene students/OHCPs in clinical/community settings
- Oral health screening questions as a component of nutrition screening & assessment activities

2. Supervised Practice (Pre-professional) Activities/Competencies

- Complete rotations in dental school and community dental clinic rotations
  - Complete nutrition screening and diet counseling relative to oral health
- Throughout rotations integrate oral health into nutrition care process tasks
  - Nutrition foused physical exam
  - (screening, assessment, intervention, monitoring)
- Participate in oral health and nutrition research
- Perform basic nutrition focused physical assessment including oral and cranial nerve screening
- Design diet & nutrition care plans for patients with compromised oral health

3. Graduate Education

- Design, conduct and participate in oral health and nutrition research
- Perform nutrition focused physical assessment exams including intra/extra oral screening and cranial nerve examinations
- As appropriate partner with dental students/OHCPs in patient/client experiences

4. Continuing Professional Education

- Collaboration between dietetics and OHCPs in case presentations, multidisciplinary care meetings, conferences about diseases and the lifespan, interprofessional seminars, publications
- Training opportunities using different media, e.g. distance learning, CD-ROMs, videotapes

Dental Education

1. Pre-doctoral Program

a. Didactic topics

- Nutritional biochemistry
- Nutrition and oral health throughout the lifespan
- WHO and U.S. Dietary Guidelines and Diet Recommendations from other organizations
- Diet education and intervention relative to oral health/diseases
- Effect(s) of oral disease(s), symptomatology and their treatment(s) on diet and nutrition status
- The relationship between diet/nutrition and oral health in acute and chronic diseases and disorders
- Diet/nutrition screening, education and referral in dental practice
- Diet/nutrition risk factors for chronic diseases and management strategies of high risk patients

b. Clinical and Research Experiences

- Complete self evaluation of diet
- Integrate basic diet education relative to oral health into patient education
- Provide diet and nutrition risk screening relative to oral health to patients
- Consult with RDs regarding diet evaluation and education
- Participate in oral health and nutrition/diet research
- Complete rotations with dietetics students in supervised practice rotations

2. Graduate Programs

- Design, conduct and participate in oral health and nutrition research
- Integrate nutrition screening and diet education into OHCP practice and curricula
- Complete collaborative education endeavors on related topics with dietetics programs

3. Continuing Professional Education

- Collaboration between dietetics and OHCPs in case presentations, multidisciplinary care meetings, conferences, about diseases and the lifespan multidisciplinary seminars, publications
- Training opportunities using different media, e.g. distance learning, CD-ROMs, videotapes

From Ref. [4]

Nutrition in Dental School Training

While the classroom-based learning allows for transmission of knowledge, training is essential to achieve competency. Epstein and Hundert [23] define "competency as the habitual and judicious use of communication, knowledge, technical skills, clinical reasoning, emotions values and reflection in daily practice for the benefit of the individual and the community being served" [23] referring to the clinical training road to competency in care for individual patients/clients and the population. The American Dental Education Association defines a "competency" as a complex behavior or ability of consistent quality essential for independent, unsupervised dental practice that may include knowledge, experience, critical thinking and problem-solving skills, professionalism, ethical values, and technical and procedural skills [13]. Models for interprofessional training are proposed by the Lancet Commission which are not specific to dental or dietetics education but provide a basic infrastructure that can be adapted; these are consistent with the framework proposed by the 2011 IOM report [2]. The Lancet Commission proposes a competency-based model in which the health needs and health system drive the competencies that must be integrated into the curriculum and assessed [1]. The relationships among oral, systemic, and nutritional well-being are increasingly being stressed in dental and other health professions education [3, 4] yet, assessments on a global scale [15] reveal they are not taught to adequate degrees in schools. Given the dialog on the role of the dentist in chronic disease health screening [17–19, 24] that includes nutrition and diet principles and practices, it would seem logical that competency-based training be similarly aligned. Table 20.2 provides a model that addresses both dental and dietetic competency training.

Competencies for nutrition and dietetics as part of dental education, considering the interprofessional approach should address: measurement of height and weight and calculation of body mass index, communication of the findings of such measurements to the patient/care giver, conduct and analysis of 24 hours dietary recalls, diet education relative to the U.S. Dietary Guidelines, dental caries and dental procedures such as dentures (partial or full), oral surgery, trauma, head/neck cancer therapies, and referral approaches. Achievement of these competencies would contribute to the preparation of the emerging new graduate with the skills for interprofessional health screening and referral. Dental schools that include instruction and competencies on chronic disease screening (including diabetes, cardiovascular disease) should likewise address basic education on diet and lifestyle and referral strategies to Registered dietitians (RD). Adding these clinical requirements would increase the likelihood that competency will be addressed and required during the training years.

Oral Health in Dietetics Education and Training

Similar to the approach taken toward nutrition in dental education, oral health education is not outlined as a specific competency or criterion in the standards of education for dietetics education [25]. The standards do require that dietetic internships and coordinated programs include competencies on use of the *Nutrition Care Process and Model* [25] which includes nutrition-focused physical examination (NFPE). NFPE of the head, neck, and oral cavity refers to inspection for clinical manifestations of nutrient deficiencies, and head, neck, oral cavity, and cranial nerve screening conducted by the RD as part of his/her nutrition assessment [26, 27]. Clinical dietetics and nutrition practice by the RD include use of the nutrition diagnosis codes of the International Dietetics and Nutrition Terminology which addresses the integrity and functions of the oral cavity [28]. RDs in clinical practice are expected to include oral health as a component of their counseling, and monitoring.

Strategies for addressing oral health and disease concepts as part of dietetics education and training are addressed in Table 20.2. Undergraduate courses on systemic health, physiology, nutrition assessment and diet, and disease can infuse oral health and disease lectures, assignments, and seminars which would demonstrate the bidirectional associations and relationships among oral, systemic and nutritional health, and diseases [29]. The didactic education can provide the infrastructure upon which clinical training competencies are based.

The clinical training of dietetics professionals during dietetic internship or coordinated program clinical experiences should include opportunities for clinical experiences in dental school clinic or dental office settings as shown in Tables 20.1 and 20.2 [16, 29]. Students in these programs should be given opportunities to work side by side with dental students or residents in the clinical setting to provide nutrition and diet intervention as a component of oral health and disease management. Competency in NFPE should be required of students in the preprofessional settings [29]. The outcomes of NFPE of the oral cavity for entry-level training should include recognition and detection of nutrition/diet-related risk factors (e.g., non-normal conditions of the hard and soft tissue affecting ability to eat or drink) to incorporate into nutrition interventions or referrals [26]. Competencies in oral screening (head, neck, intra/extraoral assessment, and cranial nerves) are needed for students in the preprofessional settings. Additional competencies based on the generic ones proposed by the Lancet Commission and 2011 IOM report should include interprofessional training, oral health education, and counseling and referral strategies to OHCPs.

The educational outcomes of such training includes competencies in the identification of non-normal conditions of the oral cavity, oral dysfunction factors affecting biting, chewing, drinking, and swallowing, and potential nutrient deficiencies. As individuals progress from entry-level to beyond entry-level and advanced-level training, so will their competency in the performance of these outcome competencies [29]. The value of these competencies in nutrition assessment, monitoring, and evaluation across the life span in health and disease will significantly impact development of nutrition care plans and diet protocols.

A Model for Collaboration in Nutrition and Oral Health Education

The continual shifting of the social and economic realities of today's healthcare system have had a dramatic effect on the preparation and training of health professionals, including dietetics professionals, dentists, and allied dental personnel. The need for the recognition of nutrition as an essential part of training for dental professionals and as an important component of educational programs for dietetic and other health professionals is clearly delineated in the reports addressed in this chapter for the past two decades [1, 2, 7, 8]. In order to be successful, educators and leaders in oral health and nutrition must promote this dual content area in the curricula of other allied health professions. Interprofessional teams of oral health and dietetics and other health professionals (e.g., physicians, physician assistants, speech and language pathologists, nurses) can advance health promotion and preventive and community health initiatives that promote oral health and nutrition as they relate to general health [2–4, 30]. These new models of healthcare provider transformational learning experiences will successfully translate into practice that requires innovative approaches to new models of healthcare delivery. By developing "complementary" competencies the qualities of all professionals in the multiple roles of health care can be enhanced. When common dietetic and dental education competencies consistently overlap the scopes of practice within each profession can include "collaborative" competencies that translate into interprofessional performance [31]. See Fig. 20.2.

Fig. 20.2 Integrated collaborative competencies [31]

Summary and Next Steps

This chapter has provided a historical perspective on nutrition and dental education along with twenty-first century initiatives and recommendations for nutrition education of dental professionals and oral health education of dietetics professionals (Tables 20.1 and 20.2, Fig. 20.1). A collaborative effort of members of both disciplines including academicians, clinicians, and administrators is needed to actualize the recommendations into practice. The practical model envisioned as an outcome of the recommendations within this chapter includes teams of RD nutrition experts in dental schools and dental faculty in dietetics programs, with both disciplines represented on accreditation boards for dietetics and dentistry. Initiatives to identify and create strategies for collaborative competencies in public health promotion and clinical care are needed. Advocacy for professional initiatives and federal grants to build such curriculum models and a forum for creating and sharing model curricula would provide the infrastructure to grow and develop models of excellence is critical. Dietetics professionals and OHCPs need to identify and establish opportunities for collaboration across multiple disciplines to extend inclusive collaborative efforts.

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Appendix 1
Web Resources for Diet and Nutrition Information

Note to Readers: The Editors have chosen to provide titles and URLs to helpful sources for guidelines and references for nutrient and diet information since this information is often updated frequently.

U.S. Department of Agriculture

Dietary Guidelines for Individuals 2010: http://fnic.nal.usda.gov/dietary-guidance/dietary-guidelines

Supertracker to Assess Dietary Intake: https://www.supertracker.usda.gov/default.aspx

USDA MyPLATE: http://fnic.nal.usda.gov/dietary-guidance/myplatefood-pyramid-resources/usda-myplate-food-pyramid-resources

National Academy of Sciences Institute of Medicine Food and Nutrition Board Dietary Reference Intakes (DRI)

Interactive DRI for Health Professionals: http://fnic.nal.usda.gov/fnic/interactiveDRI/

DRI Tables: http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables

Individual DRI reports: http://search.nap.edu/napsearch.php?term=DRI

World Health Organization

Dietary Recommendations/Nutritional Requirements Publications: http://www.who.int/nutrition/publications/nutrientrequirements/en/

Global Strategy on Diet, Physical Activity and Health: http://www.who.int/dietphysicalactivity/en/index.html

American Heart Association

Diet and Lifestyle Recommendations: http://www.heart.org/HEARTORG/GettingHealthy/Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp

U.S. National Cancer Institute

Diet and Nutrition Fact Sheets: http://www.cancer.gov/cancertopics/factsheet/diet

American Cancer Society

Guidelines on Nutrition and Physical Activity for Cancer Prevention: http://www.cancer.org/healthy/eathealthygetactive/acsguidelinesonnutritionphysicalactivityforcancerprevention/nupa-guidelines-toc

American Diabetes Association

Food and Fitness Tools: http://www.diabetes.org/food-and-fitness/food/

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National Institute of Diabetes and Digestive and Kidney Diseases National Diabetes Information Clearing House

Diet Tools: http://diabetes.niddk.nih.gov/dm/pubs/eating_ez/

National Institute of Dental and Craniofacial Research

Free Publications for Patient and Health Professional Education: https://www.nidcr.nih.gov/orderpublications/

Centers for Disease Control and Prevention: Oral Health Section

Surveillance Data on Oral Conditions, Patient and Health Professional Education resources: http://www.cdc.gov/OralHealth/index.htm

Appendix 2A
Diet and Nutritional Considerations for Cancer Prevention

- General Dietary Guidelines for Cancer Prevention:
  - Eat a variety of healthful foods, with an emphasis on plant sources of protein.

    Five or more servings of fruits and vegetables (especially citrus and yellow and dark green leafy sources)
    Choose whole grains and other high fiber foods

    Limit red meat and egg consumption 
  - Decrease the dietary fat (especially saturated fat) intake

    Bake or broil foods; choose non-fat and low-fat milk and dairy products.
    Saturated fats may increase cancer risk. Omega-3 fatty acids, found in fish, may reduce cancer risk.
  - Adopt a physically active lifestyle.
  - Maintain a healthy weight throughout life.

    Balance calorie intake with physical activity; if overweight, consider a weight loss program.
  - If you drink alcoholic beverages, limit consumption.

    No more than 2 drinks for men; 1 drink for women per day 
- For more information:
  - American Cancer Society—http://www.cancer.org
  - American Dental Association—http://www.ada.org/prof/resources/topics/cancer.asp
  - National Cancer Institute—http://www.cancer.gov

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Appendix 2B: Diet and Nutritional Considerations for Patients with Head and Neck Cancer

Management

- Diet considerations for individuals with head and neck cancer consider nutritional needs as well as individual functional and sensory capabilities. Roles of nutrients are addressed below:

	Protein	Carbohydrates and Fats	Vitamins and Minerals	
	–Helps to repair body tissue and maintain a healthy immune system	–Carbohydrates and fats supply the body with the bulk of the calories it needs	–Vitamins and minerals help ensure proper growth and development, and allow the body to use the energy supplied in foods	
	–Additional protein, especially following surgery, chemotherapy, and radiation therapy is important	–Good sources of carbohydrates include fruits, vegetables, breads, pasta, grains and cereal products, beans, and peas	–Fortunately, balanced diets with enough calories and protein usually contain plenty of vitamins and minerals	
	–Good sources of protein include lean meat, fish, poultry, dairy products, nuts, beans, and soy foods	–Good sources of fat include, olive oil, nuts, and seeds		

- The cancer itself along with your treatment can change your ability to eat and drink. Frequently encountered side effects and diet considerations for individuals are highlighted below:

Clinical feature	Diet and nutritional considerations
Xerostomia or Hyposalivation	*Increase fluids; minimize amount/frequency of cariogenic foods; modify food consistency (moist, soft foods); limit spicy or hot foods; suck on sugar-free mints/candies; cut foods into small pieces; and mix with sauces and gravies to make moist
Sore mouth and throat	*Increase fluids; modify food consistency (moist, soft foods that won't scratch mouth or throat); avoid citrus, spicy, and seasoned foods (especially salty foods); choose lukewarm or cool foods—avoid very hot or cold foods; use sauces and gravies to blend or moisten foods that are dry or solid
Dysgeusia	*Use plastic utensils if metallic taste present; season foods without art flavors such as citrus fruits; flavor foods with onion, garlic, barbecue sauce, and other seasonings; adding sugar can improve the flavor of salty foods; adding salt can decrease the sweetness of sugary foods; serve foods cold or at room temperature
Difficulty chewing	*Modify diet consistency as tolerated; try soft or pureed foods; moisten dry items such as meat, cereal, or crackers

(continued)

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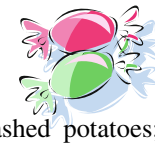
(continued)

Clinical feature	Diet and nutritional considerations
Nausea and vomiting	Eat six small meals per day; eat dry foods (crackers, toast, etc.); avoid foods with strong odor; avoid foods that are overly sweet, greasy, fried, or spicy; eat cool foods instead of hot spicy foods; sip of clear liquids frequently to prevent dehydration; suck on sugar-free mints/candies
Poor appetite	Eat small meals or snacks every 1–2 h; avoid liquids with meals; keep high-calorie, high-protein snacks on hand

Appendix 2C
Dealing with Dry Mouth



- Suck on sugar-free hard candy, ice chips, frozen grapes, or sugar-free ice pops
- Use sugar-free gums and mints that contain xylitol to help prevent cavities
- Eat mechanically soft foods that may be easier to swallow such as soups; mashed potatoes; chopped soft pasta; mashed beans; low-fat ice cream, puddings or custards; sorbets
- Use yogurt, cottage cheese, or pureed bean soups as protein sources
- Dunk or soak foods in liquids to make them softer and easier to swallow
- Use lip balm to keep lips moist

- Cut or chop food into small pieces and mix with sauces and gravies to make them moist and easy to swallow
- Have a sip of water every few minutes during meals to help you swallow
- Try mashed potatoes instead of dry crackers or bread
- Try applesauce, fruit cocktail, and other fruits canned in their own juices instead of raw or citrus fruits
- Try herbs in place of spices for seasonings
- Eating papaya may help break up thick "ropy" saliva
- Carry a bottle of water with you for easy access to keep your mouth moist

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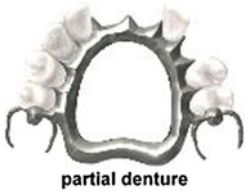
Appendix 2D
Partial Dentures and Your Diet

Tips to keep your mouth clean and healthy with your partial denture(s).

Diet

- After receiving your partial denture(s) try to adjust to the denture(s) by eating soft foods and cutting foods into small pieces for the first week.
- You may eat the foods you were eating before, but remember that you are your own judge of what foods you can handle! Liquid nutritional supplements such as *Boost*, *Ensure* or instant breakfast can help to promote tissue healing and provide calories while you adjust to your new dentures.
- For the first few days eating with your partial denture(s) may be uncomfortable, but it is very important to continuously practice eating with the denture(s) in your mouth.



- Chew on both sides of the mouth to keep even pressure on the denture(s).
- Avoid foods that are sticky or hard while you adjust to the denture.
- Incorporate a balanced diet, full of a variety of foods.
- Rinse your mouth often to help remove food debris.
- Brush your teeth after each meal.

Sticky Foods to Avoid

- Chewing Gum
- Soft Breads
- Rice
- Sticky Candy (Caramel/Taffy)
- Foods with seeds and/or small particles
- Nuts or Coconut

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Grains (6 oz daily)	Vegetables (2 1/2 cups daily)	Fruits (2 cups daily)	Milk (3 cups daily)	Meat and beans (5 1/2 oz. daily)
1/2 cup hot cereal, 1/2 cup cold soaked cereal, 1/2 cup rice, 1/2 cup pasta, 1 slice soft bread	Well cooked string beans, carrots, peas, potatoes	Canned fruits, applesauce, bananas	Low/non fat milk, cheese and yogurt	Eggs, baked fish, well-cooked beans, ground meats, poultry

Fats and Oils Limit your intake of foods that are mainly fats or sugar
Physical Activity Be physically active for at least 30 min most days of the week

Taking Care of Your Mouth

Before Putting Your Dentures in Your Mouth

- Always brush your remaining teeth, as well as your gums, tongue, and roof of the mouth with fluoride toothpaste for a clean and healthy mouth.
- Pay special attention to cleaning teeth that fit under the denture's metal clasps in order to reduce the risk of further tooth decay and/or loss.

Remember to clean your dentures daily

- Dentures should be cleaned with a soft-bristled toothbrush or denture cleaning brush, using a denture powder or paste, hand soap, or baking soda.
- Brush the inside and outside of the denture(s) and rinse with cool water. Do NOT use very hot water because it will cause the denture(s) to lose original shape.
- Dentures are slippery when wet so be sure to clean them over a sink full of water or lined with a towel in case they are accidentally dropped.
- If you notice your denture(s) are fitting poorly make sure to visit your dentist.

Happy Brushing!!!

Appendix 2E
Diet Recommendations Following Oral or Dental Surgery

After dental or oral surgery, your ability to resume your normal diet may take up to a few days. Below are some suggestions that may help you choose foods that are nutritious and easy to eat. Remember, good nutrition is essential for healing!

For the first meal after extractions, try to eat foods from several of the following food groups

- Carbohydrate sources: hot cereal or soups
- Protein sources: soft-cooked fish or poultry, chopped meats, mashed beans, cottage cheese
- Vegetable sources: well-cooked and chopped vegetables
- Fruit sources: applesauce, peeled and chopped, pureed or canned fruits
- Dairy sources: milk, yogurt, milkshakes, or fruit smoothies
- Fluids: tea, juices, and water
- Liquid Nutrition Supplements (can be used if food is not tolerated): Instant Breakfast, *Ensure, Boost*
- *Do not use straws to sip liquids if your dentist tells you not to. Follow guidelines provided by your dentist.*

When you progress to soft-solid foods

- Carbohydrate sources: cold cereal soaked with milk, cooked pasta, soft bread, rice, grains
- Protein sources: scrambled eggs, canned beans (mashed), tuna salad, bean soups with soaked crackers
- Vegetable sources: cooked and chopped vegetables
- Fruit sources: peeled and chopped or canned fruits in their own juice
- Dairy sources: soft cheeses, cottage cheese
- *As your mouth begins to feel better, try more foods such as soft fish, soft cheeses. Try new foods as tolerated!*

Sample Menu

- Breakfast: 1 cup cooked oatmeal, 8 oz low-fat milk, 1/2 cup applesauce, tea
- Lunch: 1 cup bean soup, 1/2 cup fruit puree, ½ cup chopped spinach, 8 oz water
- PM snack: 1 cup yogurt, 8 oz water
- Dinner: 1/2 cup mashed potatoes, 6 ounces chopped chicken with gravy, 1 mashed banana, 8 oz water
- Bedtime snack: 1/2 cup low-fat ice cream

NOTE: Portion sizes and numbers of servings from each food group vary with individual calorie and nutrient needs. Individuals with specific dietary needs may want to contact a registered dietitian for tailored advice

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Appendix 2F
Diet Recommendations Following Oral or Dental Surgery for Individuals with Diabetes

After dental or oral surgery, your ability to resume your normal diet may take up to a few days. Below are some suggestions that may help you choose foods that are nutritious and easy to eat. Remember, good nutrition is essential for healing!

For the first meal after extractions try to eat foods from several of the following food groups	**Sample Menu**
• Carbohydrate sources: hot cereal or soups	• Breakfast: 1/2 cup cooked oatmeal, 4 oz milk, 1/2 cup cottage cheese
• Protein sources: soft-cooked fish or poultry, chopped meats, mashed beans, cottage cheese	• AM snack: Determine based on your diabetes meal plan
• Vegetable sources: well-cooked and chopped vegetables	• Lunch: 1 cup bean soup, 1/2 cup fruit puree, 1/2 cup chopped spinach, 8 oz water
• Fruit sources: applesauce, peeled and chopped, pureed or canned fruits	• PM snack: Determine based on your diabetes meal plan
• Dairy sources: milk, yogurt, milkshakes, or fruit smoothies	• Dinner: 1/2 cup mashed potatoes, 6 ounces chopped chicken with gravy, 1 mashed banana, 8 oz water
• Fluids: tea, juices, and water	• Bedtime snack: Determine based on your diabetes meal plan
• Liquid Nutrition Supplements (can be used if food is not tolerated): Instant Breakfast, *Ensure, Boost. Several of these supplements are also available in a variety for individuals with Diabetes*	• NOTE: Portion sizes and numbers of servings from each food group vary with individual calorie and nutrient needs. Individuals with specific dietary needs may want to contact a registered dietitian for tailored advice
• *Do not use straws to sip liquids if your dentist tells you not to. Follow guidelines provided by your dentist*	
When you progress to soft-solid foods	**Sample Menu**
• Carbohydrate sources: cold cereal soaked with milk,, cooked pasta, soft bread, rice, grains	• Breakfast: 1/2 Banana, 1 cup milk, 1 english muffin with 1 oz soft cheese
• Protein sources: scrambled eggs, canned beans (mashed), tuna salad, bean soups with soaked crackers	• AM snack: Determine based on your diabetes meal plan
• Vegetable sources: cooked and chopped vegetables	• Lunch: 1 scoop tuna salad, 1/2 cup soft pasta, 1/2 cup chopped fruit, 8 oz water
• Fruit sources: peeled and chopped or canned fruits	• PM snack: Determine based on your diabetes meal plan
• Dairy sources: soft cheeses, cottage cheese	• Dinner: 1 cup mashed, canned beans, 1/3 cup brown rice, 1/2 cup soft-chopped vegetables; 1/2 chop low-fat vanilla ice cream, 1/2 cup chopped fruit
• *As your mouth begins to feel better, try more foods such as soft fish, soft cheeses. Try new foods as tolerated!*	• Bedtime snack: Determine based on your diabetes meal plan

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Appendix 2G
Eating with a Sore Mouth

Lesions or sores in your mouth, painful gums, and sore throats may occur following some cancer therapies. Some foods can irritate an already sore mouth and make chewing and swallowing difficult. Proper food selection and good oral hygiene can make eating easier. Here are some suggestions that may help:

- **Include soft, nonirritating foods that are easy to chew and swallow such as:**
  - bananas, applesauce, peach, pear, and apricot (fresh or canned)
  - milkshakes, cottage cheese, yogurt
  - mashed potatoes, noodles, macaroni, and cheese
  - custards, puddings, and gelatin
  - oatmeal or other cooked cereals, soaked cereals
  - scrambled eggs and pureed meats and vegetables
  - Instant breakfast

- **Avoid foods that can cause irritation such as:**
  - oranges, grapefruits, lemons, or other citrus fruit or juice
  - tomato sauces, spicy, or salty foods
  - raw vegetables, granola, toast, crackers
  - commercial mouthwashes that contain alcohol
- **Food preparation:**
  - Cook foods until they are soft and tender
  - Cut foods into small pieces
  - Puree food with a blender or food processor

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- **Tips on consuming food:**

  - Try foods cold or at room temperature. Hot foods can irritate a tender mouth and throat
  - Try sucking on ice chips and rinsing your mouth often with water to remove food and bacteria
  - Try drinking through a straw

Appendix 3A

RUTGERS

Infant Diet and Oral Health Tips

Wipe your baby's gums with a soft moist cloth immediately after feeding from breast or bottle.

Once teeth erupt, clean with a soft, moist cloth at least twice a day.

Baby's 1st Dental Checkup!!

BIRTH — 6 months: first baby teeth — 12 months

Sucking on a cool teething toy can help soothe your child during teething.

Avoid the transfer of harmful bacteria from your mouth to your baby's mouth:

Do not pre-chew or put food into your mouth before feeding it to your child.

When feeding your child, **Do not** share utensils.

Avoid putting bottle nipples or pacifiers into your mouth.

Avoid cooling food by blowing on it to prevent contamination with saliva

When using a bottle or pacifier:

Do not dip pacifiers in honey or other sweeteners.

Give juice to your child **only** after 6 months of age.

Give no more than **4 ounces** of juice per day.

Give juice in a cup, **NEVER** from a bottle.

Limit frequent bottle feedings at night.

Children should **not** be put to sleep with a bottle, unless it ONLY contain water

Use a **bottle only for formula, water, or breast milk** all other liquids should go in a cup.

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Appendix 3B

RUTGERS

Diet and Oral Health
Tips for your Toddler

- Decrease the use of a bottle after 12 months of age.
- Drinking from a cup or Sippy cup **over a prolonged period of time** can contribute to tooth decay **unless** it only contains water
- Wean use of pacifiers.

Limit foods that promote dental decay such as candy, potato chips, and soda.

Limit foods high in sugar **especially** as snacks or at the end of meal.

Limit acid containing beverages (sports drinks or sugar-sweetened drinks) with the exception of 4 ounces of juice a day. Acidic beverages break down the enamel on teeth, making dental decay more likely to happen.

- Plan healthy snacks to limit foods that are potentially cariogenic (promote decay).
- Dairy foods and proteins have a buffering quality—combine these foods with those that increase the risk of dental decay.
- Encourage foods that don't promote decay such as eggs, fish, meat, poultry, and most vegetables at meals and snacks.

REMEMBER:

- Do NOT share eating utensils with your child as this may transfer bacteria from your mouth to your child.
- Brush your child's teeth at least 2 times a day, especially after breakfast and before bedtime.
- Teach your child to spit toothpaste out.
- End meals and snacks with dairy foods: low-fat milk and cheese.

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Appendix 3C

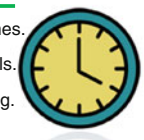
RUTGERS

Diet and Oral Health Tips for

Pre-School Children

- **Assist** your child in brushing his/her teeth demonstrating proper technique.
- Your child should **brush at least 2 times a day** using a pea-sized amount of toothpaste as shown below.
- **Avoid** having your child drink from a cup over a prolonged period of time unless it only contain swater.
- **Use sugar-free vitamins** and medications when possible.

- **Encourage** routine meal and snack times.
- **Avoid** frequent, unplanned snacking between meals.
- **Limit** bed time snacking.



- **Avoid** giving your child more than 4 ounces of juice a day.
- **Limit** acid/sugar containing drinks such as sodas, soft drinks, and sports drinks.
- **Encourage foods that don't promote decay** such as eggs, fish, meat, poultry, and most vegetables

Combine "good" and "bad" foods to help prevent dental decay:

- Consume foods that are cariogenic (sugary, acidic) with meals, instead of as snacks.
- Consume dairy products such as a glass of milk, cheese, or yogurt with meals and snacks.
- Combine fermentable carbohydrates with chewy foods such as fresh fruits and vegetables.
- Combine proteins with carbohydrates as snacks. For example: apples and cheese

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Appendix 3D

RUTGERS

Diet and Oral Health Tips for School-Aged Children

Oral Health Tips:

- **Limit** snacks between meals and before bed.
- **Limit** length of time spent snacking to no more than 15 minutes and wait at least 2 hours between eating occurrences.
- **Use sugar-free** chewable vitamins and syrup-based medications when possible.
- Children over the age of 4 can chew xylitol/sorbitol sweetened chewing gum and candies immediately following meals or snacks **when brushing is not an option**.

Tips for healthier meals and snacks:

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Appendix 3E

RUTGERS

Your Guide to Preventing Dental Decay

- Food and/or beverage choices may contribute to risk of dental decay (dental caries).
- Fermentable carbohydrates also known as "sugars" can increase the risk of decay.
- Fermentable carbohydrates can be found in:

Grains: crackers, chips, pretzels, cereals, rice and breads.

Fruits: fresh, canned, and dried as well as fruit juices.

Dairy: those products sweetened with added sugars.

Empty Calories: sweetened beverages, sodas, desserts, candies, cookies, cakes, sugar sweetened gum.

Sugar can be found as sucrose (table sugar), fructose (fruits, honey), glucose (fruits, honey), lactose (milk sugar), and maltose (grains such as bread, rice, pasta) - all of which can contribute to dental decay.

- Foods which are protective or do not contribute to decay include eggs, fish, meat, poultry, most vegetables, cheese, dairy foods, fats and sugarless gum.
- Food Factors which affect dental decay include:

Form and consistency

- Liquids are quickly cleared from the mouth and have low adherence.
- Solids have higher adherence.
- Hard candies, sugared mints result in prolonged exposure.

Expose duration

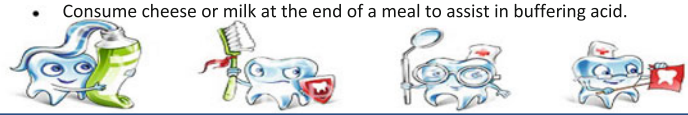
- The longer the food remains in the mouth the higher decay risk.

Nutrient composition

- Dairy foods have a buffering quality (reduce to risk of decay).
- Nuts and proteins do not promote decay.

Sequence and frequency of eating

- Frequent meals, snacks, and sweetened beverage intake promote decay.
- Consume cheese or milk at the end of a meal to assist in buffering acid.



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Appendix 3F

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