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Nutrition, infection, and periodontal disease

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Comprehensive dental care requires dental professionals to assess the general health of their patients and to understand the implications of underlying factors that may impact oral health. One of these underlying factors is the interaction between nutritional status and the immune response to the bacterial challenge in periodontal disease. Alterations in immune response increase the risk and extent of infectious diseases such as periodontal disease. Since the 1970s, the interrelationships of nutrition, immunity, and susceptibility to infection have received increasing attention and rigorous study [1–7].

Patients at risk for inadequate nutritional intakes that compromise the immune response are seen with increasing frequency in private dental practice due to the many advances in medical treatment that allow people (even those with chronic diseases) to live much longer lives. It is important that dental professionals be able to identify patients at risk for poor nutrition, which may compromise their immune response and place them at higher risk for infection. Deterioration of oral health is highly correlated with deterioration of general health, making it essential that the patient be well nourished in order to respond to the challenge of infectious disease like periodontal diseases [8].

Gingivitis and periodontitis are chronic infectious diseases [9]. Gingivitis is defined as "inflammation of the gingiva in which the junctional epithelium remains attached to the tooth at its original level" [10]. In contrast, periodontitis is defined as occurring when the "inflammatory process involves the gingiva and the periodontium resulting in loss of periodontal attachment" [10]. The most recent National Health and Nutrition Examination Survey

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(NHANES III) found the prevalence of gingivitis in those aged 13 years and older to be 54% and the prevalence of periodontitis (defined as attachment loss in at least one site) to be 53.1% [10].

Although the primary etiology of periodontal diseases is bacterial, host and environmental factors modulate the severity of disease. Host and environmental factors include genetics, chronic disease (osteoporosis and diabetes), tobacco use, socioeconomic level, educational level, frequency of dental visits, and both local and systemic nutrition [10]. This article focuses on the interrelationship between nutrition and host immune response and its impact on periodontal disease. In addition, nutrition recommendations to enhance immunity are offered based on current literature.

Oral microbiologic flora

In recent years, research has made significant advances in recognizing the complexity of dental plaque and its impact on oral health and disease. In the mid-1900s, all bacteria were believed to have an equal capacity for initiating dental disease and it was believed that periodontal disease developed as a result of exposure to these bacteria [11]. Over the intervening decades, a small number of bacteria have been identified as being associated with periodontal disease [11]. These bacteria, however, are also often found in periodontal health, leading to a need to investigate the properties that allow these bacteria to function as pathogens that ultimately result in the breakdown of periodontal tissues [11].

Plaque biofilm

Dental plaque is a complex environment called a biofilm. The biofilm is made up primarily of microorganisms that include bacteria, fungi, yeasts, and viruses [11]. In addition, 20% to 30% of the plaque mass is made up of an intracellular matrix consisting of organic and inorganic components [11]. The organic components include polysaccharides, proteins, glycoproteins, and lipids, whereas the inorganic components are primarily calcium and phosphorus, with trace amounts of sodium, potassium, and fluoride [11].

The formation of plaque biofilm begins with the dental pellicle that provides a substrate to which the bacteria attach [11]. The early bacteria colonizing the dental pellicle are aerobic, gram-positive organisms and primarily use sugars as an energy source [12]. The secondary colonizers of the more mature plaque biofilm are anaerobic, gram-negative bacteria and use amino acids and small peptides as energy sources [12]. The bacteria in the biofilm have been shown to have physiologic interactions that support their growth. For example, the growth of *Porphyromonas gingivalis* is facilitated by the metabolic by-product succinate from organisms like *Campylobacter rectus* [13,14]. The organisms colonizing the biofilm tend to form complexes (or communities) that are mutually supportive of each other's growth.

Microorganisms associated with periodontal diseases

Microorganisms found in periodontal health are primarily gram-positive species such as *Streptococcus sanguis* and *Actinomyces naeslundii*, with only a small number of gram-negative bacteria. Certain bacteria, such as *Capnocytophaga ochracea* and *S sanguis*, appear to be protective or beneficial to the host and are found more often in periodontal sites without active disease [15]. The mechanism for this protective effect may be the production of hydrogen peroxide, which is known to be lethal to bacterial species involved in periodontal disease [15].

The microorganisms found in dental plaque–induced gingivitis are 56% gram-positive and 44% gram-negative [11]. Predominant gram-positive bacteria include *S sanguis*, *Streptococcus mitis*, *Streptococcus intermedius*, *Streptococcus oralis*, *Actinomyces viscosus*, *Actinomyces naeslundii*, and *Peptostretococcus micros* [11,16]. The gram-negative bacteria present include *Fusobacterium nucleatum*, *Prevotella intermedia*, *Veillonella parvula*, and *Hemophilus*, *Capnocytophaga*, and *Campylobacter* species [16]. Although gingivitis usually precedes the development of periodontitis, it should be stressed that not all gingivitis progresses to periodontitis [11].

In periodontitis, the microorganisms are primarily gram-negative (75%), with a majority being anaerobic (90%) [11]. The virulence factors of microorganisms refer to an organism's ability to cause disease. The virulence factors of periodontal pathogens can be divided into two groups: (1) factors that facilitate bacterial invasion and colonization of host tissues, and (2) factors that allow a pathogen to directly or indirectly cause breakdown of periodontal tissues [9].

The bacteria most often found in periodontal disease include *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Prevotella intermedia*, *Campylobacter rectus*, *Eikenella corrodens*, *F nucleatum*, *Actinomyces actinomycetemcomitans*, *Peptostretococcus micros*, and *Treponema* and *Eubacterium* species [12,15–17]. Many of these organisms are associated with disease progression and must be eliminated in order to ensure a favorable outcome to periodontal therapy [11].

Host nutrition and plaque biofilm

Nutrition has both direct and indirect effects on the development and composition of plaque biofilm. The primary mechanism by which nutrition impacts the biofilm is through a direct supply of specific nutrients (such as sucrose) as substrates for energy, nitrogen, or carbon for the bacteria. An example of this is the introduction of excess glucose to a plaque biofilm, which has been shown to result in an increased rate of bacterial growth in the early stages of biofilm development [18].

The second mechanism by which nutrition has an (indirect) impact on plaque biofilm is by having an effect on the production of metabolic byproducts from one organism that provide nutrients for other organisms [18].

These by-products include lactate and formate from *Streptococcus* and *Actinomyces* species, which are used as nutrients by other bacteria [11].

The third mechanism by which nutrition impacts the biofilm is through the production of specific polymers used by other bacteria [18]. An example of this is the use of sucrose to produce the glucans used to facilitate the adherence of bacteria such as *Streptococcus mutans* and *Streptococcus sobrinus* to the dental pellicle [19]. Glucose and other carbohydrates are also used to produce extracellular polysaccharides and, therefore, diets containing sucrose, glucose, and other disaccharides can increase the plaque mass and facilitate the retention and colonization of the plaque biofilm [18].

Finally, nutrition impacts the plaque biofilm indirectly through by-products of bacterial metabolism of a nutrient to alter the environment of the biofilm and thereby influence the bacteria colonizing the biofilm [18]. As a by-product of the metabolism of sucrose and glucose, bacteria produce acids that lower the pH, resulting in a more favorable environment for the development of certain bacteria such as *S mutans* [18]. The biofilm development eventually reaches a steady state and, at this point, the influence of host nutrition is thought to be less important in the process of maturation of the plaque biofilm [20].

This short overview of the bacteria involved in plaque biofilm and the impact of nutrition on its development offers a foundation for the following brief review of how the immune system responds to the challenge presented by the bacteria involved in periodontal diseases.

Interaction of immunity, infection, and nutritional status

Nutrition is a ''critical determinant of immune responses'' [21] due to the fact that ''nutrients derived from food sources such as proteins, carbohydrates, and fats as well as micronutrients, vitamins, and minerals interact with immune cells in the blood stream, lymph nodes and specialized immune system of the gastrointestinal tract'' [22]. Infections, no matter how mild, have adverse effects on nutritional status [4]. The effects of these nutrients are dependent on several factors: (1) the concentration of a nutrient and its interactions with other key nutrients, (2) the duration of the nutrient imbalance, and (3) the age of the host [22]. Conversely, a majority of nutrient deficiencies will impair the immune response and predispose the individual to infection [4]. Even though significant literature exists regarding the impact of nutrition on systemic immunity, little is known specifically about the direct impact of nutrition on the immune response in periodontal disease. It is likely, however, that much of what is known about the interaction of nutrition and systemic immunity also is applicable to the issues encountered in periodontal disease.

Immune function can be described as the response of healthy tissue when presented with harmful or disease-promoting factors such as bacteria. In periodontal disease, the host immune system responds to a bacterial

challenge with a well-regulated response consisting of (1) innate factors that signal the endothelium to initiate an inflammatory response, (2) neutrophils that attempt to protect the periodontal tissues by controlling pathogens in an acute inflammatory response, and (3) a chronic inflammatory response that ensues in which the macrophages and lymphocytes try to manage the local infection to prevent it from becoming systemic and life threatening [9]. Before discussing the impact of nutrients on host defense mechanisms involved in periodontal disease, a short overview of the components of the immune system and their functions is provided.

Overview of the immune system and its role in periodontal disease

The immune system is made up of innate immunity and adaptive immunity. Innate immunity is naturally present and is not influenced by prior exposure to a pathogen. Adaptive immune responses develop through exposure to an antigen and are enhanced with repeated exposure to the same stimuli [22].

Innate immunity

Innate immunity consists of nonspecific defenses that include the skin and mucous membranes, phagocytic cells, saliva, mucous, defensins, cilia, and other humoral factors [21]. Monocytes, macrophages, and neutrophils make up the phagocytic cells of innate immunity. These cells contain substances that lyse and kill many different pathogens, rather than only one specific variety of bacteria. These innate processes are the first line of defense against infectious agents.

In the oral cavity, healthy oral mucosa acts as the first line of defense in innate immunity by preventing the penetration of bacterial virulence factors into the body. Epithelium covers the gastrointestinal tract, respiratory tract, and all exposed body surfaces. Epithelial cells have rapid rates of metabolism, differentiation, and maturation, which require a steady supply of essential nutrients. The oral mucosa is made up of keratinized tissues found on the hard palate, the gingiva, and the dorsum of the tongue, as well as nonkeratinized tissues that line the oral cavity. The cells of the oral mucosa turnover every 3 to 7 days, which makes the oral cavity one of the most sensitive indicators of adequate nutritional status. Intact mucosa is especially important in the oral environment because it is under constant attack by microorganisms and at high risk of trauma from food and oral hygiene activities.

Saliva also acts as a protective agent against periodontal pathogens because of several antibacterial components including lysozyme, lactoperoxidase, and antibodies [23]. Lysozymes exert a protective effect by breaking down the cell walls of both gram-negative and gram-positive bacteria [24], whereas lactoperoxidase's mechanism of action is to interfere with the accumulation of amino acids essential for bacterial growth [23]. Antibodies

found in saliva, such as immunoglobulin A (IgA), appear to protect oral tissues by inhibiting the attachment of bacteria to mucosal and tooth surfaces [23].

Leukocytes, including neutrophils and monocytes/macrophages, are the next line of defense in the oral cavity. These leukocytes mediate the immune response characteristic of periodontal diseases. The primary function of neutrophils is to contain the acute bacterial challenge through phagocytosis and killing of the pathogens that may result in "local tissue changes by releasing tissue-degrading enzymes" [9]. In contrast, monocytes are involved in the chronic inflammatory response by communicating with lymphocytes and presenting antigens to T cells [25]. The macrophages are central to the inflammatory process, in part, because of their ability to migrate through the vascular endothelium and enter the connective tissue where they rely on chemotaxis to help locate and migrate to the site of bacterial challenge. Chemotaxis is defined as movement in response to a chemical concentration gradient, such as movement from an area of low concentration to one of high concentration [25]. A defect in this ability to migrate is associated with the more severe types of periodontal diseases such as aggressive periodontitis [25].

Adaptive immunity

Lymphocytes (ie, T cells and B cells) are fundamental in adaptive immunity. These cells have the ability to recognize pathogens and generate offspring that also recognize the pathogens to allow the immune system to respond more quickly and efficiently when challenged [25]. Immune cells important in inflammation and host defense include mast cells, dermal dendrocytes, peripheral dendritic cells, neutrophils, monocytes/macrophages, T cells, B cells, and natural killer cells [25]. Mast cells and dermal dendrocytes are involved in acute inflammation and stimulate receptors that cause secretion of substances that cause vasodilation and increase vascular permeability [25]. Peripheral dendritic cells participate by ingesting antigens locally and transporting them to the lymph nodes [25]. The lymphocytes consist of T cells, B cells, and natural killer cells. T cells are cytotoxic and control intracellular antigens found in certain bacteria and fungi, whereas B cells help control extracellular antigens [25]. Natural killer cells are large phagocytic cells that recognize and kill certain tumor and virally infected cells [25]. Lymphocytes and monocytes are involved in the changes in the connective tissue associated with periodontal infection, repair, and healing [9].

Effects of nutrition on the immune response

The epidemiologic and clinical data suggest that nutritional deficiencies alter immune response and increase the risk of infection [21]. Most clinical studies of the impact of nutrition on the immune system in humans,

however, have been complicated by multiple nutrient deficiencies, as well as by infection. Thus, data from animal studies along with the clinical data have been useful in arriving at a consensus of how single nutrients affect the immune system [21]. Table 1 summarizes the impact of specific nutrient deficiencies on immune response.

Malnutrition and immunity

Although rarely seen in the United States, protein energy malnutrition (PEM) may be seen in certain high-risk groups, particularly in elderly and in hospitalized or institutionalized patients with chronic diseases [7,21,26]. Infection is a common precipitating factor for malnutrition among these high-risk groups [4]. Most host defense mechanisms are impaired in PEM [21]. The severity and the extent of immune function dysfunction in malnutrition are dependent on several factors that include (1) the rate of cell proliferation, (2) the amount and rate of protein synthesis, and (3) the role of nutrients in the various metabolic pathways [1].

Mild PEM may impair the acute-phase response to infection, resulting in reduced host ability to mount an effective inflammatory response to the invading pathogens [27]. The activation of lymphocytes and production of antibodies is correlated with PEM and protein intake [28]. Although leukocytes are still able to phagocytize bacteria, they are less effective at the subsequent intracellular destruction of the bacteria [29]. In animal models, the volume and antimicrobial properties of saliva are also severely compromised when protein intake drops to 5% to 8% of calories [30]. One of the antimicrobial properties decreased in saliva by a restriction in protein intake is in the amount of immunoglobulin secreted, such as IgA [29]. The lysozyme concentrations of saliva are also decreased as a result of a reduction in production by monocytes and neutrophils [1]. In addition, bacterial adhesion to epithelial cells appears to be increased in PEM, thereby increasing the risk of invasion and infection [31]. This compromise in the antimicrobial properties of saliva leads to an overgrowth of pathogenic microorganisms, particularly the anaerobic microflora [32]. These factors all act together to depress both the innate and adaptive immune responses, which increases the risk for infection.

Micronutrient deficiencies and immune response

Changes in immune response occur early in the course of reduction in micronutrient intake [21]. Several concepts have been suggested for the effect of micronutrient deficiencies on immune response: (1) the extent of impairment depends on the type of nutrient involved, its interaction with other essential nutrients, the severity of the deficiency, the presence of concomitant infection, and the age of the patient; (2) the extent of the abnormalities in the immune response predict the risk of infection and mortality; (3) excessive intake of micronutrients is associated with impaired immunity; and (4) tests of immunocompetence may be useful in assessing

Table 1
Summary of nutrient effects on immune response

Nutrient	Function	Deficiency impact on immune response[a]
Protein energy intake	Energy metabolism DNA/RNA synthesis	↓ salivary antimicrobial properties ↓ immunoglobulin production ↓ lysozymes ↑ bacterial adhesion ↓ activation of lymphocytes ↓ production of antibodies
Vitamin A	Cellular differentiation and proliferation Integrity of the immune system	↓ immune cell differentiation ↓ response to antigens ↓ antibody production ↑ bacterial adhesion ↓ immunoglobulin production ↓ production of lymphocytes
Vitamin E	Antioxidant protecting lipid membranes from oxidation	↓ antibody synthesis ↓ response of lymphocytes ↓ phagocytic function
Vitamin C	Antioxidant that reduces free radicals that cause DNA damage to immune cells	↓ phagocytic function of neutrophils and macrophages ↓ antibody response ↓ cytotoxic T-cell activity
Riboflavin, vitamin B_6, and panthothenic acid	Coenzymes in metabolic processes	↓ antibody synthesis ↓ cytotoxic T-cell activity ↓ lymphocyte response
Folic acid and vitamin B_{12}	Involved in DNA/RNA synthesis	↓ production of lymphocytes ↓ cytotoxic T-cell activity ↓ phagocytic function of neutrophils
Zinc	More than 100 enzymes associated with carbohydrate and energy metabolism Protein catabolism and synthesis Nucleic acid synthesis	↓ antibody response ↓ phagocytic function of macrophages ↓ B-cell and T-cell proliferation
Iron	Involved in hemoglobin, myoglobin, and cytochrome systems	↓ lymphocyte proliferation ↓ neutrophil cytotoxic activity ↓ antibody response

[a] ↓ indicates decrease, ↑ indicates increase.

appropriate levels of micronutrient intakes to optimize the immune response [21].

Fat-soluble vitamins and immune function. Experimental animals with vitamin A deficiency generally have an increased susceptibility to infection [4].

Vitamin A deficiency affects host defenses directly through its role in metabolism in immune cells and indirectly through its role in cell differentiation [6]. Immune cell proliferation is decreased, along with antigen-specific responses and antibody production [33–35]. In addition, bacterial adherence to epithelial cells is enhanced [31]. In humans, low plasma or serum vitamin A levels have been linked with impairment in immunity [36,37]. Conversely, vitamin A supplementation in deficiency enhances antibody levels and lymphocyte proliferation [36].

Vitamin E is a lipid-soluble antioxidant whose primary function is to reduce damage to lipid membranes [6]. In animal studies, vitamin E deficiency impairs adaptive immunity and results in a reduction in antibody synthesis [1]. In subjects who had levels 10% of normal, supplementation with vitamin E returned immune function to normal levels [38]. Vitamin E supplementation has been reported to enhance both innate and adaptive immunity; however, the level of supplementation that is effective in improving immunity requires further research [4,39,40].

Water-soluble vitamins and immune function. In view of the fact that water-soluble vitamins are involved in RNA and DNA synthesis and in cellular metabolism, deficiencies are likely to impact proliferation of immune cells. Deficiencies of vitamin C, vitamin B_6, panthothenic acid, riboflavin, folate, and vitamin B_{12} have the greatest effect, with biotin and thiamin having lesser effects.

Vitamin C is present in high amounts in neutrophils [41]. Due to its antioxidant properties, which reduce free radicals that cause DNA damage to immune cells, vitamin C enhances the migration of neutrophils to the site of infection, preserves the integrity of neutrophil cell structure, facilitates the oxidative destruction of microorganisms, and aids the host by neutralizing the toxic bacterial products produced by neutrophils during phagocytosis [32]. Moderate deficiencies of vitamin C result in a decrease in locomotion and a reduction in the bactericidal capacity of neutrophils and macrophages [1]. In animals, vitamin B_6, riboflavin, and panthothenic acid deficiencies cause profound changes in immune response. The aspects of adaptive immunity that are impacted include reductions in T-cell cytotoxicity, reduced lymphocyte response to antigens, and a decrease in antibody formation [42]. In humans, those deficient in both vitamin B_6 and panthothenic acid had a greater impairment of antibody response than when either nutrient was deficient alone [1]. These changes are primarily due to the function of these B vitamins as coenzymes in many metabolic processes.

Both folic acid and vitamin B_{12} have central roles in the nucleic acid synthesis necessary for cell growth and proliferation. Studies in both animals and humans demonstrate a reduction in T-cell populations, decreased cytotoxic function of the T cells, and impairment of phagocytosis by neutrophils in the presence of deficient intakes of folic acid and vitamin B_{12} [43–45].

Minerals and immune function. Significant literature exists linking the deficiency of certain minerals with negative changes in the immune response. The nutrients most widely studied have been iron and zinc because deficiencies in these minerals are still common in some populations in the United States. Both minerals also have essential functions in growth and development, making them necessary for the function of immune cells.

Zinc is involved in more than 100 enzymes associated with carbohydrate and energy metabolism, protein catabolism and synthesis, nucleic acid synthesis, and heme biosynthesis [46]. Even mild zinc deficiency may negatively impact the immune system, leading to an increased susceptibility to infection [6,46]. Examination of the NHANES III data suggests that children aged 1 to 3 years, adolescent females, and persons aged 71 years and over are at greater risk for inadequate zinc intakes [47].

Zinc deficiency is associated with an impaired T-cell and B-cell formation in the bone marrow resulting in a depressed lymphocyte response to antigens [21,48]. In addition, suboptimal levels of zinc have been demonstrated to lower the killing ability of macrophages [48,49]. In animal studies, mortality was increased due to infectious organisms [50]. Conversely, excessive intake of supplemental zinc has been shown to cause functional impairment of the immune response [51]. The tolerable upper-intake level is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for a majority of individuals [46]. The tolerable upper-intake level of zinc for those aged 19 years and over has been set at 40 mg/day [46]. These recommendations suggest that zinc supplementation should be approached with caution.

Iron deficiency remains one of the most common deficiencies worldwide and is the most prevalent nutrient deficiency in the United States in children and women of childbearing age [6]. The prevalence ranges from 9% in children under 4 years of age to 29% in low-income pregnant females [52,53].

Iron is involved in hemoglobin, myoglobin, and cytochrome systems [46]. Its role in the movement of oxygen from the environment to cells such as those of the immune system and its role in cytochrome enzymes impact both innate and adaptive immunity. The neutrophils' bactericidal activity is impaired by iron deficiency [21,54]. In addition, the proliferation of lymphocytes is reduced, along with their response to antigens, increasing the risk and severity of infection [21,54]. The ability of an infectious pathogen to sequester iron from the host tissues is considered an important virulence factor, and it explains recommendations to limit iron supplementation during active infection.

Effect of infection on nutritional status

Infection has adverse effects on nutritional status through its catabolic effects on body systems [4]. During infection, a series of metabolic events are

set in motion that lead to a state of negative nitrogen balance and loss of lean body mass [55].

This process occurs as a consequence of an imbalance between catabolic and anabolic substances such as cytokines and glucocorticoids produced by the body in response to infection. Cytokines are responsible for producing fever and enhancing thermogenesis, body weight loss, and skeletal muscle depletion [55].

The extent of the increased nutrition needs of a patient is determined by the extent of the infection and the degree of stress imposed on the patient [56]. The average loss of protein during infection is 0.6 g of protein per kilogram per day, with higher losses being seen in those with more severe infections [4]. The increased excretion of nitrogen, leading to negative nitrogen balance associated with infection, may also result from the trauma induced by surgery. Medical nutrition therapy guidelines suggest that mild stress increases the protein requirement from 0.8 g/kg of body weight per day to 1.0 g/kg of body weight per day [56]. Although nitrogen balance studies have not been performed with individuals following oral surgery and, therefore, the extent of the impact on nitrogen balance is not known, it is likely that most oral and periodontal surgeries fall into the category of minor surgery with mild stress, so these guidelines are likely to be a reasonable recommendation for patients.

Anorexia is often a consequence of infection and results in undernutrition and contributes to negative nitrogen balance. The term *anorexia* in this context refers to a loss of appetite that often accompanies malaise, fever, and infections [57]. A consequence of anorexia is the precipitation of nutrient deficiencies for any nutrients for which the individual already had marginal or suboptimal intakes [4].

The gastrointestinal tract is negatively impacted by infection and alterations in nutrient intake, which may result in symptoms such as diarrhea, nausea, and vomiting. The disruption in the gastrointestinal mucosa results in decreased nutrient absorption [4]. As a result of malabsorption, protein absorption may be reduced as much as 10% to 30% [4]. In addition, vitamin A absorption may be reduced as much as 30% to 70% [4].

Infections tend to induce a state of hypermetabolism, causing an increase in energy requirements that range from 1.2% of normal caloric requirements to 100% of normal caloric requirements in burn victims [56]. It is extremely important during periods of infection for individuals to have adequate caloric intakes in order to spare amino acids for maintenance and synthesis of body proteins [56]. If the individual does not obtain adequate calories, then the body will break down the amino acids and body protein stores for energy [56].

During infections, it is not uncommon for fevers to develop that also increase caloric needs. Fever adds another 9% beyond normal calorie requirements for each 1°F greater than 98.6 [56]. During periods of fever, basal metabolic rate may increase by nearly one third [4].

In addition, infection causes negative balances of vitamin A, vitamin C, B vitamins, zinc, iron, potassium, phosphates, magnesium, sulfates, and plasma amino acids. This decrease may be a result of malabsorption, losses in diarrhea, and/or increased needs to combat the infection. Interestingly, infection decreases serum iron as a result of it being sequestered in the reticuloendothelial system, which deprives the infectious agent of the iron it needs for replication and inhibits the spread of infection [4].

Populations at risk for alterations in immune status

Patients with compromised immune systems are being seen with increasing frequency in private dental practice due to advances in medical treatment. Changes in immunity may result in an impaired ability to respond to a bacterial challenge. The impaired immunity may be either a primary or secondary immunodeficiency disorder.

Most of the problems seen in dental offices are likely to be a result of secondary immunodeficiencies that result in the immune system being depressed due to a medication or underlying illness in a person who was previously "healthy" [57]. Immune depression commonly occurs in AIDS, cancer, organ transplant, and autoimmune disease such as rheumatoid arthritis and lupus erythematosis. In addition to direct effects on the immune system, these conditions also impact nutritional status by a number of mechanisms including interference with nutrient absorption, inadequate dietary intake due to anorexia, and increased need for some nutrients. Other conditions such as alcoholism, renal disease, burns, and gastrointestinal disorders may also impact nutritional status by the same mechanisms [6].

Nutritional status may also be impacted by drug-nutrient interactions such as with corticosteroids, dilantin, methotrexate, and cyclosporine used to treat chronic diseases and conditions [58]. For example, corticosteroids increase catabolism of protein and interfere with absorption of calcium, vitamin D, folic acid, and other nutrients, placing the patient at risk for inadequate nutrient intakes that may further impact the immune system.

In addition to the effects of chronic disease and drug-nutrient interactions, there is evidence that the immune system becomes depressed in older populations [7,21,26]. *Immune senescence* appears to be a natural consequence of aging and is defined as the decline of the immune response [7]. Lesourd and Mazari [5], however, disagreed with this finding and, instead, suggested that "there is strong evidence that nutritional status greatly influences immune responses in aged individuals, and that this is an important part of what is known as immune aging." In healthy elderly subjects with normal serum values for trace elements, no ongoing or developing degenerative diseases, and no drugs that impacted nutrient or immune status, measures of adaptive immunity closely resembled those of young adult controls, supporting the idea that it is undernutrition that induces changes in immune response [5].

Up to 65% of elderly patients admitted to the hospital are undernourished, which is associated with adverse clinical outcomes [59]. In the European Reference Study on Nutrition and Aging, 30% of aging adults had a low serum level of at least one nutrient, which might be responsible for the reduction seen in the immune response [5]. It is likely that the appearance of immune senescence is due to this group's high risk for malnutrition and suboptimal nutrient intakes because of a variety of issues common to this age group. These issues include physical conditions common to the aged, such as disability, medication-induced anorexia, oral disorders, gastrointestinal disease, and metabolic disorders (such as diabetes mellitus and renal disorders). In addition, this age group has psychosocial issues such as living alone, bereavement, and depression that may lead to a reduction in nutrient intakes [7]. Research suggests that the primary goal of nutrition in the elderly is to prevent or reverse secondary immune deficiencies resulting from undernutrition [5,7].

Effects of dietary intake on periodontal health

Although the nutritional risks contributing to periodontal disease are not well established at present, recent epidemiologic findings suggest that there is some association between inadequate intakes of certain nutrients and periodontal disease [60,61]. The difficulty in determining the impact of nutrition on periodontal diseases is complicated by confounding factors and ethical issues in conducting controlled deficiency studies on human subjects.

The epidemiologic data from NHANES III suggest that the odds of having periodontal disease were 20% greater with low intakes of vitamin C [60]. Controlled studies of patients with periodontal disease and apparently healthy adults with vitamin C intakes of 5 mg/day to 1500 mg/day have shown mixed results regarding the influence of vitamin C status on periodontal integrity [38,62–66]. In summary, there appears to be some link between vitamin C and periodontal health, but the nature of that relationship remains unclear [38].

The NHANES III data regarding calcium intake suggest that there is a 56% greater risk of periodontal disease with calcium intakes of 500 mg/day and a 27% greater risk for those consuming from 500 mg/day to 800 mg/day of calcium [61]. These numbers become important when we consider that the average calcium intake for females aged 9 years and over is 657 mg/day and that the intake for individuals with lactose intolerance averages 320 mg/day, placing these groups at higher risk for periodontal disease [67].

Conversely, a study in adolescent girls found a significantly decreased risk for gingivitis with higher intakes of calcium and riboflavin and increased frequency of fiber intake [68]. The number of meals and snacks with fiber intake were associated with healthy gingivae, whereas total quantity of fiber was not [68]. The researchers hypothesize that this effect may have been from

the antioxidant substances in fruits and vegetables that promoted healing of the periodontal tissues [68–70]. In terms of the low probability of gingivitis in the adolescents with higher intakes of calcium and riboflavin, the effect may be explained by the importance of these nutrients in maintaining host resistance and periodontal health [68]. It also is likely, however, that because these nutrients are both prominent in milk products, it is some other component of milk not yet identified that had the antigingivitis effect.

To sum up, none of these findings prove the cause and effect of nutrition on periodontal diseases but instead suggest an association. It is likely that rather than a direct effect on periodontal diseases, suboptimal nutrition may be a conditioning factor, making a host more susceptible to the development of periodontal disease such as gingivitis [63].

Nutrition strategies to enhance immunity and prevent infection

Nutrition plays an important role in maintenance of the optimal functioning of the immune response. Individuals who are undernourished have impaired immune responses including abnormalities in adaptive immunity, phagocytosis, and antibody function [21]. Animal studies suggest that providing adequate levels of specific nutrients such as protein is associated with improved immunocompetence and reduced mortality after infectious challenge [3]. These findings point to the need to initiate nutritional strategies that may help reduce the occurrence of opportunistic infections in immunocompromised patients [3].

The previous nutritional status of the patient, the nature and duration of the infection, and dietary intake during recovery are important aspects of nutrition that must be considered in order to improve the outcomes of periodontal treatment, as well as other invasive dental procedures. A nutritional assessment will help identify individuals with marginal nutritional status or poor dietary habits who will benefit from nutritional rehabilitation prior to extensive dental treatment.

The American Dental Association and the American Dental Hygiene Association recommend following nutrition recommendations such as the USDA Food Guide Pyramid and the *Dietary Guidelines for Americans* [71,72] as basic guidelines for ''educating and counseling their patients about proper nutrition and oral health.'' The average American diet contains more than adequate amounts of protein and calories; however, patients should also be encouraged to include nuts and legumes to meet some of their protein needs, which will also increase intakes of vitamin E, copper, and boron.

The average intake of fruits and vegetables in the United States is around two servings per day, which is significantly below the recommendation of three to five servings of vegetables and two to four servings of fruit. Fruits and vegetables are excellent sources of vitamins A, C, and K, beta-carotene, and magnesium.

Low-fat dairy products should also be encouraged as excellent sources of protein, calcium, vitamin A, and vitamin D. Two to four servings of dairy products per day are needed to meet the new recommended dietary allowance. Those who are lactose intolerant consume an average of 325 mg/day of calcium, which is only 25% of the current recommended dietary allowance of 1000 mg/day to 1300 mg/day, placing these patients at risk of poor healing following implants and regeneration procedures. Patients avoiding dairy products need to find alternative sources of calcium such as fortified soy milk, rice milk, or orange juice, to name a few. Supplements should be a last resort because they are often forgotten and are more expensive than using food as a nutrient source.

For anyone with marginal nutrient intakes, more than the average intakes of the USDA Food Guide Pyramid may be required to replete nutrient levels. In individuals with chronic disease and in the elderly, a multivitamin with minerals that has 100% of the recommended dietary allowance levels taken daily may be beneficial for the prevention of infection and to facilitate healing [7]. Supplementation with individual nutrients may need to be provided for individuals with documented nutrient deficiencies, but the use megadoses of nutrients should be discouraged until more research supports their long-term daily use. Any patient with complex nutritional needs should be referred to a registered dietitian for individualized nutritional advice.

Summary

Even though nutrition is not recognized as a risk factor for periodontal diseases, nutrition is acknowledged to have a significant impact on optimal functioning of the immune response. Dental professionals need to routinely assess nutritional status and provide basic nutrition counseling to their patients to ensure optimal functioning of the immune system in combating infection and to promote optimal periodontal health.

References

[1] Chandra RK. Nutrition and immunity: lessons from the past and new insights into the future. Am J Clin Nutr 1991;53:1087–101.
[2] Chandra RK. Cellular molecular basis of nutrition-immunity interactions. Adv Exp Med Biol 1990;262:13–8.
[3] Chandra RK. Nutrition and immunoregulation. Significance for host resistance to tumors and infectious disease in human and rodents. J Nutr 1992;122:754–7.
[4] Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr 1997;66:464S–77S.
[5] Lesourd B, Mazari L. Nutrition and immunity in the elderly. Proc Nutr Soc 1999;58:685–95.
[6] Field CJ, Johnson IR, Schley PD. Nutrients and their role in host resistance to infection. J Leukoc Biol 2002;71:16–32.

[7] High KP. Nutritional strategies to boost immunity and prevent infection in elderly individuals. Clin Infect Dis 2001;33:1852–900.
[8] Hollister MC, Weintraub JA. The association of oral status with systemic health, quality of life, and economic productivity. J Dent Educ 1993;75:901–12.
[9] Haake SK, Nisengard RJ, Newman MG, Miyasaki KT. Microbial interactions with the host in periodontal diseases. In: Newman MG, Takei HH, Carranza FA, editors. Carranza's clinical periodontology. 9th edition. Philadelphia: W.B. Saunders; 2002. p. 132–52.
[10] Beck JD, Arbes SJ. Epidemiology of gingival and periodontal diseases. In: Newman MG, Takei HH, Carranza FA, editors. Carranza's clinical periodontology. 9th edition. Philadelphia: W.B. Saunders; 2002. p. 74–94.
[11] Haake SK, Newman MG, Nisengard RJ, Sanz M. Periodontal microbiology. In: Newman MG, Takei HH, Carranza FA, editors. Carranza's clinical periodontology. 9th edition. Philadelphia: W.B. Saunders; 2002. p. 96–112.
[12] Loesche WJ. Importance of nutrition in gingival crevice microbial ecology. Periodontics 1968;6:245–49.
[13] Grenier D. Nutritional interaction between two suspected periodontopathogens, *Trepnema denticola* and *Porphyromonas gingivalis*. Infect Immun 1992;60:5298.
[14] Mayrand D, McBride BC. Ecological relationships of bacteria involved in a simple, mixed anaerobic infection. Infect Immun 1980;27:44.
[15] Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: current concepts. J Periodontol 1992;63:322.
[16] Moore WE, Moore LV. The bacteria of periodontal diseases. Periodontol 2000 1994; 5:66.
[17] Slots J. Subgingival microflora and periodontal disease. J Clin Peridontol 1979;6:351.
[18] Bowden GH, Li YH. Nutritional influences on biofilm development. Adv Dent Res 1997;11:81–9.
[19] Schilling KM, Blitzer MH, Bowen WH. Adherence of *Streptococcus mutans* to glucans formed *in situ* in salivary pellicle. J Dent Res 1989;68:1678–80.
[20] Fletcher M. The physiological activity of bacteria attached to solid surfaces. Adv Microb Physiol 1991;32:52–85.
[21] Chandra RK. Nutrition and the immune system: an introduction. Am J Clin Nutr 1997;66:440S–3S.
[22] Cunningham-Rundles S. Analytical methods for evaluation of immune response in nutrient intervention. Nutr Rev 1998;56:S27–37.
[23] Bulkacz J, Carranza FA. Defense mechanisms of the gingiva. In: Newman MG, Takei HH, Carranza FA, editors. Carranza's clinical periodontology. 9th edition. Philadelphia: W.B. Saunders; 2002. p. 254–62.
[24] Iacono VC, Bolot PR, Mackay JB, et al. Lytic sensitivity of *Actinobacillus actinomycetemcomitans* to lysozyme. Infect Immun 1983;40:773.
[25] Miyasaki KT, Nisengard RJ, Haake SK. Immunity and inflammation: basic concepts. In: Newman MG, Takei HH, Carranza FA, editors. Carranza's clinical periodontology. 9th edition. Philadelphia: W.B. Saunders; 2002. p. 113–31.
[26] Meydani SN. Micronutrients and immune function in the elderly. Ann N Y Acad Sci 1990;587:196–207.
[27] Sherman AR. Zinc, copper, and iron nutriture and immunity. J Nutr 1992;122:604–9.
[28] Cooper WC, Good RA, Mariani T. Effects of protein insufficiency on immune response. Am J Clin Nutr 1974;27:212–8.
[29] Chandra RK. Numerical and functional deficiency in T helper cells in protein-energy malnutrition. Clin Exp Immunol 1983;51:126–32.
[30] Johnson DA, Lopez H, Navia JM. Effects of protein deficiency and diet consistency on the parotid gland and parotid saliva of rats. J Dent Res 1995;74:1444–52.
[31] Chandra RK, Gupta SP. Increased bacterial adherence to respiratory and buccal epithelial cells in protein-energy malnutrition. Immunol Infect Dis 1991;1:55–7.

[32] Enwonwu CO. Cellular and molecular effects of malnutrition and their relevance to periodontal diseases. J Clin Periodontol 1994;21:643–57.
[33] Butera ST, Krakowka S. Assessment of lymphocyte function during vitamin A deficiency. Am J Vet Res 1986;47:850–5.
[34] Cohen BE, Elin RJ. Vitamin A-induced nonspecific resistance to infection. J Infect Dis 1974;129:597–600.
[35] Carman JA, Smith SN, Hayes CE. Charcterization of a helper T-lymphocyte defect in vitamin A deficient mice. J Immunol 1989;142:388–92.
[36] Coutsoudis A, Kiepiela P, Coovadia HM, Broughton M. Vitamin A supplementation enhances specific IgG antibody levels and total lymphocyte numbers while improving morbidity in measles. Pediatr Infect Dis 1992;11:203–9.
[37] Semba RD, Scott AL, Natadisastra G, Wirasasmita S, et al. Depressed immune response to tetatnus in children with vitamin A deficiency. J Nutr 1992;122:101–7.
[38] Food and Nutrition Board. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: Institute of Medicine; 2000.
[39] Meydani SN, Barklund PM, Liu S. Effect of vitamin E supplementation on immune responsiveness of healthy elderly subjects. Am J Clin Nutr 1990;52:557–63.
[40] Meydani SN, Meydani M, Blumberg JB, Leka LS, Siber G, Loszewski R, et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. J Am Med Assoc 1997;277:1380–6.
[41] Washko P, Rotrosen D, Levine M. Ascorbic acid in human neutrophils. Am J Clin Nutr 1991;54:1221S–7S.
[42] Sudhakaran L, Chandra RK. Vitamin B_6 and immune regulation. Ann N Y Acad Sci 1990;585:404–23.
[43] Gross RL, Reid JVO, Newberne PM, et al. Depressed cell-mediated immunity in megaloblastic anemia due to folic acid. Am J Clin Nutr 1975;28:225–32.
[44] Youinou PY, Garre MA, Menez JF, et al. Folic acid deficiency and neutrophil dysfunction. Am J Med 1982;73:652–7.
[45] MacCuish AC, Urbaniak SJ, Goldstone AH, et al. PHA responsiveness and subpopulations of circulating lymphocytes in pernicious anemia. Blood 1974;44:849–55.
[46] Food and Nutrition Board. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academy Press; 2001.
[47] Briefel RR, Bialostosky K, Kennedy-Stephenson J, McDowell MA, Ervin RB, Wright JD. Zinc intake of the U.S. population: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Nutr 2000;130:1367S–73S.
[48] Fraker PJ, King LE, Laako T, Vollmer TL. The dynamic link between the integrity of the immune system and zinc status. J Nutr 2000;130:1399S–411S.
[49] Wirth JJ, Fraker PJ, Kierszenbaum F. Zinc requirement for macrophage function: effect of zinc deficiency on uptake and killing of a protozoan parasite. Immunology 1989;68:114–9.
[50] Fraker PJ, Caruso R, Kierszenbaum F. Alteration of the immune and nutritional status of mice by synergy between zinc deficiency and infection with *Trypanosoma cruzi*. J Nutr 1982;112:1224–9.
[51] Chandra RK. Excessive intake of zinc impairs immune responses. JAMA 1984;252:1443–6.
[52] U.S. Department of Health and Human Services. Healthy people 2010: understanding and improving health and objectives for improving health. 2nd edition. Washington (DC): USDHHS, Government Printing Office; 2000.
[53] Frith-Terhune AL, Cogswell ME, Khan LK, Will JC, Ramakrishnan U. Iron deficiency anemia: higher prevalence in Mexican American than in non-Hispanic white females in the Third National Health and Nurtition Examination Survey, 1988–1994. Am J Clin Nutr 2000;72:963–8.
[54] Oppenheimer SJ. Iron and its relation to immunity and infectious disease. J Nutr 2001; 131:616S–33S.

[55] Chang HR, Bistrain B. The role of cytokines in the catabolic consequences of infection and injury. J Parenter Enteral Nutr 1999;22:156–66.
[56] Zeman FJ, Ney DM. Applications of clinical nutrition. Englewood Cliffs (NJ): Prentice Hall; 1988.
[57] Thomas CL. Taber's cyclopedic medical dictionary. 17th edition. Philadelphia: FA Davis; 1993.
[58] Moons P, De Geest S, Abraham I, Cleemput JV, Van Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: patients' appraisal of side effects. Heart Lung 1998;27:315–25.
[59] Covinsky KE, Martin GE, Beyth RJ, et al. The relationship between clinical assessments of nutritional status and adverse outcomes in older hospitalized medical patients. J Am Geriatr Soc 1999;47:532–8.
[60] Nishida M, Grossi SG, Dunford RG, Ho AW, Trevisan M, Genco RJ. Dietary vitamin C and the risk for periodontal disease. J Periodontol 2000;71:1215–23.
[61] Nishida M, Grossi SG, Dunford RG, Ho AW, Trevisan M, Genco RJ. Calcium and the risk for periodontal disease. J Periodontol 2000;71:1057–66.
[62] Woolfe SN, Kenney EB, Hume WR, Carranza FA. Relationship of ascorbic acid levels of blood and gingival tissue with response to periodontal therapy. J Clin Peridontol 1984;11:159–65.
[63] Nakamoto T, McCroskey M, Mallek HM. The role of ascorbic acid deficiency in human gingivitis—a new hypothesis. J Theor Biol 1984;108:163–71.
[64] Leggott PJ, Robertson PB, Rothman DL, Murray PA, Jacob RA. The effect of controlled ascorbic acid depletion and supplementation on periodontal health. J Periodontol 1986; 57:480–5.
[65] Vogel RI, Lamster IB, Wechsler SA, et al. The effects of megadoses of ascorbic acid on PMN chemotaxis and experiemental gingivitis. J Periodontol 1986;57:471–9.
[66] Leggott PJ, Robertson PB, Jacob RA, Zambon JJ, Walsh M, Armitage GC. Effects of ascorbic acid depletion and supplementation on periodontal health and subgingival microflora in humans. J Dent Res 1991;70:1531–6.
[67] Food and Nutrition Board. Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington (DC): National Institute of Medicine; 1997.
[68] Petti S, Cairella G, Tarsitani G. Nutritional variables related to gingival health in adolescent girls. Community Dent Oral Epidemiol 2000;28:407–13.
[69] Konig KG, Navia JM. Nutritional role of sugars in oral health. Am J Clin Nutr 1995;62:275S–83S.
[70] Asman B, Wijkander P, Hjerpe A. Reduction of collagen degradation in experimental granulation tissue by vitamin E and selenium. J Clin Peridontol 1995;21:45–7.
[71] American Dental Hygiene Association. Public health: nutrition. Chicago (IL): American Dental Hygiene Association.
[72] American Dental Association. Preventive health statement on nutrition and oral health. Transactions 1996;682.