Public Health Implications of Periodontal Infections in Adults: Conference Proceedings

Introduction

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The Centers for Disease Control and Prevention (CDC) plays a major role in assuring a strong science base for public health action. CDC's mission focuses on detecting, assessing, and monitoring threats to public health; building the capacity of state and local health agencies; and supporting applied and community-based research and population-level efforts to prevent disease and promote health. Such efforts can include health policy changes at many levels (e.g., clean indoor air laws, mandatory insurance coverage for specific health services, proof of immunization for school enrollment), and health communication designed for key groups.

In light of these responsibilities and recent professional and public interest in the expanding science base on the association of periodontal infections and systemic disease, CDC convened a meeting of experts from multiple disciplines to address the "Public Health Implications of Periodontal Infections in Adults." That meeting was held April 8-9, 2003, in Atlanta, Georgia. The experts presented research findings and provided insight regarding associations between periodontal infections and four categories of systemic disease (cardiovascular diseases, diabetes, reproductive health and respiratory infections), and examined the public health implications for each association. A goal of this meeting was to determine if the science behind these associations is of sufficient quality and strength to warrant population-based interventions to prevent and control periodontal infections as a risk factor for these systemic outcomes. Representatives from dental professional associations were invited to hear the presentations and contribute to open discussion of issues raised. The following pages provide abstracts of the expert's presentations.

CDC and others have recognized that the development, implementation, and evaluation of public health interventions require an ability to monitor periodontal diseases in populations. Such monitoring should be ongoing and systematic, and analysis and interpretation of health-related data should be used to guide public health practice. Current measures of periodontal infections are extremely resource-intensive and often outside the reach for inclusion in state and local surveillance systems. A second goal of this meeting was to establish an expert work group to research and recommend alternative pragmatic and valid population-based surveillance measures for periodontal disease. A summary of the group's initial activities is included.

This conference was initiated by the Division of Oral Health, and supported by three other Divisions of the National Center for Chronic Disease Prevention and Health Promotion, specifically, those responsible for reproductive health, cardiovascular health, and diabetes. The Center also has an office that addresses issues related to tobacco and health. Collectively, the Center and its divisions have many years of experience building public health programs in the states to prevent and control chronic diseases. That experience can help guide and foster future activities and efforts resulting from this meeting.

We are especially grateful to the American Academy of Periodontology (AAP) for its active role in collaborating with CDC to plan the content and format of this meeting and shape the goals and ongoing efforts of the surveillance work group. AAP's partner, Sunstar Inc. (and the John O. Butler Company) generously underwrote the meeting hospitality and amenities.

Introduction to Periodontal Diseases: Clinical Presentations, Etiology, and Pathogenesis

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Periodontitis is a chronic infectious disease that affects approximately 34% of the American population over age 30 (about 36 million persons). It is of sufficient severity to lead to tooth loss in about 13 % of adults. The disease begins as an acute inflammation of the gingival tissue known as gingivitis, manifested by bleeding especially upon tooth brushing. In susceptible individuals, gingivitis progresses to periodontitis in which the destructive inflammatory process extends into the deeper periodontal tissues. Periodontitis is manifested clinically by gingival bleeding, loss of periodontal attachment as detected by increasing probing depth around the necks of the teeth, and radiographic loss of alveolar bone. As the disease advances, the teeth may become loose, periodontal abscesses may form and the affected teeth may be lost. The disease is a major cause of tooth loss in adults.

Periodontitis is caused by a small group of predominantly gram-negative, anaerobic bacteria among which *Porphyromonas gingivalis* is especially important. Biofilms containing these pathogenic bacteria form on the tooth surfaces and extend apically between the surface of the tooth root and gingiva to cause a destructive inflammation that destroys the attachment of gingival tissue to the tooth. Consequently, periodontal pockets form and col-

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lagenous fibers of the periodontal ligament and the bony housing of the tooth roots are destroyed.

Lipopolysaccharide, antigenic bacterial components, and intact bacteria have ready access through the ulcerated pocket wall into the inflamed tissue where they may enter the circulation and become systemically disseminated. Bacteria and their components incite a dense infiltrate of inflammatory cells including neutrophilic granulocytes, macrophages, and lymphoid cells. Bacterial substances activate macrophages and neutrophilic granulocytes to produce and release large quantities of proinflammatory cytokines and prostanoids especially IL-l, TNF-alpha, PGE_2 and matrix metalloproteinases. Resident connective tissue fibroblasts also participate in this process. Binding of the Cl component of complement and cytokines such as IL-1 and TNF-alpha causes the fibroblasts to contribute to the growing concentrations of proinflammatory cytokines, prostaglandins, and matrix metalloproteinases. Prostaglandin E_2 mediates alveolar bone destruction, and the matrix metalloproteinases destroy the collagens and other connective tissue components of the gingiva and periodontal ligament.

A growing body of evidence suggests that periodontitis, in addition to being a major cause of tooth loss in adults, also enhances risk for several potentially death-dealing systemic diseases and conditions. This enhanced risk may be related to the systemic dissemination of gram-negative, anaerobic bacteria and their components present in subgingival biofilms, as well as inflammatory mediators that reach very high levels in the diseased periodontal tissues.

Population Aspects, Smoking, and Other Modifiable Risk Factors for Periodontal Disease

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This review considers the distribution of gingivitis and chronic periodontitis in the U.S. population and the effects of oral hygiene and smoking as risk factors for those conditions. Gingivitis is widely prevalent in its milder forms, but only a few gingivitis sites progress to periodontitis. The majority of any adult population has periodontitis to some degree, though only 5% to 15% of any population suffers from severe, generalized periodontitis.

Two important incidence studies have confirmed both the episodic nature of periodontal destruction and how susceptibility varies in a population. The apparent increase in the severity of periodontitis with age, noted in cross-sectional studies, is considered to come from the long-term cumulative effects of bacterial plaque rather than from increasing susceptibility with age. While it is clear that plaque deposits are the prime cause of gingivitis, the relationship of oral hygiene to periodontitis is less straightforward. Oral hygiene can favorably influence the ecology of the microbial flora in shallow-to-moderate pockets but because it does not affect host response oral hygiene alone has little effect on established periodontitis. There is evidence however, that frequent professional supragingival cleaning, when added to good oral hygiene, inhibits the proliferation of subgingival microbiota in moderately deep pockets.

Smoking is clearly a risk factor for periodontal diseases, with the relative risk of periodontitis attributable to tobacco, compared to its non-use, on the order of 2.5 to 6.0 or even higher. Smoking has adverse effects on periodontitis progression and healing after treatment, and widespread tobacco use in past decades may have contributed periodontitis in the population. Cessation of smoking is basic to any periodontitis treatment.

Genetic Aspects of Periodontal Diseases

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Both clinical observation and experimental evidence indicate that there is a genetic component to risk for periodontitis in adults. Severe and aggressive forms of periodontitis are not common in the population, indicating that host susceptibility is important in determining such risk. Since all forms of periodontitis are associated with bacterial infections, the challenge of defining the relative roles of genes and environmental factors in these complex diseases is substantial. In the case of chronic periodontitis, studies of adult twins indicate that a substantial proportion of the population variance for periodontal measures such as pocket depth, attachment loss, and bone loss maybe attributable to heritable factors. Heritability estimates for these factors are approximately 50%. For aggressive periodontitis, data indicate that this group of diseases is commonly familial and family studies indicate that there is a substantial heritable component to risk for these diseases.

Current approaches to defining genetic risk factors for periodontitis include examination of genetic polymorphisms in candidate genes associated with the pathobiology of periodontitis and linkage and association studies in families demonstrating disease. Some genetic polymorphisms that have thus far been shown to be associated with risk for various forms of periodontitis in various populations are in genes that code for inflammatory cytokines such as interleukin 1 and tumor necrosis factor, immunoglobulin receptors that are present on phagocytes, and the vitamin D receptor. In addition, genes associated with environmental risk factors such as smoking also may influence periodontitis.

Fundamental problems in studying genetic risk for these diseases are associated with: 1) phenotype definition, which is confounded by their heterogeneity and overlapping clinical definitions; 2) clinical variability in disease presentation that may include age-dependent criteria for diagnoses; 3) the substantial dependence of disease expression on environmental etiologies such as bacterial flora and smoking; 4) systemic diseases influencing disease initiation and 5) severity and modification of the phenotype by intentional or inadvertent intervention.

Thus far, results of studies of genetic risk for periodontitis indicate that these diseases are etiologically complex.

Although the ultimate utility of knowledge of genetic risk factors for periodontitis is not known, it is likely that genetic tests could help clinicians and researchers to determine diagnoses based on etiology, better assess prognoses for symptomatic patients, predict future onset of disease, and tailor therapy based on this information. It is likely that genetic factors, once defined, will become one component of the overall risk profile for periodontitis.

Periodontal Diseases and Respiratory Infections

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Several studies have suggested an association among dental plaque, poor oral health, and respiratory disease. Many case studies have described bacteria normally found in the oral cavity to be associated with lung infections. In addition, oral health status may affect nosocomial pneumonia and chronic obstructive pulmonary disease.

It has been demonstrated that the mouth may serve as a reservoir of infection for potential respiratory pathogens in high-risk patients, for example those admitted to intensive care units of hospitals or nursing homes. Bacteria recognized as potential respiratory pathogens have been routinely cultured from the dental plaque of these subjects. It is possible that these organisms can be aspirated into the lower airway to cause infection.

The most provocative evidence obtained to date that supports a role for dental plaque in the etiology of pneumonia comes from several intervention studies that have demonstrated a reduction in respiratory infection following improvements in oral hygiene in high-risk subjects.

One prospective, randomized, double-blind, placebo-controlled clinical trial found that patients given oral topical 0.12% chlorhexidine gluconate had a reduced rate of pneumonia (by 65%) in contrast to control group given a placebo. Other studies have found that dental plaque colonization by PRPs and a higher dental plaque score on admission to the intensive care unit predict the onset of pneumonia within 15 days. Studies of nursing-home patients demonstrate that simple mechanical tooth brushing supplemented with mouth irrigation with an iodine solution significantly reduces the rate of pneumonia. These studies suggest that oral disinfection shows promise as a simple and inexpensive strategy for reducing the rate of pneumonia in high-risk subjects.

The available evidence suggests that poor oral hygiene resulting in the formation of extensive oral biofilms (plaque) promotes oral colonization by potential respiratory pathogens. Pneumonia is a very prevalent disease, causing 100,000 deaths in the United States each year. A significant proportion of the general population (~10%) and an even greater proportion of older subjects demonstrate destructive periodontal disease (~50%). The latter group is most affected by pneumonia. Hence, even a modest effect of poor oral health on pneumonia would have great public health implications.

The Inflammatory Link between Periodontitis and Cardiovascular Diseases

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Within the oral health community, there is considerable interest in recently identified associations between periodontal disease and other systemic inflammatory diseases; such as cardiovascular disease. Recent work in animal models suggests that there may be a cause-effect relationship between periodontal disease and cardiovascular lesions. New technology has been developed to control inflammation in periodontal disease with the aim of preventing periodontal disease progression.

Naturally occurring novel lipid compounds have been identified; they are responsible for the natural resolution of an inflammatory lesion. These compounds, called lipoxins, act on specific inflammatory cells through specific receptors that result in down regulation of inflammatory cell function. Proof-of-principle experiments have been conducted in animals that demonstrate that topical application of stable lipoxin analogs are effective in preventing the onset of gingivitis and periodontitis. Further experiments investigating the relationship between periodontal disease and cardiovascular disease were carried out to determine the effect of lipoxins on the progression of both conditions. Results revealed that lipoxins were effective in preventing both periodontitis and cardiovascular lesions in the same animal.

These data suggest that a relationship exists between periodontitis and the initiation of atherosclerosis and that anti-inflammatory therapy using this novel class of compounds was effective in preventing the onset of both diseases. Lipoxins and their analogs are safe, none toxic, and readily absorbed with topical application.

Periodontitis and Cardiovascular Diseases – Comorbid Conditions?

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Apparently well-controlled epidemiological analyses of data from the First National Health and Nutrition Examination Survey (NHANES I) demonstrate that coronary heart disease increases the risk for incident lung cancer by 60% ($p < 0.05$). Does this mean that coronary heart disease causes lung cancer? Probablynot. Lung cancer and coronary heart disease are comorbid conditions - conditions or diseases that co-exist due to common causal factors. By definition, associations between comorbid conditions are to be expected.

Are periodontitis-systemic disease associations a reflection of comorbidity? Periodontitis, lung cancer, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, and low birth weight are additional examples of comorbid conditions –diseases or conditions that co-exist due the presence of a common causal factor – smoking.

Five lines of evidence indicate that smoking is the primary contributor of the purported periodontitis-systemic disease associations. First, no periodontitis-systemic dis-

ease associations have been identified among never-smokers. Second, periodontitis and smoking mimic one another almost perfectly with respect to the types of diseases they are associated with. Third, only studies with inadequate adjustment for smoking report significant periodontitis-systemic disease associations. Fourth, dental infection elimination, unlike smoking cessation, does not reduce coronary heart disease risk or C-reactive protein levels. Fifth, in NHANES III, probing attachment levels predict serum cotinine levels, even when taking into consideration self-reported cigarette use. Unless it can be shown that plaque secretes nicotine, or that attachment loss causes alterations in nicotine absorption or metabolism, the latter observation is the strongest direct evidence that adjustment for self-reported smoking characteristics is insufficient to eliminate spurious periodontitis-systemic disease associations.

How can causal associations between comorbid conditions be investigated? In the journal *Nature*, a review article on epidemiology in the 21st century indicated that the impact of smoking on early morbidity and mortality is so large that progress in understanding the more subtle disease etiologies can only be made when analyses are restricted to never-smokers. For instance, it is now generally accepted that reliable evidence regarding the impact of obesity on cancer can only be obtained when the analyses are limited to never-smokers. These lessons learned in medical epidemiology apply to dental epidemiology. A logical start for an earnest investigation into the association between periodontitis and cardiovascular diseases is a reanalysis of existing data among never-smokers. While each separate study is likely to be underpowered, a synthesis of available studies can provide guidance about the direction, if any, the periodontitis-systemic disease research needs to take to progress. Such a synthesis will provide reliable evidence regarding the veracity of the associations between periodontitis and cardiovascular disease, and more generally identify which periodontitis-systemic disease associations, if any, are worthy of further investigation.

What's next? Until file drawers are opened and a synthesis of available data among never-smokers is performed, the public health implications of the current research findings are clear – smoking destroys both oral health and systemic health. The dental profession should continue to play an important role in counseling patients on the hazards of smoking for oral diseases.

Difficulties in Evaluating the Relationships between Periodontal Disease and Cardiovascular Diseases

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There has been a great deal of controversy about whether periodontal disease is associated with the severity and/or incidence of cardiovascular disease. To date there have been multiple cross-section, cohort, and case-control studies with conflicting results.

Some studies have reported a moderate relationship and others have reported no relationship at all. It has been difficult to compare these studies due to a lack of consistency of study designs, outcome measures of cardiovascular disease and periodontal disease. This consistency is especially evident in measurement of periodontal disease and could be a major source of inconsistent findings. If there is a relationship between cardiovascular disease and periodontal disease, there must be an adequate exposure of periodontal disease to create cardiovascular disease. It is even difficult, however, to determine criteria for classifying an individual as having periodontal disease. In general, numerous criteria have been used in studies of periodontal disease; no consistent criteria separate individuals who have disease from periodontally healthy individuals. Further complicating this problem is that periodontal disease is measured at multiple places on multiple teeth, so criteria are usually stated as an extent and severity of disease (i. e. 3 mm. of attachment loss at four or more sites). Thus, both threshold and number of sites or teeth may vary.

Further complicating the problem of defining criteria for periodontal disease is the variety of measures of periodontal disease that have been used at these multiple locations. In studies relating periodontal disease to cardiovascular disease authors have used probing measurements (attachment level and pocket depth), radiographic measurements, a combination of bony defects and deep pockets, a combination of periodontal and gingivitis measurements and none probing indices (Russell's Index). Almost all of the studies investigating this relationship have used different criteria for periodontal disease.

Studies based on non-probing measures such as Russell's index have generally failed to find a relationship between periodontal disease and cardiovascular disease. Half the studies that used self-reported history of periodontal disease failed to show a relationship between periodontal disease and cardiovascular disease. In contrast, among studies that have used probing periodontal measurements (such as attachment level), a largerpercentage have found a relationship between periodontal disease and cardiovascular disease. In some of these studies the authors used progressively more severe criteria for periodontal disease; they found a stronger relationship between periodontal disease and cardiovascular disease as the criteria became more severe. In contrast, using varying extent criteria with the Russell index another author could not find the same relationship.

In summary, the lack of consistent results in these studies make it difficult to determine if an association exists between the two diseases. The types of measurements used in these studies may have contributed to this problem. Lack of consistency has also made it difficult to combine the results of these studies in meta-analysis to further identify the strength of the potential association of the diseases.

Potential Public Health Implications of Periodontal Disease and Cardiovascular Disease Relationships

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Periodontitis is a destructive disease that affects the supporting structures of the teeth including the periodontal ligament, cementum, and the alveolar bone. Periodontitis represents a chronic, mixed infection by gram-negative bacteria, such as *Porphyromonas gingivalis, Prevotella intermedia, Bacteroides forsythus, Actinobacillus actinomycetemcomitans,* and gram positive organisms, such as *Peptostreptococcus micros* and *Streptococcus intermedius.* Due to periodic changes in concepts of periodontal disease pathogenesis and restructuring and renaming periodontal disease types, actual prevalence and incidence estimates for periodontal disease have been debated for decades. It is generally thought that the prevalence of moderate periodontitis in developed countries is between 44% and 57% of adults, while about 7 to 15% have advanced periodontitis. Partly because of uncertainty about the public health importance of this disease and partly because primary prevention depends on personal oral hygiene behavior and professional services, public health programs to prevent periodontal disease are underdeveloped.

Since 1989, there have been a number of cross-sectional, case-control, and longitudinal studies that reported that the clinical signs of periodontitis may be associated with cardiovascular events, other studies have reported no significant association. Several basic science and animal studies also have reported systemic effects of periodontal infection. Cardiovascular disease is the top cause of death in the United States for men and women and carries with it considerable morbidity. In addition, total costs for 2003 were estimated to reach almost $352 billion. This presentation assumes that periodontal disease will be shown to be a risk factor for cardiovascular disease. Because periodontal and cardiovascular diseases are highly prevalent in the population, periodontal disease also becomes a public health problem worthy of attention, even though the strength of the association may only be moderate.

As a result of this link with cardiovascular disease, interest in periodontal disease prevention and treatment is likely to intensify in the private and public health sectors and among the general public. One consequence of this link is that dentists and physicians may need to focus more on primary prevention of infection by periodontal pathogens and, in patients with disease, they may need to focus more on secondary prevention. End-points for secondary prevention will involve eliminating periodontal pathogens and reducing inflammation, while pocket reduction, tooth retention and regenerative procedures may become less important. Controlling inflammation and infection may create an increased need for anti-infective and anti-inflammatory pharmacological strategies for high-risk patients. Other actions likely to be needed are: (1) educating health professionals and the public about the relationship, (2) re-structuring benefits for public programs to provide infection control services to Medicaid and Medicare recipients (3) advocating for medical insurance coverage of periodontal services; and, (4) establishing a surveillance program to monitor periodontal disease population trends and identify high-risk groups to target for intervention programs. Finally, coordinating efforts with groups that are active in reducing other cardiovascular risk factors, such as smoking, diabetes, and obesity may be a useful strategy.

Diabetes and Periodontal Disease: Current Concepts

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Diabetes mellitus appears to be the best- studied disease related to periodontal disease. Extensive studies show that individuals with diabetes are more susceptible to periodontal disease. For example, diabetes mellitus, types 1 and 2, are well established as increasing the risk for severe periodontal disease, with earlier onset in diabetics than in non-diabetics subjects (1, 2, 3).

Recently, the concept has developed that diabetics with periodontal disease suffer from more severe diabetes over time as a result of the systemic effects of periodontal infection. For example, Taylor and co-workers (4) found that diabetics with periodontal disease suffered from worsened glycated hemoglobin over time than did diabetics who did not have periodontal disease. This and similar observations led to a series of clinical trials in which periodontal therapy, especially therapy involving adjunctive systemic and/or local antibiotics, was found to be effective in treating periodontal disease in diabetics, and furthermore resulted in reduction of glycated hemoglobin levels (5). Further studies, especially randomized controlled clinical trials, are required to determine if the reduction of glycated hemoglobin brought about by resolving periodontal infections in patients with diabetes will result in reducing complications such as retinopathy, nephropathy, and other clinical complications of diabetes.

Other studies have assessed why patients with diabetes respond to periodontal infection with aggravated host destructive responses. One theory (6) suggests that there is a general hyperinflammatory response associated with advanced glycation end products (AGE) that triggers inflammatory cells through AGE receptors with a release of proinflammatory mediators leading to excessive tissue destruction. This hyperinflammatory response is manifest at the monocyte and the neutrophil level. Other mechanisms that explain the increased pathology seen in diabetic patients as a result of periodontal infection include altered vascular physiology (7); reduced immune response, particularly protective response, by neutrophils; and reduced ability for tissues to heal.

Many possible theories explain the reduction of glycated hemoglobin by resolving periodontal infections in diabetic patients. There is some evidence that systemic overflow of TNF-alpha and other inflammatory cytokines from periodontal lesions may act in concert with TNF from

other sources, such as adipocytes, to increase insulin resistance (8). In addition to insulin resistance, it is thought that impaired beta cell function leads to reduced insulin secretion resulting in sustained elevated glucose concentrations and elevated glycated hemoglobin with associated increase in complication rates in diabetes patients. The role of periodontal infection on beta cell dysfunction is not known, however.

Clinical consequences of reduced glycated hemoglobin in response to treating periodontal infection are yet to be determined. It is possible however that treating periodontal infection in patients with diabetes will reduce systemic TNF-alpha and other mediators derived from infected periodontal tissues and, thus, reduce systemic effects of periodontal infections. Hence, treating periodontal disease may modulate, in some part, factors associated with increased insulin resistance. Studies are necessary to assess the mechanisms involved in this two-way street of diabetes mellitus increasing the risk for periodontal disease, and periodontal infections increasing or resulting in poor glycemic control. In addition, large prospective, randomized controlled trials are warranted to determine the effects of periodontal therapy on glycemic control and important complications of diabetes including cardiovascular disease, nephropathy, and retinopathy. The public health implications of these studies are potentially important because periodontal disease and diabetes mellitus are common chronic diseases.

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Diabetes and Periodontal Disease: Important Gaps in Knowledge and Methodological Issues

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This presentation reviews evidence for interrelationships between diabetes and periodontal diseases based the body of knowledge in the post-1960 English-language literature.

The review of adverse effects of diabetes on periodontal health is restricted to those comparing periodontal health in subjects with and without diabetes. Review of adverse effects of periodontal infection on glycemic control will include reports of periodontal treatment studies and follow-up observational studies in which changes in glycemic control could be assessed.

Observational studies reporting adverse effects of diabetes on periodontal health provide consistent evidence of greater prevalence, severity, extent, or progression of at least one manifestation of periodontal diseases in the large majority of reports. No studies with superior design features to refute this association have been identified.

Reports of several treatment studies provide direct evidence to support periodontal infections having an adverse, yet modifiable, effect on glycemic control. However, not all investigations have reported improvement in glycemic control after periodontal treatment. Additional evidence to support the effect of severe periodontitis on increased risk for poorer glycemic control comes from follow-up observational studies.

The evidence reviewed supports viewing the relationship between diabetes and periodontal diseases as bi-directional. Studies of biologic mechanisms of these interrelationships and intervention trials to further substantiate a beneficial effect of treating periodontal infection on glycemic control will further our understanding of this two-way relationship.

Diabetes and its Complications: Designing New Therapies for this Epidemic

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The problems of diabetes are increasing all over the world. In the United States alone, the number of people with diabetes is expected to increase to 18 million by 2010. This increase affects all socioeconomic levels, male and female, many ethnic backgrounds, and occurs in types 1 and 2 diabetes.

Medical care cost for diabetic patients are also increasing dramatically. Direct medical costs for diabetes care in 1997 in the United States were $44 billion in contrast to $91.8 billion in 2002. Treatment for diabetic complications accounts for approximately 30% of medical care costs ($24.8 billion). The increase in diabetes is directly related to the rising percentage of the population who are described as obese and to the aging of the population. Most of the increase in diabetes prevalence has come from type 2 diabetes, which usually is diagnosed in adults, related

to obesity, and not insulin dependant. Evidence of type 1 diabetes is also rising, but the cause is unknown at this time although it is an autoimmune induced disease. Since type 1 diabetes accounts for only 10% of the diabetic population, its increase does not substantially affect the prevalence of diabetes in the general population.

Molecular understanding of both types 1 and 2 diabetes and diabetes complications have improved dramatically over the past 20 years, leading to a host of new therapeutics that are just beginning to reach the clinical arena. New treatments for type 1 and 2 diabetes include islet cell transplant, agents to induce tolerance and prevent type 1 diabetes, custom designed insulin to mimic physiological response, hypoglycemic agents to improve insulin secretion and sensitivity. New treatments for diabetic complications are also being designed based on the molecular understanding on the pathogenesis of diabetic vascular and neurological complications. Hyperglycemia appears to be the main causal factor for diabetic microvascular and neurological diseases such as neuropathy, retinopathy, and nephropathy.

Both hyperglycemia and insulin resistance are important for cardiovascular complications of diabetes. It is very likely that the increased prevalence of periodontal disease in diabetic patients is due to adverse effects of hyperglycemia and possibly insulin resistance. Several theories such as increases in oxidative stress, glycation of proteins, and activation of cellular signaling such as protein kinase C (PKC) have been proposed to mediate most of hyperglycemia's adverse effects. Both vascular and neurological changes have been shown to occur in correlation with changes in oxidant production, glycated protein and PKC activation.

It is likely that these changes also occur in periodontal tissues. Further studies are needed to confirm the relationship between these molecular pathways and the occurrence of periodontal disease in diabetic patients. New treatments for periodontal disease in diabetic patients can improve dental health and may also improve diabetes care and other systemic problems in diabetic patients.

Potential Impact of Maternal Periodontitis on Reproductive Outcomes

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Recent studies conducted in the United States have indicated that periodontal disease may be a newly identified obstetric risk factor for preterm delivery and fetal growth restriction (1-3). Mothers with periodontal disease early in pregnancy or with worsening periodontal status during pregnancy appear to be at 2 – to -8 fold increased risk for prematurity. Maternal periodontitis confers risk that is particularly high at the earlier gestational ages, rather than late in pregnancy resulting in a dramatic impact on neonatal morbidity and mortality. Babies of mothers with periodontal infections that disseminate to the fetus are twice as likely to be admitted to the neonatal intensive care unit and three times more likely to require extended hospital stay beyond seven days. Other studies conducted on Bangladeshi patients in London, however, failed to find an association between maternal clinical signs of periodontitis and prematurity, suggesting that there may be significant ethnoracial or geographical differences in attributable risk (4). Early findings from antepartum periodontal treatment intervention trials point to a potentially dramatic 5-fold reduction in the rate of prematurity (5).

This trial, conducted by Lopez of almost 400 women divided into a treatment and a delayed treatment group suggests that periodontal treatment during pregnancy is not only safe, but may improve pregnancy outcomes. Other new findings suggest that approximately 25% of pregnant women demonstrate increased periodontal pocketing during pregnancy and that this worsening of periodontal status during pregnancy contributes additional risk for prematurity. This study suggests that preventing periodontal disease initiation and progression, even in relatively healthy individuals, may improve pregnancy outcomes (3). The transfer of maternal oral organisms or microbial components to the fetus has been documented, suggesting that there may be translocation of specific oral organisms, such as *Campylobacter rectus* (6), contributing to prematurity and growth restriction. Thus, there is emerging evidence that this linkage with prematurity may represent a specific infection of the fetus by oral organisms of maternal origin. The identification of specific infectious etiological organisms in this pathology will have diagnostic and therapeutic implications. Definitive demonstration of the potential protective benefits of periodontal therapy on obstetric complications, however, awaits the conduct and completion of multi-centered, randomized clinical trials.

Periodontal care will become integrated as part of obstetric management if maternal periodontal disease intervention and/or elimination of specific periodontal pathogens eventually are shown to improve pregnancy outcomes. Further studies to define the key pathogens and pathology mechanisms to optimize potential for diagnostic and therapeutic strategies will enable characterization of appropriate at-risk populations for demonstration projects to determine the effectiveness of reducing the burden of oral infection on obstetric and neonatal morbidity and mortality. In addition, the data seem to suggest the need to design education and out-reach programs to help coordinate and integrate obstetric and dental services.

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Periodontal Disease as a Risk Factor for Preterm Birth: Epidemiology and a Pilot Intervention Study

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Preterm birth, resulting in babies born too little and too soon, is a major cause of morbidity. Evidence indicates that infections can be major risk factors in preterm birth. Case-control studies point to an association between periodontal infection and increased rates of preterm birth.

Evidence points to a possible role for periodontal pathogens in preterm birth. In a case-control study of 124 pregnant or post-partum, mothers preterm or low-birth-weight mothers had significantly worse periodontal disease than respective normal-birth-weight controls. Multivariate logistic regression models, controlling for other risk factors and covariates, showed that periodontal disease is a significant risk factor with impressive odds ratios of 7.9 for all preterm low-birth-weight cases, and 7.5 for primiparous preterm low-birth-weight cases (1). Other case-control studies show an increased risk of preterm birth of 3 to 8 fold in mothers with periodontal disease (3). In a longitudinal study, more than 1300 women with periodontal disease indicated overall adjusted odds ratio of 2.83 (95% C.I. 1.79 - 4.47) for patients with mild-to- moderate disease, and 4.18 (95% C.I. 1.41 - 12.42) for patients with severe periodontal disease (2, 3).

A recently completed pilot study examined whether periodontal treatment reduces the risk of preterm birth (PTB) in pregnant women with periodontitis (4).

Methods: Three hundred and sixty-six women with periodontitis between 21^6 and 25^6 weeks gestation were recruited and randomized to one of three treatment groups with stratification on the following two factors (1) previous SPTB at less than 35 weeks, (2) body mass index less than 19.8 or bacterial vaginosis as assessed by gram stain. The treatment groups consisted of (1) dental prophylaxis plus placebo capsule; (2) scaling and root planning plus placebo capsule; and (3) scaling and root planning plus metronidazole capsule (250 mg tid for 1 week). Another group of 723 pregnant women meeting the same criteria for periodontitis and enrolled in a prospective study served as an untreated reference group.

Results: The rate of PTB at less than 35 weeks was 4.9% in the prophylaxis group, 3.3% in the scaling and root planning plus metronidazole group, and 0.8% in the root planning and placebo group. The rate of PTB at less than 35 weeks was 6.3% in the reference group.

Conclusion: This trial indicates that root planning dental treatment of pregnant women with periodontitis may reduce PTB in this population. Adjunctive metronidazole therapy did not improve pregnancy outcome. Larger trials are needed to achieve statistical significance, especially at less than 35 weeks gestational age.

References

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Potential Public Health Implications of Associations Between Periodontitis and Reproductive Outcomes

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Preterm birth is a major public health problem under investigation. Medical care costs are an estimated $5 billion annually for the approximately 467,000 preterm births. That is an average of $10,706 per preterm birth. In 2000, 11.6% of infants were born preterm in the United States. That rate results in nearly 1300 preterm deliveries each day for the 4,058,808 babies born in the United States in 2000. Between 1991 and 2000, the percentage of all U.S. babies born preterm increased more than 7%, major risk factors for preterm birth include: multiple birth, history of preterm delivery, stress, infection, bleeding, smoking, illicit drugs, and maternal age extremes.

The role of infection, specifically periodontal infection, in reproductive outcomes is explored in today's presentations. As described in the Institute of Medicine report, public health efforts include a description of the problem, regular data collection and dissemination, promotion of scientific knowledge in decision making on policy matters, and assurance that services necessary to achieve the goals are available. In following this outline, studies are indicated to better describe the inflammatory and host responses and also the role of periodontitis microbes in preterm births. Periodontal infections are preventable and treatable. Periodontitis can be viewed as a modifiable risk factor and pilot intervention studies provide evidence that does not indicate an increase in adverse obstetric event rate associated with dental treatment during pregnancy. Evidence from some studies supports periodontal treatment as a means to reduce preterm births. The implication for dental care professionals is to learn, or unlearn and relearn, how to best care for pregnant women.

The American Academy of Periodontology recommends that a periodontal evaluation be included as part of prenatal care. Implications for the pregnant woman suggest that preventing periodontal disease is the better option; however, she can safely receive periodontal treatment. The *Healthy People 2010* objectives include reducing the low birth weight from 7.6% to 5.0% of births and reduce preterm births from 11.6 % to 7.6 %. The association of periodontitis and preterm births suggest the potential merit of conducting additional studies of infection, host response, and preterm births; and additional intervention studies.

Concluding Remarks

William Maas, DDS, MPH, MS

Because this meeting was neither organized nor conducted to achieve consensus among participants, each departs with a unique take home message. The depth of expertise and breadth of backgrounds of the speakers as well as the mix of attendees enriched both formal discussions and the informal ones that occurred during breaks. Presenters were particularly responsive in sharing their thoughts about the public health implications of associations considered, and discussion periods addressed the two contexts of periodontitis, i.e., both as an undesirable threat to oral health, in its own right, and as a potential risk factor for systemic disease.

Throughout this conference, such public health implications were conditional, predicated on future demonstration of causal relationships and effective interventions. Based on the current state of the evidence for these associations and interventions, recommendations for periodontal treatment on the basis of potential systemic disease outcomes remain premature. Thus, it seems inappropriate to initiate new public health programs to prvent these outcomes. It is clearly important, however, to prevent and treat periodontal infections to maintain and improve oral health to prevent these outcomes.

Clearly, much more research is needed. Where randomized clinical trials are feasible, they can provide evidence of the effect of periodontal treatment on systemic outcomes. Another approach would add assessment of periodontal status to ongoing trials addressing the disease outcomes of interest. During discussion periods, attendees raised questions about the costs of and justification for randomized trials, given limited and inconclusive current evidence from observational studies published in the peer-reviewed literature. Additional observational studies of representative populations might permit estimation of potential benefits from preventing and controlling periodontal infections and guide further research.

In spite of the preliminary, inconclusive nature of accumulated evidence, the reported association between severe periodontitis among pregnant women and their birth outcomes represents one of the more compelling arguments for public health intervention considered at this meeting. Although meeting participants focused on treatment of periodontitis during pregnancy, their discussions only briefly considered the potential benefits of primary prevention. As a public health goal, it may be possible to create a situation in which women have healthy gums *before* they become pregnant. Then, it is not a large leap to broaden the commitment and ask what public health aspirations should be for young adults, both men and women. How can the 15% likely to experience severe destruction of their periodontium be predicted? How early can persons with the hyper-inflammatory phenotype be identified? Using public health approaches, could the situation that exists today—many young adults reaching middle age without ever having early periodontal infection identified and treated—be rectified?

A second compelling finding, one that should prompt serious thinking about health care in the U.S., comes from data showing that persons with diabetes report lower use of dental care than do those without diabetes. This lower use is particularly evident among Hispanics and non-Hispanic blacks, who are overrepresented among those with diabetes. So, if dental public health professionals believe that diabetes and its complications are serious, how should they respond to the fact that many of those who don't seek or receive regular dental care are black, Hispanic, or poor? If the only way to detect those at risk for periodontal destruction is through clinical assessment, what approaches might increase the number of young adults with diabetes who receive such an assessment? What interventions might reach dental and other health professionals, as well as persons with diabetes and the general public with this important message?

Smoking represents yet a third major issue from this meeting. Because it is an independent, very strong risk factor both for periodontal infection and for cardiovascular disease, future research must address whether their association represents co-morbidity resulting from smoking. Public health action need not wait for these research findings, however. Good evidence documents that tobacco cessation counseling provided by dentists and other dental personnel can be just as effective as that by other health care providers. For some persons, the dental setting may even be more effective, because ill effects of the tobacco habit are readily apparent in the smoker's mouth. Public policies are making it more difficult for people to smoke; places to smoke have been reduced, while the cost of cigarettes has increased. Still, people with nicotine addiction typically must make many serious attempts to quit smoking before achieving success. Dental personnel have to accept that such multiple attempts are the nature of this particular intervention—and thus, they must persist in asking about the patient's readiness to quit, as well as in offering encouragement for any cessation efforts. Given smoking's role in periodontal infection, dental clinicians should spend as much time on tobacco prevention and cessation as on oral hygiene behaviors. Periodontists and their staffs probably ought to be among the most successful tobacco cessation counselors in all of health care, and could provide leadership for the rest of the dental profession, and the community at large.

Based on what is now known, it seems clear that there are several public health approaches to explore for preventing and controlling periodontal infections. The capacity of oral health programs within state and local health agencies can be built, so they become active partners in broader ongoing efforts to: 1) reduce tobacco use, particularly smoking, at the individual and community levels; 2) educate persons with diabetes—and their health care professionals—about the periodontal implications of that disease and the benefits of regular care; and 3) consider targeted health communication efforts to make key groups aware of effective preventive interventions.

While applying what is known, research investments also must occur, to expand the knowledge base. Some of that research will focus on basic science questions or test interventions with clinical trials, but substantial needs for epidemiologic, health services, and applied, community-based research also exist. For example, could susceptible groups best be reached by adding an oral health component to an existing intervention trial or ongoing program? This meeting has revealed how far we have come with the science—yet how far we must still go to achieve the goal of periodontal health for all.

WORKING GROUP ON SURVEILLANCE MEASURES FOR PERIODONTAL INFECTIONS

April 7, 2003 - Atlanta, GA

Summary of Proceedings from First Meeting

CDC and others have recognized that the development, implementation, and evaluation of public health interventions for periodontal infections will require an ability to monitor the disease in populations. Such monitoring should be ongoing and systematic, and data analysis and interpretation should guide public health practice. Current measures of periodontal infections are extremely resource intensive. A second goal of this meeting was to establish an expert work group, to consider and recommend pragmatic population-based surveillance measures for periodontal infections.

A summary of the group's initial activities:

Defining Long-term Goal: To develop a surveillance system for periodontal infection that includes self-reported measures and that may include monitoring sites, events, providers, and payers. Data must be at least state specific and possibly county and local specific.

Major Tasks:

1) Identify existing tools that involve self-reported measures
   - Literature search
   - Analysis of existing databases for possible valid questions
2) Identify existing possible sentinel sites, events, providers, and payers that can be used to monitor periodontal infection
   - Literature search
   - Survey sites (military, federal clinics, ADA, insurance providers; i.e., Delta and HMOs such as Kaiser Permanente)
3) Reevaluate information obtained from Tasks 1 and 2 to determine further efforts of the Working Group
4) Studies to validate possible question measures
5) Final recommendation of acceptable measures (at the end of 2 years)

Membership/Leadership Roles

The Working Group consists of experts in the fields of periodontology, epidemiology, and public health. Paul Eke is the CDC liaison. Initial members of this group are Robert Genco, James Beck, Scott Tomar, Roy Page, George Taylor, Gary Slade, Gordon Douglass (AAP), Kaumudi Joshipura, Jeff Hyman and Paul Eke (CDC). Additional members after the initial meeting include Gregg Gilbert, Wenche Borgnakke, Karen Falkner and Stuart Gansky.

By consensus, the group selected Robert Genco as chair. It also agreed to divide into two subgroups to address its major tasks. The subgroups are:

Working Group on Self-Reported Measures (Jim Beck, chair)

Working Group on Clinically Derived Data (Scott Tomar, chair)

The subgroups defined their particular tasks and discussed the importance of reviewing the literature, contacting key personnel to serve as advisors or resource persons, and analyzing existing databases. The next meeting was scheduled for October, 2003.