

REPORT OF THE INDEPENDENT PANEL OF EXPERTS OF THE SCOTTSDALE PROJECT

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The Scottsdale Project and the *Report of the Independent Panel of Experts of The Scottsdale Project* were funded by an unrestricted educational grant awarded to PennWell® Corporation by Colgate-Palmolive

Periodontal Disease and Endocrinology/Diabetology

by Shailesh B. Patel, BM, ChB, DPhil, FRCP



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The art and science of medicine has a long and rich history. A new concept highlighted and championed can alter the practice of medicine. For over 1,000 years, such ideas have frequently led to practice changes. What is new and modern is the rigor with which we view these innovative concepts. Evidence-based medicine is now the standard. However, rounds or teaching sessions are too often stifled by cries of “There are no clinical trials”, or “Where is the evidence”? In the absence of clinical data, these excuses should not temper “judgment-based practice”.

“Judgment-based practice” relies on established basic and clinical scientific principles, on experience (personal and collective), and on using procedures or therapies that have been shown to be effective, pose no untoward risk (do no harm), and may prove beneficial (a positive risk-benefit ratio).

The Scottsdale Project brought together a group of professionals from all branches of healthcare to highlight an important and neglected area: the constellation of periodontitis, diabetes, and adverse outcomes. The link between dental health, oral flora, and systemic illness is well known, e.g., in subacute bacterial endocarditis. Enlightened cardiothoracic surgeons now ask their patients before undergoing elective cardiac surgery to receive clearance from their dentists (as this improves patient morbidity and mortality), above and beyond valvular procedures. Purulence anywhere in the body needs to be treated and the mouth is no different. Judgment-based practice would dictate that treating purulence in the mouths of diabetic patients is something good.

Periodontitis can be readily screened, treated and controlled, but we are not doing it. Good management of any patient with a chronic disease demands a holistic approach; treating not just the organ, but the body, the mind and even the soul. There are many reasons why we as clinicians fail to be holistic. Finding the time to take a good clinical history, perform a thorough physical exam, adequately answer our patients’ questions and then meet extensive practice guidelines is challenging.

For diabetic patients, annual eye, foot, lipid, and urine protein exams are documented routinely. However, we do not examine the diabetic patient’s mouth systematically or document if they have had their annual dental exam. This highlights the difference between evidence-based medicine and judgment-based practice.

In the systematic review of the literature considered for *The Scottsdale Project*, a wealth of evidence shows that periodontitis is a significant comorbidity in patients with diabetes. Yes, we still need more studies for evidence-based medicine. However, the lack of these trials should not derail judgment-based practice. I would urge the American Diabetes Association and the American College of Clinical Endocrinologists to consider, at a minimum, a “judgment-based” statement that an annual dental exam for gum and periodontal health in all diabetic patients is required.

However, another aspect of this problem may be more difficult to solve. In clinical medicine, whether a patient has insurance or not, chronic illnesses can usually be managed, as there are both state and federal resources to help provide care, despite struggles.

Unfortunately, there are few resources for dental coverage in the state and federal systems (even the Veterans Administration does not provide for dental coverage). With already burdensome medical costs, to pay out-of-pocket to receive a dental exam is unaffordable for those that are at the greatest risk. Despite sound judgment, the oral-systemic connection between health and disease remains lost to our healthcare insurers and our politicians. Periodontitis, the inflammation of the gums, is part of medicine and as such should be part of medical healthcare.

Periodontal Disease and Cardiology

by Robert J. Ostfeld, MD, MSc

When I learned about the opportunity to become involved in *The Scottsdale Project*, a cross-disciplinary conference examining the potential connection between periodontal disease and systemic health, I was very intrigued. Often, as medical professionals, we are accused of being myopic, focusing on our own particular area of expertise to the exclusion of others. Clearly, diseases impact all aspects of a person. Hence, the theme of uniting specialists across disciplines was exciting, as we all share the same goals of preventing and treating disease. And it made intuitive sense that teamwork would lead to better science and better outcomes for our patients.

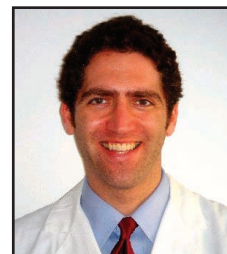
From the beginning it was clear that everyone shared that excitement; however, we found that we did not necessarily share the same language. Phrases such as “ROMI”, rule out myocardial infarction, or “DOE”, dyspnea on exertion, are common knowledge to physicians (or at least cardiologists), but not with dentists. The same holds true for terms specific to dentistry. We found that we needed to bridge this semantic divide.

With the vernacular hurdles behind us, we set out to rigorously examine the data. There were many fantastic perspectives. There was an endocrinologist, numerous epidemiologists, periodontists, dentists, primary care providers, a cardiologist and an obstetrician. With each person sharing their expertise and analysis of the literature, it was evident that the end product would be very well thought out and guided by data, not preconception.

As a myopic cardiologist, one particular area I found myself drawn to was the potential link between periodontal disease and atherosclerosis. The first question that came to mind was about causality. Does periodontal disease cause atherosclerosis? The answer is that we do not know. We do know, however, that many studies demonstrate that periodontal disease is associated with an increased risk of atherosclerosis. But there is the chicken and egg question. Which one came first? Perhaps persons with atherosclerosis simply care for their teeth less and have more periodontal disease. Or perhaps periodontal disease promotes atherosclerosis. We cannot be sure at this time, but the picture does become somewhat clearer. We know that periodontal disease is associated with elevated markers of systemic inflammation, a known promoter of atherosclerosis. Furthermore, data suggests that treating periodontal disease may reduce markers of systemic inflammation and improve vascular function. So intriguing hints are there.

Although there is no conclusive evidence that periodontal disease is directly implicated in atherosclerosis, no one is suggesting that this lack of evidence should preempt prevention and progressive intervention of periodontal disease. Wouldn't it be both fascinating and motivating to know that in addition to keeping your gums healthy, your smile attractive and perhaps even diabetes at bay, treating periodontal disease may actually be healthy for your heart as well? Time and further research will tell. Based on the data to date I believe this is something very important to explore.

Equally important is the theme of coming together. Given the large burden of atherosclerosis, diabetes and periodontal disease, increasing awareness across disciplines may help to facilitate both research and patient care. Clearly no one expects the cardiologist to know the nuances of periodontal disease or the dentist to be up to date on the latest study about atherosclerosis. But if the cardiologist and/or dentist can help to identify diseases that previously were considered out of their spheres of reference and can enable patients to obtain appropriate care, then something great will have evolved from this body of science, regardless of whether evidence supports a causal relationship.



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Report of the Independent Panel of Experts of *The Scottsdale Project*



FOREWORD

BEYOND RESEARCH: BUILDING A SOLID FOUNDATION FOR IMPLEMENTATION OF PERIODONTAL-SYSTEMIC SCIENCE

A disconnect between scientific knowledge and primary healthcare practice is not a new phenomenon; it has been well described for many chronic diseases throughout the history of medicine. It was 264 years after the discovery that citrus fruits prevent scurvy that Britain finally adopted universal preventive policy to help scorbutic sailors.* Fast forward to today and consider the length of time it took for the National Cholesterol Education Program to promote understanding of the dangers of high blood cholesterol as a major cause of coronary heart disease and the relatively long adoption curve associated with the acceptance of cholesterol-lowering drugs we know today as “statins”.† The first adult treatment panel report, the *Report on the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*, was published in 1988.‡ In the clinical advisory statement§ published in 2002, members of the writing committee concluded, “Statin therapy holds great promise for reducing the incidence of major coronary events, coronary procedures, and stroke in high-risk patients. At present this potential has not been fully realized...” Unfortunately, the application of emerging research related to periodontal-systemic links appears to follow this slow pace of knowledge diffusion and like the delayed acceptance of statin drugs, the potential for intervention of periodontal disease to decrease the risk for systemic injury has not been fully recognized. The *Report of the Independent Panel of Experts of The Scottsdale Project* addresses this disconnect.

In this landmark report, the significance of oral health in promoting whole body health and the importance of medical-dental collaboration in ensuring this outcome is redefined. As a result, *The Scottsdale Project* has special significance for medical and dental communities in that it represents an initial attempt to begin diffusing this information into both medical and dental practice by proposing development of a transdisciplinary model of care with the hope of improving health outcomes. Simultaneously, it is important to recognize areas of uncertainty where other research is needed.

In many respects *The Scottsdale Project* was unprecedented. This was the first time a panel composed of medical and dental experts from research, academia, and clinical practice examined the scientific evidence to determine whether it was strong enough to support the development of guidelines for the clinical practice of dentistry and medicine to assist practitioners in identifying, cross-referring, and coordinating care of patients who are either undiagnosed or at risk for periodontal disease, diabetes, and cardiovascular disease (CVD). To ensure that *The Scottsdale Project* would yield meaningful outcomes and forward thinking opinions on the state of this research, health professionals with expertise in periodontology, endocrinology/diabetology, cardiology, cerebrovascular medicine, and epidemiology were represented. This 18-member panel was charged with weighing the evidence to determine whether it was appropriate to develop guidelines. Experts were selected based on expertise in areas of relevant research, clinical capability, willingness to consider the data objectively, and in an unbiased and balanced manner. The outcome of the proceedings was made infinitely more valuable by the collective strength of the combined intellectual capital and unique perspectives of the individuals involved in this initiative. *The Scottsdale Project* was an independent initiative, and as such, the individual participants were not financially compensated nor did they represent any professional organizations. Rather, the opinions derived from the conference represent a collaborative effort to offer direction to better serve the health needs of the U.S. population.

The opinions derived by the expert panel were the product of careful deliberation over 3 days of proceedings that included expert testimony, intense discussion of the evidence gathered from a systematic review of over 118 articles, and debate over the strength of the evidence to support the experts’ answers to 8 focused questions. These findings, subsequent recommendations, and discussion of their scientific rationale are detailed in the following report. This methodology was adopted to enable the panel of experts to address the broader goal of *The Scottsdale Project*, which was to determine whether there was sufficient evidence to support the development of guidelines. Accordingly, the independent panel of experts of *The Scottsdale Project* sought to resolve 2 key issues, addressed in the following questions:

* Lind J. *A Treatise of the Scurvy*. Edinburgh: Printed by Sands, Murray and Cochran for A. Kincaid and A. Donaldson. 1753.

† University of Texas Southwestern Medical Center. National Cholesterol Education Program. Available at: <http://www.utsouthwestern.edu/utsw/cda/dept27717/files/97623.html>. Accessed July 30, 2007.

‡ Report on the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *Arch Intern Med*. 1988;148:36-69.

§ Pasternak RC, Smith SC Jr., Bairey-Merz CN, et al. ACC/AHA/NHLBI Advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;40:567-572.

Key Issue I – Is it appropriate to develop guidelines that assist dental providers in identifying patients who have or who are at risk for diabetes and/or CVD, or screening patients for undiagnosed diabetes and/or CVD who need to be referred to physicians?

Key Issue II – Is it appropriate to develop guidelines that assist medical providers in identifying patients who have or who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists?

The panel of experts was concordant in their recommendation that indeed it is appropriate to develop guidelines to assist dental and medical providers in identifying patients at risk for periodontal disease, diabetes, and CVD. Furthermore, members of the expert panel felt that it is an obligation of the professions to be as thorough as possible in searching for information that may lead to a diagnosis of periodontal disease, diabetes, and CVD. The following report provides greater detail of the recommendations offered by the expert panel in addition to scientifically supported rationale to support those recommendations.

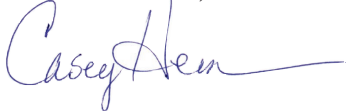
Ultimately, broad change in clinical practice will depend on reform in healthcare policy and professional education, both of which are influenced by the various organizations that represent physicians, dentists, nurses, dental hygienists, diabetes educators, physician assistants, dietitians, and other allied healthcare disciplines, in addition to the insurance industry. As such, the recommendations derived from *The Scottsdale Project* should be viewed as a foundation for building a broader consensus by concerned organizations. It must be recognized that there are medical and dental providers who not only provide state-of-the-art care to their patients, but also communicate to their peers the importance of doing the same. Accordingly, the purpose of this report is to disseminate what a group of highly respected researchers, academicians, and practitioners believe is an initial appropriate course of action regarding development of clinical practice guidelines that may assist both medical and dental practitioners in identifying and managing patients at risk for serious disease states with oral-systemic implications.

I want to thank the many scientists, clinicians, and advocates from professional groups who gave generously of their time and expertise without expectation of remuneration. Without their support, commitment to serve, and dedication to seeking unbiased opinion, *The Scottsdale Project* would not have been possible, and the important recommendations derived from the conference would have been forfeited. In addition, I appreciate the representatives and their respective organizations for participating and observing during the opening day of the proceedings.

Most importantly, I want to acknowledge Colgate's commitment to oral-systemic science, and thank the company for its timely and generous educational grant in funding the 18 months of planning, scientific review, and conference proceedings necessary to bring about the level of credible and unbiased expert opinions provided in the *Report of the Independent Panel of Experts of The Scottsdale Project*. In fact, this report may have already had far reaching implications for the healthcare community at large. The report was prereleased to several organizations and at the time the report went to press, these organizations were considering the findings of the report as the basis for developing guidelines, or revising existing guidelines, to promote medical-dental collaboration in diabetes, CVD, and periodontal disease intervention. Accordingly, I believe this report has fulfilled one of its predefined purposes, i.e., to provide a framework for change and to challenge professional organizations within medicine and dentistry to engage in meaningful dialogue relative to implementation of this body of science, which up until this time had eluded discussions on healthcare reform. Other organizations have awaited the outcome of *The Scottsdale Project* to carry forward the messages and promote recommendations detailed by the panel of experts in the report. Clearly there is a need for shared responsibility in medicine and dentistry in the comanagement of chronic disease states associated with the oral-systemic link. To that end, it is my hope, along with the others who served on *The Scottsdale Project*, that discussions stimulated by this report will lead to the creation of innovative models for medical-dental collaboration that may be embraced by healthcare providers, educational institutions, government agencies, and public-private partnerships.

"Health care is among the best endowed of all industries in the richness of its science base...yet, an enormous amount of that scientific knowledge remains unused."** So true, yet this results in a delay of evidence-based practice. Consequently, the public we are privileged to serve fails to reap the benefit of the research that they have funded through tax supported grants for scientific investigation. In seeking to reverse this trend, *The Scottsdale Project* may provide an historical marker that pinpointed the time when real change in prevention and treatment of chronic diseases associated with oral diseases began to take shape. Time will tell.

To universal health,



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** Berwick DM. Disseminating innovations in health care. *JAMA*. 2003;289(15):1969-1975.

INTRODUCTION

The impetus for *The Scottsdale Project* was the need to increase recognition among various health professionals of the expanding base of evidence supporting interrelationships between inflammatory periodontal disease, diabetes, coronary heart disease, and ischemic stroke. The purpose of *The Scottsdale Project* was to bring together a wide range of medical and dental experts to dialogue about the meaningfulness and usefulness of this current body of knowledge as it relates to the need for and appropriateness of guidelines for clinical decisions and patient management. The conference, which was convened on April 11-13 in Scottsdale, Arizona, was the culmination of over 14 months of extensive planning, communication with various professional stakeholder groups, and an in-depth review and summary of relevant scientific literature.

As defined in its preamble, *The Scottsdale Project* was led during the planning phase by a group of individuals representing academic, research, and clinical medicine and dentistry. Their common bond was recognition of the potential threat that periodontal disease may pose to systemic health, specifically related to the increased risk for complications of diabetes, and the development of atherosclerotic induced diseases, i.e., coronary heart disease and ischemic stroke. Accordingly, as a primary effort, it was suggested that a conference be convened to determine whether current evidence is strong enough to support the adoption of periodontal disease as a modifiable risk factor in decreasing the risk for diabetic complications and the development of heart disease and stroke.

Secondly, this group of individuals perceived a need among clinicians for basic guidelines for the medical-dental comanagement of patients who have increased risk for diabetes, or who have already been diagnosed with diabetes, who may also have periodontal disease. In this regard, those who were involved in the planning phase of *The Scottsdale Project* acknowledged that there are a number of studies that demonstrate that periodontal therapy has the potential to positively impact glycemic control; however, these individuals also succinctly noted that the evidence to support this is inconclusive at this time.

Thirdly, those involved in the planning phase of *The Scottsdale Project* acknowledged that medical-dental collaboration in bilateral screening may promote early identification of patients either at risk for, or who have undiagnosed periodontal disease, diabetes or cardiovascular disease (CVD). Subsequently, it was proposed that guidelines for bilateral point-of-care screening for certain diseases (i.e., medical providers screening for periodontal disease and dental providers screening for diabetes and CVD) be developed. Given that diabetes is now considered a risk equivalent for myocardial infarctions, it was also recognized that any gains in early identification of patients at risk for diabetes or undiagnosed diabetes has the potential to impact the epidemic nature of CVD.

If there is sufficient evidence to support the proposals as set forth in the preamble of *The Scottsdale Project* (as stated above), this has far reaching implications for the healthcare community at large. In seeking these answers, the expert panel of *The Scottsdale Project* responded to 8 focused questions which provided the framework for resolution of the following 2 key issues related to guideline development:

Key Issue I – Is it appropriate to develop guidelines that assist dental providers in identifying patients who have or who are at risk for diabetes and/or CVD, or screening patients for undiagnosed diabetes and/or CVD who need to be referred to physicians?

Key Issue II – Is it appropriate to develop guidelines that assist medical providers in identifying patients who have or who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists?

OVERVIEW OF PERIODONTAL-SYSTEMIC MEDICINE

Broadly classified, periodontal diseases include gingival diseases (both plaque-induced and non-plaque induced), chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic diseases, necrotizing periodontal diseases, in addition to several other classifications that are less prevalent.¹ This classification system is based on the concept of bacterial-host interaction, which maintains that plaque-induced periodontal diseases are infections and that the host response is largely determined by risk factors such as smoking, diabetes, and genetic predisposition.² The most common periodontal diseases are plaque-induced gingivitis and chronic periodontitis; both are infections that require a dental management process parallel to that of infections that require medical management. Much of the destruction observed in these infections occurs as a result of host inflammatory and immunologic responses to predominately gram-negative anaerobic bacteria within the subgingival biofilm.

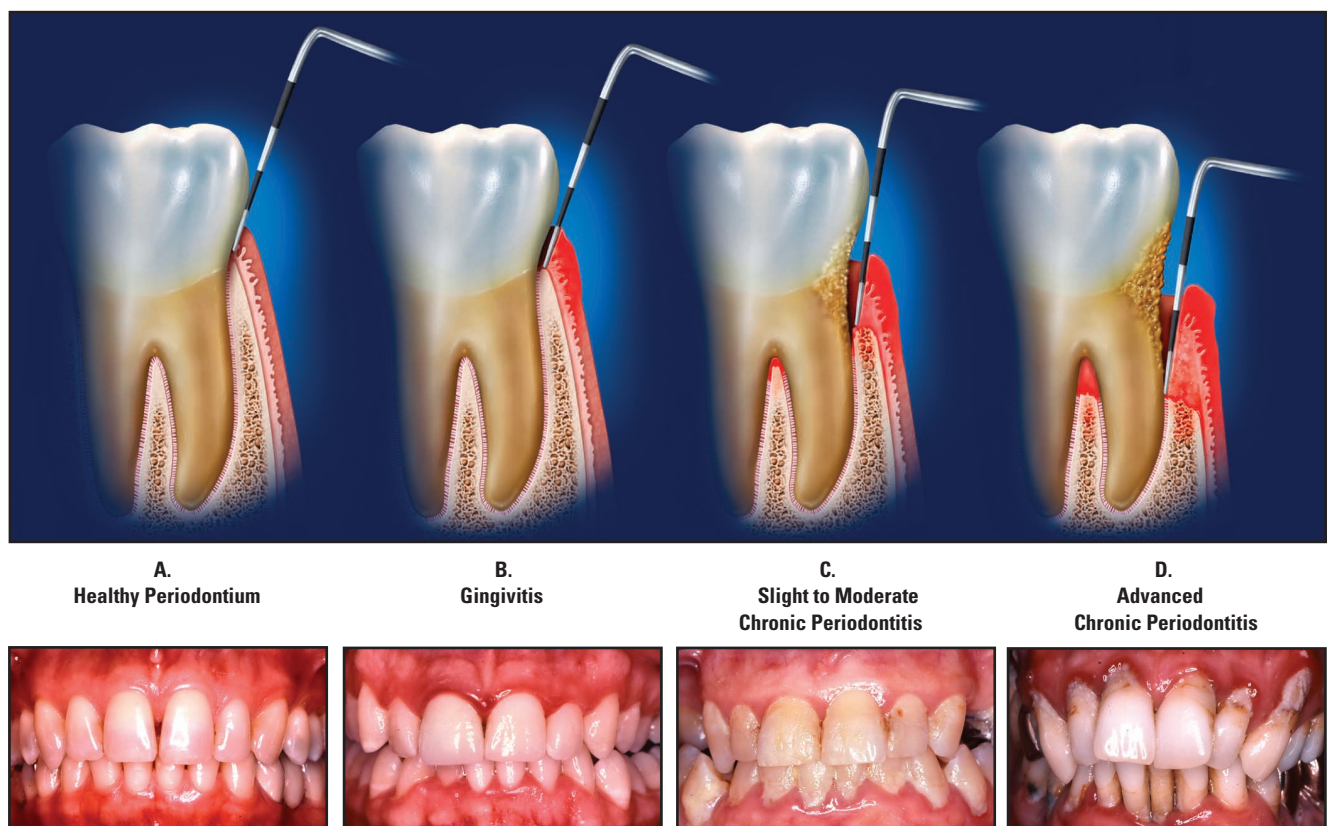
A healthy periodontium is clinically characterized by firm gingival tissue with a coral pink color (variations in melanin pigmentation among different racial groups),² a scalloped shape coming to a triangular point between teeth,³ and a shallow (2-3 mm) gingival sulcus (Figure 1A).³ Plaque-induced gingivitis is a reversible condition that is diagnosed by the presence of inflammation of the gingival tissue. The inflammation is limited to the gingival tissue and does not extend into surrounding attachment or bone (Figure 1B).⁴ Gingivitis may be characterized by the presence of any of the following clinical signs: redness and edema of the gingival tissue, bleeding upon provocation, changes in contour and consistency, presence of calculus and/or plaque, and no radiographic evidence of crestal bone loss. Chronic periodontitis is defined as inflammation of the gingiva extending into the adjacent attachment apparatus.⁵ This disease process is characterized by loss of clinical attachment due to the destruction of the periodontal ligament and loss of adjacent supporting bone. In cases of slight to moderate chronic periodontitis (Figure 1C), up to 1/3 of the supporting periodontal tissues have been lost, with pocket depths (PD) up to 6 mm.⁵ Clinical presentation includes edema, erythema, gingival bleeding upon probing, and/or suppuration. Bone loss may be evident in

radiographs and tooth mobility may be present. An advanced case of chronic periodontitis is characterized by a loss of greater than 1/3 of the supporting periodontal tissues and PD greater than 6 mm with clinical features similar to slight to moderate stage of periodontitis (Figure 1D).⁶ Attachment and bone loss seen in chronic periodontitis are associated with an increase in gram-negative organisms (known to be especially pathogenic and virulent)³ in the subgingival plaque biofilm. Most forms of periodontitis represent chronic inflammatory lesions that may exhibit slow continuous progression or relatively short bursts of disease activity.^{7,8}

Periodontitis usually has a coexisting gingivitis associated with it though many of the studies reported in *The Scottsdale Report* are mainly dealing with patients with periodontitis rather than gingivitis alone. Much of the destruction observed in these infections occurs as a result of host inflammatory and immunologic responses to the bacteria within dental plaque.² The infection begins when gram-negative anaerobic bacteria* form colonies that grow and embed themselves (along with

* *Porphyromonas gingivalis*, *Tannerella forsythensis*, and *Treponema denticola*

Figure 1. Anatomical depiction and clinical presentation of the progression from a healthy periodontium to advanced chronic periodontitis.



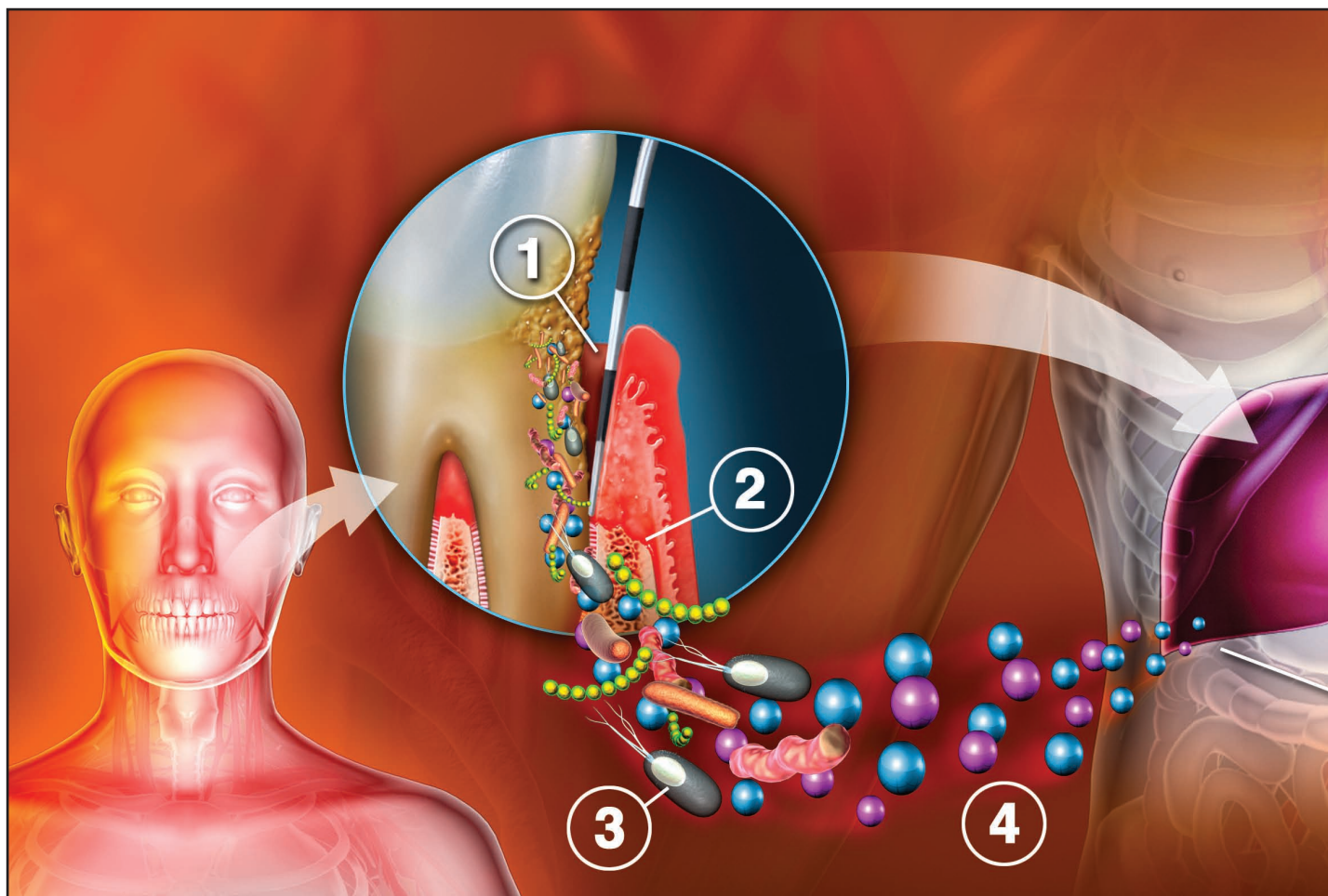
Photographs courtesy of Charles Cobb, DDS, PhD

other species) in biofilms. These biofilms extend apically along the surface of tooth roots to incite formation of the periodontal pockets and destruction of the alveolar bone and the collagenous attachment fibers of the periodontal ligament.⁹

Over the last 50 years the etiological theory of periodontal disease has evolved from rather simplistic hypotheses to a closer understanding of the complexities of host-bacterial interaction and the realization that periodontitis has a systemic effect. In the 1960s researchers thought periodontal disease was simply caused by the mechanical irritation of calculus deposits located either near gingival tissues and/or attached to root surfaces subgingivally. During the decade of 1965-1975, the nonspecific plaque hypothesis dominated research. This postulated that it was the quantity of nonspecified bacteria, and not the virulence of individual species that was responsible for periodontal

destruction.¹⁰ During the late 1970s and early 1980s, researchers isolated specific gram-negative microorganisms thought to be particularly virulent periodontal pathogens and adopted the specific plaque hypothesis. A few years later, researchers began to realize that periodontitis in patients could vary greatly despite the quantity or qualitative levels of bacteria and that the existence of bacterial plaque alone was insufficient to explain the sequelae of periodontal disease, namely the loss of connective tissue and alveolar bone. When it was discovered that all individuals are not equally susceptible to periodontal diseases, scientists during the mid-1980s theorized that the degradation of the periodontium was mediated by host-bacterial interaction, and that it is the host's response to the presence of bacteria that determines this tissue destruction. The host-bacterial interaction theory recognizes that although bacteria is necessary to initiate the cascade of events that occur in periodontal diseases, bacteria alone is insufficient

Figure 2. Illustration of theorized mechanism linking periodontal disease to atherosclerosis-induced diseases such as coronary heart disease and ischemic stroke.



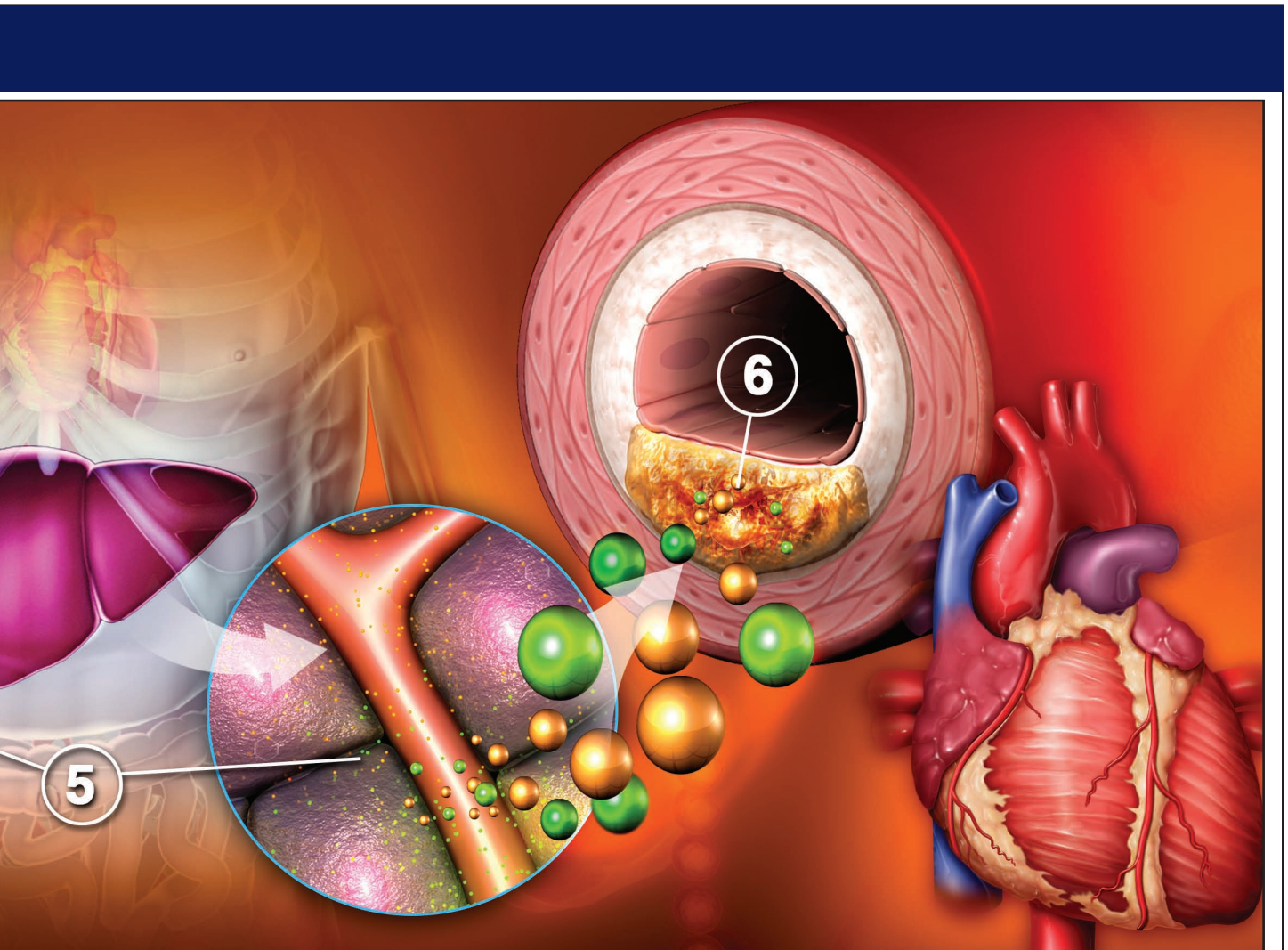
1. Oral flora forms subgingival biofilm and initiates periodontal disease with resultant bone loss and periodontal pocketing
2. Endotoxins, enzymes, and metabolic by-products produced by gram-negative microflora cause ulceration and necrosis of pocket epithelial lining
3. Epithelial breach leads to invasion of underlying connective tissue and blood vessels by bacteria and endotoxins (bacteremia/endotoxemia)
4. Host immune response leads to accumulation of inflammatory cells (neutrophils, monocytes) and production of pro-inflammatory cytokines (IL-1, TNF-α)

in inducing periodontal disease or its progression. Subsequently, there has been much investigation of risk factors that influence the host response, such as smoking, diabetes, and genetic risk factors.¹¹ These risk factors have become generally accepted as having a negative influence on the host response; the role of other risk indicators such as stress, obesity, hormonal influences, immunocompromised states, and osteoporosis (among others) are also under investigation.

Little did we know that Hippocrates' claim that "infectious diseases can cause inflammatory changes at distant body sites" and the Focal Infection Theory of the 1920s would become the prevailing hypothesis in periodontology. As evidence of periodontal infection's influence on chronic inflammatory disease states continues to mount, the current etiological theory of periodontal disease extends beyond its local affect, making a compel-

ling rationale for prevention and early intervention. Accumulating evidence suggests that periodontal infection may increase the risk for atherosclerosis induced conditions such as coronary heart disease and stroke (Figure 2), adverse pregnancy outcomes, complications of diabetes, respiratory diseases, neurodegenerative diseases, among other oral-systemic relationships currently under investigation. Three etiological mechanisms are implicated in the inflammatory pathway linking periodontal disease to systemic damage: 1) metastatic spread of gram negative bacteria that gain access to the vasculature as a result of breach of the compromised epithelial lining of periodontal pockets; 2) metastatic injury from the effects of the circulating toxins of periodontal pathogens; and 3) metastatic inflammation caused by the immunologic response to the pathogens and their toxins.^{12,13}

Throughout *Oral Health in America*,¹⁴ then Surgeon General



5. Cytokines are transported to liver and stimulate production of acute phase proteins (C-reactive protein, fibrinogen)

6. Combined effect of bacteremia/endotoxemia, circulating cytokines, and acute phase proteins damages endothelial lining of coronary arteries leading to atheroma formation

Satcher reinforced the message that “oral health and general health are inseparable”, and that “oral health is integral to general health”. Another common thread running through the report was that the mouth “is a portal of entry for infections that can affect local tissues and may spread to other parts of the body” with references to the associations between periodontal disease and diabetes, heart disease and stroke and adverse pregnancy outcomes. The report went on to say that improvements in oral health depend on multidisciplinary and interdisciplinary approaches to research and on the ability of practitioners to apply that research effectively. The need to change nondental healthcare providers’ perception of the importance of oral health was also discussed. Satcher challenged medical and dental healthcare providers that they “should be ready, willing, and able to work in collaboration to provide optimal healthcare for their patients”. As a prerequisite for interdisciplinary services, the report highlighted the need for curriculum changes and multidisciplinary training. The report also called for the development of risk assessment tools and diagnostic markers to allow clinicians to determine which individuals are more susceptible to a given disease, thereby providing a basis for more targeted intervention strategies for those at high risk. Given the estimates of periodontal disease prevalence and speculation that it is dramatically underdiagnosed, early identification and appropriate treatment of periodontal disease is critical in achieving these intervention strategies.

The lack of a standard definition of periodontal disease and issues related to access to dental care for a substantial percentage of the U.S. population confounds the attempts of epidemiologists to pinpoint the prevalence of periodontal diseases. However, recent investigation into the validity of self-reported periodontal disease and its use in attaining more accurate measurements of periodontal disease prevalence is promising.¹⁵ It has recently been estimated that at least 50% of adults in the U.S. have some level of gingival inflammation, or gingivitis.¹⁶ Periodontal disease is highly prevalent, affecting about 34% of the U.S. population older than 30 years, with severe periodontal disease estimated in 13% of the population.¹⁷ Given the prevalence of periodontal disease and statistics generated from consumer surveys and practice management statistics, it appears that periodontal disease may be significantly underdiagnosed in the United States. In a 2005 paper entitled “Diagnosis and Treatment of Periodontal Disease: A Crisis of Direction”, Cobb¹⁸ wrote: “In spite of our current understanding of the etiology and clinical characteristics of chronic periodontitis, there is still a conflict between what many private practitioners consider to be chronic periodontitis requiring treatment versus the recent description and reclassification of periodontitis by the 1999 International Workshop for a Classification of Periodontal Disease and Conditions. In other words, when clinically defining (i.e., diagnosing) chronic periodontitis for the purpose of treatment,

dentistry is faced with the conundrum of ‘what is’ versus ‘what should be’.”

If the medical profession begins to identify patients who have periodontal disease or who may be at risk for periodontal disease, and the dental profession screens patients for undiagnosed CVD and/or diabetes, the impact on the prevalence of these life-threatening chronic conditions may offer unprecedented gains in longevity. Over 70 million Americans have CVD.¹⁹ This translates into 1 in 4 people with some form of CVD. Statistics related to the failure to assess risk and diagnose CVD are haunting. For example, research indicates that for 50% of men and 64% of women who died suddenly of coronary heart disease, there was no previous recognition of the disease.²⁰ Furthermore, a significant proportion of the population with identified risk factors for CVD are not diagnosed with CVD, and are therefore not being treated adequately for CVD.²⁰

Current predictions suggest that by 2030 there will be 23 million individuals with diagnosed diabetes, 7 million with undiagnosed diabetes, with another estimated 70 million with impaired fasting or postprandial glucose.²¹ Direct costs of diabetes could be close to \$175 billion/year; indirect costs could be an additional \$75 billion/year. Even now the economic and personal burden of diabetes outpaces our current healthcare delivery system.

How might medical-dental collaboration impact these disease trajectories? This was the focus of *The Scottsdale Project*.

ORDER OF PROCEEDINGS AND DESCRIPTION OF OPINION BUILDING PROCESS

The Scottsdale Project was a 3-day conference. The conference was organized to provide an opportunity for professional organizations and other relevant stakeholder groups to observe the proceedings on the opening day. Several key organizations* were invited to send a representative to deliver a short presentation during the morning of the first day that specifically addressed several important questions:

1. Does your organization recognize the evolving body of evidence that supports a relationship between oral and systemic health/disease?
2. If so, what has your organization done to create awareness among its constituency or develop clinical protocols that address the oral-systemic relationship?
3. If not, what have been the hurdles to acceptance of the evidence of oral-systemic links?
4. What future direction would your organization propose in order to advance oral-systemic medicine and collaboration among healthcare providers?

* American Academy of Periodontology, American Diabetes Association, National Dental Association, American Dental Hygienists’ Association, America’s Health Insurance Plans

A number of other key organizations[†] sent representatives to observe the first day of the proceedings. On the first morning, Dr. Maria Ryan presented an overview of relevant research. The afternoon session began with Dr. Charles Cobb's presentation on the etiology of periodontal disease, which provided important background information to medical experts serving on the panel. Dr. Karen Williams acted as the moderator of the opinion building process. A series of focused questions were individually discussed. Prerecorded video testimony of Dr. Brian Mealey was played to provide the expert panel with a starting point for their discussions. Small working groups comprised of experts with heterogeneous backgrounds were assigned responsibility for drafting recommendations. Answers to the focused questions, recommendations, and final conclusions related to the appropriateness of guidelines for clinical decision making and comanagement of patients who are at risk for or already diagnosed with periodontal disease and CVD were derived by the expert panel during open forum, and facilitated highly interactive discussions. Proceedings throughout the 3 day conference were

voice recorded and transcribed to ensure accuracy of findings.

METHODOLOGY

The development of *The Scottsdale Project* was directed by a conference planning committee, which consisted of 8 individuals from the expert panel. The planning meeting was held 4 months before the consensus conference; language specific to the preamble was discussed, issues related to scientific methodology were addressed, and the committee identified a small group of professional organizations that would be invited to observe and/or present during the opening day of the proceedings in Scottsdale.

Following this planning meeting, the planning committee developed 5 questions designed to determine whether there was sufficient evidence to support collaboration between medical and dental providers in the intervention of periodontal disease, diabetes, and CVD. In addition, the committee developed a system for grading the evidence. During the conference proceedings, the expert panel revised and expanded the 5 original focused questions to 8 focused questions listed in the sections below ("Grading the Evidence" and "Weighing the Evidence").

Table 1. Oxford Grades for Level of Evidence

(Used for grading of evidence to support answers to focused questions derived from experts' opinion from *The Scottsdale Project*)

Evidence	Description
Level 1a	SR (with homogeneity*) of RCTs
Level 1b	Individual RCT (with narrow confidence interval)
Level 1c	All or none*
Level 2a	SR (with homogeneity*) of cohort studies
Level 2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
Level 2c	"Outcomes" research; ecological studies
Level 3a	SR (with homogeneity*) of case-control studies
Level 3b	Individual case-control study
Level 4	Case series (and poor quality cohort and case control studies†)
Level 5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

SR: Systematic Review; RCTs: Randomized Clinical Trials

* The term homogeneity refers to a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant.

+ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

† A poor quality cohort study is one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and nonexposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. A poor quality case control study is one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

Source: Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Available at: http://www.mcw.edu/display/displayFile.asp?docid=5540&filename=/User/fvastalo/Oxford_Levels.pdf. Accessed April 27, 2007.

As part of the planning process, a search of the literature and review of the evidence was conducted by independent research analysts with expertise in medical/dental literature. The search was limited to studies in humans including (only) randomized controlled clinical trials, meta-analyses, literature reviews, epidemiologic studies specific to relevant topics, and consensus papers published from 2000 to March 2007. The search was conducted through PubMed utilizing MeSH key words specifically related to associations between the following relevant links:

- periodontal disease and inflammation
- diabetes and periodontal disease
- inflammation and diabetes
- periodontal disease and CVD
- inflammation and CVD
- diabetes and CVD

In addition, all of the participating experts were asked to submit articles that met the inclusion criteria but that may not have been identified during the literature search. Several experts identified and recommended additional articles with earlier

publication dates for the purpose of supporting additional discussions during the proceedings of *The Scottsdale Project*. A total of 118 articles met the initial inclusion criteria and were incorporated into the review. Methodology and data were extrapolated from full text versions of these articles and reviewed by independent research analysts, who graded the evidence according to criteria, originally defined by the conference planning committee, and organized relevant information into evidence summaries. Panel experts were provided online access to evidence summaries and primary source documents via a portal specially designed for *The Scottsdale Project*, as well as hard copies of summaries. Members of the expert panel were asked to review the evidence summaries prior to the conference so that discussions at the conference would be based on existing literature. Where literature was not available, the panel of experts offered concordant expert opinions in addressing focused questions and recommendations.

GRADING OF EVIDENCE TO SUPPORT ANSWERS TO FOCUSED QUESTIONS

During the initial proceedings, the panel of experts evaluated the adequacy and appropriateness of the system the conference

planning committee had proposed for grading the level of evidence. After careful consideration during early discussions in Scottsdale, the expert panel recommended that this grading system be replaced by the more rigorous criteria contained in the Oxford Grades for Level of Evidence (Table 1). Two members of the expert panel (physician and dentist, both PhD trained) performed a calibrated review of previously graded evidence summaries of all articles to ensure that the level of evidence was graded according to the Oxford Grades for Level of Evidence criteria, making revisions to evidence grades as necessary.

Eight Focused Questions: The expert panel was tasked with considering the quality of evidence during ensuing discussion of 8 focused questions.

1. Is there evidence that periodontal diseases result in an increase in local and systemic inflammatory response?
2. Does the evidence support the concept that periodontal disease is a complication of diabetes?
3. Is there evidence that in people with diabetes, periodontal disease is associated with poor glycemic control and/or other complications of diabetes?

Table 2. Oxford Criteria for Grading Recommendations

(Used to grade the experts' recommendations derived from answers to focused questions specific to *The Scottsdale Project*)

Evidence	Description
Level A	Recommendation supported by consistent level 1 studies
Level B	Recommendation supported by consistent level 2 or 3 studies or extrapolations* from level 1 studies
Level C	Recommendation supported by level 4 studies or extrapolations* from level 2 or 3 studies
Level D	Recommendation supported by level 5 evidence or troubling, inconsistent or inconclusive studies of any level
<p>*"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.</p> <p>Source: Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Available at: http://www.mcv.edu/display/displayFile.asp?docid=5540&filename=/User/fvstalo/Oxford_Levels.pdf. Accessed April 27, 2007.</p>	

Table 3. United States Preventive Services Task Force (USPSTF) System for Grading Recommendations

Evidence	Description
Level A	There is good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms. Therefore, it is recommended that clinicians routinely provide the service to eligible patients.
Level B	There is at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms. Therefore, it is recommended that clinicians routinely provide the service to eligible patients.
Level C	There is at least fair evidence that the service can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation. Therefore, there is no recommendation for or against routine provision of the service.
Level D	There is at least fair evidence that the service is ineffective or that harms outweigh benefits. Therefore, routinely providing this service to asymptomatic patients is not recommended.
Level I	The evidence is insufficient to recommend for or against routinely providing the service; evidence that the service is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.
<p>Source: United States Preventive Services Task Force (USPSTF). Screening for obesity in adults: recommendations and rationale. <i>Ann Intern Med.</i> 2003;139(11):930-932.</p>	

4. Is there evidence that treating periodontal disease results in a decrease in the local and systemic inflammatory response?
5. Is there evidence that periodontal disease interventions may improve outcomes in diabetes (glycemic control, development/progression of complications of diabetes)?
6. Is it appropriate to develop guidelines for the medical-dental comanagement of those at risk for diabetes or those previously diagnosed with diabetes who may also have periodontal disease in an attempt to positively impact glycemic control and reduce the risk of diabetic complications?
7. Is periodontal disease associated with atherosclerosis-induced diseases such as coronary heart disease or ischemic stroke?
8. Is there evidence that intervention of periodontal disease decreases the risk for CVD or reduces the incidence of coronary heart disease or ischemic stroke?

In answering these questions, statements were carefully drafted by the panel of experts during the proceedings and explicitly written to reflect solidarity of opinion using the best available evidence. The major findings and conclusions reached by the expert panel regarding these focused questions provided the basis for recommendations for guideline development, as embodied in Key Issues I and II as stated earlier.

GRADING OF RECOMMENDATIONS

The expert panel provided individual recommendations and supporting rationales for the answers for each of the focused questions. One of the difficulties in assigning a grade to the recommendations was that the Oxford Criteria for Grading Recommendations alone (Table 2) were not sufficient for grading recommendations related to direct patient care or formulation of clinical guidelines. Consequently, recommendations of the expert panel have been graded according to 2 sets of criteria; the Oxford Criteria for Grading Recommendations (not to be confused with Oxford Grades for Level of Evidence designed to weigh evidence to support answers to focused questions) and the grading criteria utilized by United States Preventive Services Task Force (USPSTF) (Table 3). The combined use of these sets of criteria allowed for grading both the strength of evidence to support recommendations that do not directly deal with patient care (Oxford), and grading the magnitude of the net benefit (benefits minus harms) of recommendations that deal with patient care and/or formulation of clinical guidelines (USPSTF).

WEIGHING THE EVIDENCE

First, evidence relevant to the expert panel's discussions during *The Scottsdale Project* was graded on a scale of 1a-5 according to criteria of the Oxford Grades for Level of Evidence, as defined in Table 1. Then, answers were developed in response to each of the 8 focused questions; the levels of evidence assigned to individual references supporting those answers are listed in Table 4. Finally, recommendations derived from experts' discussions during *The Scottsdale Project* were graded according to the Oxford

and USPSTF criteria explained in Tables 2 and 3; the graded recommendations for the 8 focused questions are described in Table 5. The scientific rationale and additional studies supporting these recommendations, as derived from the experts' discussions, are described below.

DISCUSSION OF SCIENTIFIC RATIONALE FOR RECOMMENDATIONS DERIVED FROM EXPERTS' DISCUSSION DURING *THE SCOTTSDALE PROJECT*

Focus #1 – Periodontal Disease and Increased Inflammatory Response

Eight of the reviewed articles (5 [level 5]²³⁻²⁷ and 3 [level 2b]⁹¹⁻⁹³) have addressed the bacterial/host response relationship in the pathogenesis of inflammatory periodontal disease, the potential for bacteremia, and the role of locally produced proinflammatory mediators.

Three studies (1 [level 2c]⁹⁴ and 2 [level 5]^{95,96}) speculate that the inflamed and ulcerated subgingival pocket epithelium presents a portal of entry for pathogenic periodontal bacteria, many being gram-negative anaerobes. The presence of periodontal bacteria in atheromatous plaques — supported by evidence from 5 studies (4 [level 3b]⁹⁷⁻¹⁰⁰ and 1 [level 4]¹⁰¹ — offers indirect support for the role of bacteremia in periodontal disease.

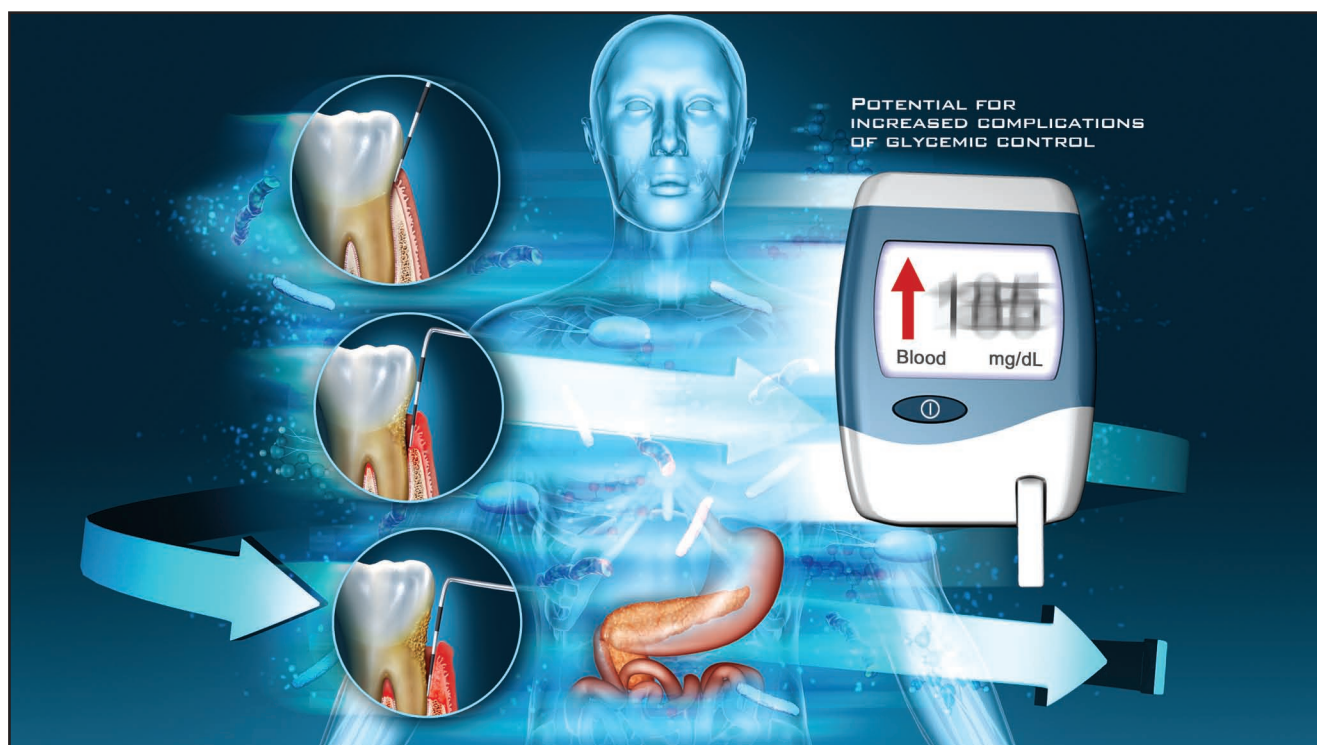
Geerts and colleagues¹⁰² (level 2c) found that endotoxin and other outer membrane antigens derived from gram-negative anaerobic microbes may gain access to the circulatory system and exert systemic or distant effects. Likewise, 3 studies (1 [level 2a],¹⁰³ 1 [level 2b],²² and 1 [level 5]²⁴) demonstrated that locally produced proinflammatory mediators (such as IL-1, TNF- α , IL-6, and PGE₂), after gaining entry into the circulatory system, exert a systemic effect.

Eight studies (5 [level 2b]^{22,30,33,104,105} and 3 [level 3b]^{35,36,106}) reported higher plasma C-reactive protein (CRP) levels in patients with periodontitis versus nondiseased controls. In addition, 2 studies^{36,107} (level 3b) reported an association of poor oral health with increased fibrinogen levels. Lastly, 5 studies (3 [level 1b],^{28,32,45} 1 [level 2b],⁴⁶ and 1 [level 4]⁴⁷) demonstrated a decrease in plasma levels of IL-1 β , IL-6, and CRP following nonsurgical treatment of periodontitis, offering indirect support for the concept that localized periodontal inflammation is associated with a systemic inflammatory response.

Focus #2 – Periodontal Disease as a Complication of Diabetes

The concept that periodontal disease is an important complication of diabetes is supported by evidence from 7 studies (6 [level 2b],^{37-39,108-110} and 1 [level 3b]⁴⁰). It is generally accepted that people with diabetes have decreased immune responses and are therefore more susceptible to infections. People with

Figure 3. The potential for a bidirectional relationship between diabetes and periodontal disease.



Evidence suggests that people with diabetes are significantly more susceptible to periodontal disease, that periodontal infection complicates glycemic control and enhances insulin resistance and hyperglycemia, and that poor glycemic control causes increased susceptibility to re-infection and increases the severity of periodontal disease.

diabetes are also known to have atherosclerotic changes in their blood vessels that make them prone to a decreased vascular supply to the periodontium. Because of this, people with diabetes are more susceptible to any infection including infections of the periodontium. Furthermore, the finding that untreated moderate to severe periodontitis appears to adversely impact glycemic control (Figure 3) is supported by 6 studies (1 [level 2a],⁵⁸ 2 [level 2b],^{43,111} 1 [level 3b],⁴⁴ and 2 [level 5]^{24,112}). Acute bacterial and viral infections are known to increase insulin resistance in people with diabetes and may, in fact, result in prolonged problems with glycemic control, as reported by Mealey and Oates⁵⁸ (level 2a).

Additionally, Engbretson and colleagues¹¹³ (level 4) suggest that periodontitis-associated circulating TNF- α may contribute to insulin resistance. Indirect evidence may be gleaned from 4 studies (3 [level 2b]^{49,51,114} and 1 [level 3b]⁵³) involving people with type 1 and type 2 diabetes with severe periodontitis with improvements in glycemic control following nonsurgical periodontal therapy, i.e., reductions in hemoglobin A_{1c} (HbA_{1c}) levels.

In contrast, 4 studies (1 [level 1a]⁵⁵ and 3 [level 2b]^{56,115,116})

reported improvements in periodontal health following therapy, but no significant reductions in HbA_{1c} values. Aldridge and colleagues¹¹⁵ (level 2b) interpreted the lack of improvement in HbA_{1c} values as an indication that metabolic control may be dominant in the relationship between diabetes and periodontal health. The study by Christgau and colleagues¹¹⁶ (level 2b) essentially demonstrated that patients with well controlled diabetes and patients without diabetes have similar responses to periodontal treatment, e.g., decreased probing depth, clinical attachment levels, bleeding on probing, oxidative burst response of polymorphonuclear leukocytes (PMN) to TNF- α and f-Met-Leu-Phe (fMLP), and decreases in periodontal pathogenic microbes.

Focus #3 – Association of Periodontal Disease with Glycemic Control

The presence of untreated moderate to severe periodontitis appears to adversely impact glycemic control, as shown in 5 studies (1 [level 2a],⁵⁸ 1 [level 2b],¹¹¹ 1 [level 3b],⁴⁴ and 2 [level 5]^{25,112}). Indirect evidence from 5 small clinical trials (3 [level 2b],^{49,51,114} 1 [level 3b],⁵³ and 1 [level 4]¹¹⁷), all involving patients with type 1 and type 2 diabetes with severe periodontitis, indicate improvements in glycemic control following nonsurgical periodontal therapy, i.e., reductions in HbA_{1c} levels.

Further, 3 studies (1 [level 3b],⁴⁴ 1 [level 2a],⁴² and 1 [level 1b]⁴¹) offer evidence supporting the concept that patients with diabetes and chronic periodontitis have a higher incidence of nephropathy. Saremi and colleagues⁴² (level 2a) reported that periodontal disease is a strong predictor of mortality from diabetic nephropathy and ischemic heart disease in Pima Indians with type 2 diabetes. Shultis and colleagues⁴¹ (level 1b) investigated the effect of periodontitis on development of overt nephropathy, defined as macroalbuminuria, and end stage renal disease in patients with type 2 diabetes. The incidence of macroalbuminuria was significantly elevated in subjects with moderate or severe periodontitis or who were edentulous (2.0, 2.1, and 2.6 times

greater respectively), compared to patients with no disease or mild periodontitis. Likewise, the incidence of end stage renal disease in individuals with moderate or severe periodontitis or in those who were edentulous was 2.3, 3.5, and 4.9 times greater, respectively, compared with those with no disease or mild periodontitis. Lastly, Thorstensson and colleagues⁴⁴ (level 3b) reported that in 39 case-control pairs, renal disease (proteinuria) was associated with severe periodontitis.

Evidence from 5 studies (1 [level 1b],¹¹⁸ 2 [level 2a],^{119,120} and 2 [level 5]^{121,122}) has well established that diabetes is a major risk factor for coronary vascular disease (CVD). As such, diabetes may

Table 4. Focused Questions, Answers, and Level of Evidence Assigned to Supporting References, Derived from Experts' Discussions during *The Scottsdale Project*

Focused Questions and Answers	Evidence	
	Level (Oxford)	Supporting References
Question #1 – Is there evidence that periodontal diseases result in an increase in local and systemic inflammatory response?		
<p>There is evidence that periodontal diseases result in an increase in local and systemic inflammatory response. Both gingivitis and periodontitis elicit a local gingival increase in inflammatory biomarkers, including interleukin-1 beta (IL - 1β), tumor necrosis factor alpha (TNF - α), interleukin-6 (IL - 6), and prostaglandin E₂ (PGE₂).</p> <p>Periodontitis is also associated with elevated serum markers of systemic inflammation, including high sensitivity C-reactive protein (hsCRP), soluble Intercellular Adhesion Molecules (sICAM), and IL - 6.</p> <p>Both the local and systemic response are positively associated with increasing severity of periodontitis.</p>	2b	Loos ²²
	5	DeNardin, ²³ Gemmell, ²⁴ Loos, ²⁵ Offenbacher ^{26,27}
	1b	D'Aiuto ²⁸
	2b	Ide, ²⁹ Noack, ³⁰ Schaumberg ³¹
	1b	D'Aiuto ³²
	2b	Ide, ²⁹ Craig, ³³ D'Aiuto ³⁴
	3b	Buhlin, ³⁵ Wu ³⁶
Question #2 – Does the evidence support the concept that periodontal disease is a complication of diabetes?		
<p>There is evidence that diabetes can affect the periodontium and that periodontitis is an important, although often unrecognized, complication of diabetes. (Note: A large body of non-human mechanistic studies, not reviewed for this project, also support that the pathogenesis of periodontitis is similar to that of other diabetic complications and justify viewing it as such.)</p>	2b	Lalla, ³⁷ Campus, ³⁸ Jones ³⁹
	3b	Lim ⁴⁰
Question #3 – Is there evidence that in people with diabetes, periodontal disease is associated with poor glycemic control and/or other complications of diabetes?		
<p>The current available evidence indicates that in people with diabetes, periodontal disease at baseline is associated with poor glycemic control, nephropathy, and CVD.</p>	1b	Shultis ⁴¹
	2a	Saremi ⁴²
	2b	Taylor ⁴³
	3b	Thorstensson ⁴⁴
Question #4 – Is there evidence that treating periodontal disease results in a decrease in the local and systemic inflammatory response?		
<p>Several studies support the concept that periodontal treatment can reduce local oral levels of inflammatory mediators and systemic markers of inflammation. Although such studies suggest that periodontal therapy may reduce serum IL - 6 and CRP, and arrest progression of periodontal disease, larger randomized controlled clinical trials are needed to investigate whether treatment of periodontal disease decreases local and systemic inflammatory responses.</p>	1b	D'Aiuto, ^{28,32} Tonetti ⁴⁵
	2b	D'Aiuto ^{34,46}
	4	Yamazaki ⁴⁷
Question #5 – Is there evidence that periodontal disease interventions may improve outcomes in diabetes?		
<p>There are mixed findings regarding whether periodontal disease interventions may improve outcomes in diabetes (glycemic control, development/progression of complications of diabetes). Some studies show that periodontal treatment improves glycemic control in patients with diabetes.</p> <p>Other studies do not show a relationship between periodontal treatment and improved glycemic control. Adequate, well-designed multicenter randomized controlled trials have not been performed. To date, no data are available regarding the potential impact of periodontal therapy on nephropathy or CVD in patients with diabetes.</p>	2b	Almas, ⁴⁸ Grossi, ⁴⁹ Rodrigues, ⁵⁰ Stewart ⁵¹
	3b	Iwamoto, ⁵² Kiran, ⁵³ Schara ⁵⁴
	1a	Janket ⁵⁵
	2b	Jones, ³⁹ Promsudthi ⁵⁶

be considered a risk equivalent for CVD.¹²³ As noted in Focus #2 above, the presence of untreated moderate to severe periodontitis has a detrimental effect on glycemic control. Further, there is considerable data from 9 studies (2 [level 1b],^{28,32} 5 [level 2b],^{29-31,33,34} and 2 [level 3b]^{35,36}) indicating that untreated moderate to severe periodontitis is associated with a systemic inflammatory response. Similarly, there is a significant amount of data from 17 studies (1 [level 2a],⁸⁵ 3 [level 2b],^{64,67,124} 12 [level 3b],^{70,72-74,76,80-84,125,126} and 1 [level 4]¹⁰¹) indicating that untreated moderate to severe periodontitis is associated with atherosclerosis and/or CVD. Thus, it would appear that a diagnosis of moderate to severe periodontitis would be considered a comorbid condition

with diabetes, further elevating the risk for development of atherosclerosis and/or CVD in people with diabetes. Only 2 studies (1 [level 2b]¹⁰⁹ and 1 [level 3b]⁴⁴) offer direct evidence supporting an association of periodontal disease in patients with diabetes or CVD. Thus, there is an obvious need for future studies that focus on patients with diabetes and a concomitant diagnosis of moderate to severe periodontitis to determine association with cardiovascular status.

The fact that evidence supports an adverse effect of diabetes on the periodontium does not necessarily mean that the practicing health-care community is aware of that evidence. Currently there

Table 4. Focused Questions, Answers, and Level of Evidence Assigned to Supporting References, Derived from Experts' Discussions during *The Scottsdale Project* (cont'd.)

Focused Questions and Answers	Evidence	
	Level (Oxford)	Supporting References
Question #6 – Is it appropriate to develop guidelines for the medical-dental comanagement of those at risk for diabetes or those previously diagnosed with diabetes who may also have periodontal disease in an attempt to positively impact glycemic control and reduce the risk of diabetic complications?		
<p>Yes, it appropriate to develop guidelines for the medical-dental comanagement of those at risk for diabetes or those previously diagnosed with diabetes who may also have periodontal disease in an attempt to positively impact glycemic control and reduce the risk of diabetic complications. Periodontal disease is a chronic disease that jeopardizes the periodontium, causing local and systemic inflammation.</p> <p>Periodontal disease is also epidemiologically associated with impaired glycemic control, nephropathy, and CVD.</p> <p>Though studies looking at the effect of treatment of periodontal disease on glycemic control, nephropathy, and CVD are limited, an improvement in glycemic control has been demonstrated (Question #5 above), and a decrease in CVD and nephropathy are also possible secondary effects of treatment.</p>	2a	Khader, ⁵⁷ Mealey ⁵⁸
	2b	Lalla ³⁷
	4	Bakhsandeh ⁵⁹
	5	Nassar, ⁶⁰ Nishimura, ⁶¹ Southerland ⁶²
	2a	Saremi ⁴²
	5	Nishimura, ⁶¹ Southerland ⁶²
	1a	Janket ⁵⁵
	2b	Almas, ⁴⁸ Grossi, ⁴⁹ Rodrigues, ⁵⁰ Stewart ⁵¹
	3b	Iwamoto, ⁵² Kiran, ⁵³ Schara ⁵⁴
	5	Southerland ⁶²
Question #7 – Is periodontal disease associated with atherosclerosis-induced diseases such as coronary heart disease or ischemic stroke?		
<p>A broad range of observational studies demonstrate a consistent moderate association between different measures of periodontal disease, coronary heart disease, ischemic stroke, and measures of atherosclerosis.</p> <p>There are also some observational studies and meta-analyses that demonstrate no associations or very weak associations between periodontal disease, coronary heart disease, ischemic stroke, and measures of atherosclerosis.</p>	1b	D'Aiuto ²⁸
	2a	Janket ⁶³
	2b	Beck, ⁶⁴ Hung, ⁶⁵ Joshupura, ⁶⁶ Montebugnoli, ⁶⁷ Wu ⁶⁸
	3a	Meurman ⁶⁹
	3b	Briggs, ⁷⁰ Czerniuk, ⁷¹ Deliagyris, ⁷² Desvarieux, ^{73,74} Dorfer, ⁷⁵ Engebretson, ⁷⁶ Grau, ⁷⁷ Holmlund, ⁷⁸ Lee, ⁷⁹ Lopez, ⁸⁰ Persson, ⁸¹ Slade, ⁸² Spahr, ⁸³ Tabrizi ⁸⁴
	2a	Khader ⁸⁵
	2b	Howell ⁸⁶
	3b	Nakib ⁸⁷
Question #8 – Is there evidence that periodontal disease intervention decreases the risk for CVD or reduces the incidence of coronary heart disease or ischemic stroke?		
<p>Whether intervention for periodontal diseases improves CVD or reduces the incidence of coronary heart disease or ischemic stroke has not been fully answered. Early studies demonstrate that periodontal treatment improves endothelial function. However, to date, intervention trials looking at the effect of periodontal treatment on coronary heart disease and ischemic stroke have not been performed. Randomized controlled trials with subclinical and clinical outcomes are needed to fully answer this question. Determination of optimal treatment schemes and identification of patient groups most likely to benefit from intervention are needed.</p>	1b	Tonetti ⁴⁵
	2b	Mercanoglu ⁸⁸
	4	Elter, ⁸⁹ Seinost ⁹⁰

Table 5. Focused Question Topics – Graded Recommendations Derived from Experts' Discussions during *The Scottsdale Project*

Grade	Recommendations
Focused Question Topic #1 – Periodontal disease and increased inflammatory response	
B[‡]	<ul style="list-style-type: none"> ■ If a patient's systemic inflammatory markers are measured and found to be elevated, the oral cavity should be considered as a potential contributor. ■ There must be greater recognition of the link between oral and systemic health. This should prompt changes in undergraduate and graduate education and Continuing Medical Education as well as Continuing Dental Education. ■ In addition, there is a need to shift away from the conventional silo thinking, which has historically divided medicine and dentistry, to the creation of a forum to stimulate and sustain ongoing dialogue on the relevance of shared responsibility for overall health outcomes.
Focused Question Topic #2 – Periodontal disease as a complication of diabetes	
B[‡]	<ul style="list-style-type: none"> ■ Novel public relations campaigns and educational programming should be created and implemented to increase awareness among current practitioners in both dentistry and medicine that diabetes can affect the periodontium and that periodontitis is an important, although often unrecognized complication of diabetes. ■ Novel campaigns should be created and implemented, with a focus on educational reform to ensure that dental and medical providers are aware that periodontitis is an important, though often unrecognized complication of diabetes and as such, understand the implications of this for the health of patients. Such campaigns might include the dissemination of packets or "tool kits" offered by professional groups such as the American Diabetes Association, American Heart Association, American Dental Association, and the American Academy of Periodontology. The information in the packet/kit would be specifically designed to help the professional constituency educate their patients. ■ A health promotion or direct-to-the-patient campaign should be created and implemented, with a focus on educating the public. In addition, a self-assessment tool that allows the public to assess individual risk for periodontal disease and educates the public on the association between periodontal disease and diabetes should be developed and posted on the Web portals of professional organizations throughout the healthcare industry.
Focused Question Topic #3 – Association of periodontal disease with glycemic control	
B[‡]	<ul style="list-style-type: none"> ■ There must be increased awareness that treatment and preventive interventions for periodontal disease have the potential to favorably affect the systemic inflammatory response. ■ Patients with diabetes should be informed of the current data regarding the effects of periodontitis on glycemic control and risk for nephropathy and CVD. ■ Due to a potential association between the inflammation generated by periodontal diseases and systemic inflammation and the associated sequelae, it is recommended that general guidelines be developed addressing the management of the inflammatory burden imposed by periodontal diseases. Said guidelines should be proposed, validated, reviewed, and appropriately updated on an ongoing basis, by an independent commission comprised of both medical and dental professionals.
Focused Question Topic #4 – Periodontal disease treatment and decreased inflammatory response	
I[§]	<ul style="list-style-type: none"> ■ Larger randomized controlled clinical trials are needed to investigate whether treatment of periodontal disease decreases local and systemic inflammatory responses before further recommendations can be made.
Focused Question Topic #5 – Periodontal disease interventions and diabetes outcomes	
B[‡]	<ul style="list-style-type: none"> ■ Additional studies are required to determine whether intervention of periodontal disease improves other health outcomes; however, there is no harm in advocating intervention of periodontal disease. Because findings are mixed, the panel cannot make specific recommendations. ■ However, given the collective and diverse experience of the members of the expert panel, the recommendation is for close, enhanced communication between medical and dental practitioners in the comanagement of treatment and response outcomes in diabetes. This is crucial for optimal case management. Feedback from physicians is critical to determining the modality of oral intervention. Feedback from dentists is critical to maximize medical intervention (e.g., glycemic control).
<p>[‡] Based on (a) current available peer reviewed literature that demonstrates consistent level 2 or 3 data and some level 1 data (Oxford); and (b) consideration of the magnitude of the net benefit (USPSTF).</p> <p>[§] Currently available data in peer reviewed literature are inconsistent and therefore no firm conclusion can be reached. Therefore, no specific practice interventions were recommended. The group emphasized the need for large, randomized, controlled clinical trials and recommended that these be done before further recommendations can be made.</p> <p>^{**} Based on (a) current available peer reviewed literature that demonstrates some level 2 or level 3 data as well as expert opinion in the field (Oxford); and (b) consideration of the potential benefits of transdisciplinary practice models (USPSTF).</p> <p>^{‡‡} Based on the current available peer reviewed literature that demonstrates consistent level 2 or 3 data and some level 1 data (Oxford). This type of evidence does not lend itself to USPSTF grading criteria.</p> <p>^{§§} Based on (a) current available peer reviewed literature that demonstrates consistent level 2 data and some level 1 data (Oxford); (b) consideration of the potential benefit (USPSTF); and (c) taking into account the lack of randomized controlled trials.</p>	

Table 5. Focused Question Topics – Graded Recommendations Derived from Experts’ Discussions during *The Scottsdale Project* (cont’d.)

Grade	Recommendations
Focused Question Topic #6 – Potential guideline development for patients at risk for diabetes and periodontal disease	
B**	<ul style="list-style-type: none"> ■ It is strongly recommended that medical and dental teams collaborate in patient identification (screening), referral and management of periodontal disease in the patient with diabetes. ■ Dental management of those at risk for diabetes or those previously diagnosed with diabetes who may also have periodontal disease should consist of the following (during the initial visit and updated as needed at follow-up visits): <ol style="list-style-type: none"> 1. Determine the date of the patient’s last medical evaluation and obtain an adequate medical history and list of current medications; there should be an emphasis on determining the level of glycemic control or average blood sugars 2. Establish communication with the treating physician to confirm the information reported by the patient <ol style="list-style-type: none"> a. Inform physician of dental diagnosis b. Establish level of glycemic control and cardiovascular status (specifically, past and current HbA_{1c} values) through communication with patient’s physician 3. Develop an integrated treatment plan <ol style="list-style-type: none"> a. Treat acute infection b. Promote a healthy lifestyle (advise about ABCs: HbA_{1c}, Blood pressure, and Cholesterol) c. Encourage tobacco use cessation d. Educate about oral-systemic links in people with diabetes e. Modify treatment plan based on patient profile <ul style="list-style-type: none"> • Nonsurgical vs. surgical therapy • Antibiotics (systemic vs. local) • Host modulatory therapy • More frequent dental visits (follow-up) 4. Consider other oral manifestations of diabetes <ol style="list-style-type: none"> a. Caries – appropriate restorative and preventive care b. Dry mouth – saliva substitutes, adequate hydration c. Candidiasis – antifungals if necessary d. Comorbidities/associated medications (e.g., calcium channel blockers) 5. Special considerations <ol style="list-style-type: none"> a. Prevent and manage hypoglycemic events <ul style="list-style-type: none"> • Use a glucometer to monitor the potential for hypoglycemic episodes • When possible, avoid treating patients during peak activity periods with insulin or oral hypoglycemic medications • Know how to manage a hypoglycemic event b. Discuss with the patient’s physician the potential impact of long and/or complicated dental procedures, or consultation with the physician should be done as deemed appropriate ■ Medical management of those at risk for diabetes or those previously diagnosed with diabetes who may also have periodontal disease should consist of the following (during the initial visit and updated as needed at follow-up visits): <ol style="list-style-type: none"> 1. Screening for signs and symptoms associated with periodontal disease 2. Referral to the dentist when periodontal disease is suspected 3. Recommendations for biannual dental examinations and treatment as necessary 4. Recommendations for strict compliance to patient self care/oral hygiene 5. Provide dental provider with routine reports of patients’ HbA_{1c} lab values and any other reports that may indicate increased risk for complications of diabetes
Focused Question Topic #7 – Periodontal diseases and atherosclerosis-induced diseases	
B**	<ul style="list-style-type: none"> ■ Medical and dental communities should begin to recognize periodontal disease as a potential source of systemic inflammation subsequently placing exposed individuals at greater risk for the development and progression of atherosclerosis-induced diseases, such as coronary heart disease and ischemic stroke. However, a strict evidence-based decision making process indicates that treatment of periodontal disease should be recommended on the basis of its benefits in oral health.
Focused Question Topic #8 – Potential of periodontal disease interventions to decrease risk for CVD	
C^{§§}	<ul style="list-style-type: none"> ■ Periodontal disease should be treated for its oral benefits, regardless of the evidence for or against the benefit in coronary heart disease and stroke. It is a chronic infection that can result in tooth loss and systemic inflammation. Since treatment of periodontal disease has been shown to improve endothelial function, it may have the potential to reduce the incidence of coronary heart disease and stroke; however, this needs to be confirmed by randomized controlled intervention trials. Until that time, it is recommended to aggressively treat periodontal disease in patients with high risk for, or a previous history of, CVD and cerebrovascular disease.

are no guidelines for management of the inflammatory burden of periodontal disease, other than to diagnose and treat according to traditional standards. There are no “best treatment” guidelines for the control of local inflammation that consider the systemic response to such treatment.

Focus #4 – Periodontal Disease Treatment and Decreased Inflammatory Response

Eight studies (3 [level 1b],^{28,32,45} 2 [level 2b],^{34,46} 2 [level 3b],^{52,127} and 1 [level 4]⁴⁷) support the concept that nonsurgical periodontal therapy can reduce local oral levels of inflammatory mediators

and systemic markers of inflammation. However, 3 studies^{29,128,129} (level 2b) report that, in fact, periodontal therapy induces an increase in plasma levels. However, the latter studies report only short-term results (3 months), and at least 1 study⁴⁵ (level 1b) has noted a transient increase in serum markers followed by a progressive decrease, achieving significant low levels at 6 months post-therapy.

The inconsistent results reported by these relatively few clinical trials indicate the need for further investigations using larger subject populations, longer posttreatment intervals for data collection, and well defined endpoints for measurement and analysis.

Focus #5 – Periodontal Disease Interventions and Diabetes Outcomes

Despite the studies that demonstrate improvements in glycemic control after periodontal therapy, inconsistencies and weak study designs remain a barrier to definitive conclusions. This is illustrated best by the meta-analysis performed by Janket and colleagues⁵⁵ (level 1a), which demonstrated that there was no statistically significant reduction in HbA_{1c} after periodontal therapy. However, the absolute reductions in HbA_{1c} (0.4% without antibiotics and 0.7% with antibiotics) might be considered clinically significant to many physicians and dentists.

The following 6 prospective cohort, case-control, and clinical trials were prominent in discussions and decision-making:

- Grossi and colleagues⁴⁹ (level 2b) represents a prospective, randomized, blinded, placebo controlled trial. The experimental groups were small, detracting from the ultimate strength of the study. However, the results demonstrated that treatment of periodontal disease using adjunctive antimicrobials in patients with type 2 diabetes improved glycemic control as evidenced by significant reductions in HbA_{1c} levels. Improved glycemic control corresponded to improved periodontal health as measured by clinical indices (PD, loss of attachment, gingival bleeding).
- Iwamoto and colleagues⁵² (level 3b) represents a single cohort study with a small number of subjects that did not use an untreated control group due to ethical concerns. Thus, the study is not considered to be particularly strong. The results demonstrated that antimicrobial periodontal therapy was effective in improving metabolic control in patients with type 2 diabetes through significant reductions in circulating TNF- α , fasting insulin levels, and HbA_{1c} levels, linking insulin resistance to the relationship of periodontal disease and type 2 diabetes.
- Kiran and colleagues⁵³ (level 3b) represents a prospective clinical study of a small group of patients with type 2 diabetes and moderate periodontal disease. These results demonstrated that nonsurgical periodontal therapy improved periodontal health (PD, loss of attachment, gingival bleeding) and glycemic control measured by significant reductions in HbA_{1c} levels. The

study is noteworthy because it also demonstrated significant reductions in serum lipid levels (low density lipoprotein cholesterol and triglycerides) after periodontal treatment, linking periodontal health to improvements in other risk factors for atherosclerosis.

- Rodrigues and colleagues⁵⁰ (level 2b) represents a prospective clinical study of a small group of people with type 2 diabetes and moderate periodontal disease. The results demonstrated that one-stage nonsurgical periodontal therapy improved periodontal health, as evidenced by clinical indices (PD, loss of attachment, gingival bleeding) and glycemic control (significant reductions in HbA_{1c} levels).
- Schara and colleagues⁵⁴ (level 3b) represents a small clinical pilot trial of people with type 1 diabetes where full mouth disinfection was used to decrease oral microbial burden. The results demonstrated that full mouth disinfection, even in the absence of mechanical removal of the plaque biofilm, improved periodontal health as evidenced by clinical indices (PD, loss of attachment, gingival bleeding) and glycemic control (significant reductions in HbA_{1c} levels). This result has important implications for settings and patients where traditional nonsurgical therapy is not possible.
- Stewart and colleagues⁵¹ (level 2b) represents a prospective clinical study of a small group of type 2 diabetes and moderate periodontal disease who received periodontal treatment over an 18-month period. Consistent with other studies, the results demonstrated that nonsurgical periodontal therapy improved periodontal health (PD, loss of attachment, gingival bleeding) and glycemic control (significant reductions in HbA_{1c} levels).

Several studies have failed to demonstrate significant changes in fasting blood glucose or HbA_{1c} levels after periodontal therapy. Jones and colleagues³⁹ (level 2b) reported on a single-blind randomized clinical trial of 4-month duration. Results demonstrated no change in HbA_{1c} levels after periodontal treatment. The moderate sample size was larger than all previous studies. The question will be whether these findings can be generalized, as the study was conducted in a Veteran's Administration setting using a predominantly white older male population. Promsudthi and colleagues³⁶ (level 2b) conducted a 3-month prospective clinical study of a very small group of subjects with type 2 diabetes. Results demonstrated that although periodontal health improved, no significant change in fasting blood glucose or HbA_{1c} levels occurred after periodontal treatment.

Focus #6 – Potential Guideline Development for Patients at Risk for Diabetes and Periodontal Disease

Despite some inconsistencies and the fact that some areas have not been adequately addressed (e.g., the effect of treatment of periodontal disease on nephropathy and CVD), 7 studies provide level 2b-3b evidence for recommendations that specifically address glycemic control (Table 4, Focus Question #5).⁴⁸⁻⁵⁴ Eight other studies (3 [level 2a],^{42,57,58} 1 [level 2b],³⁷ 1

[level 4],⁵⁹ and 3 [level 5]⁶⁰⁻⁶²) support transdisciplinary practice recommendations, demonstrating the relationship between diabetes and its complications, periodontal disease, and systemic inflammation. The members of the expert panel were unanimous in proposing that there are other benefits of systemic disease outcomes resulting from improved oral health, and that these potential benefits justify improved communication between healthcare providers.

The following 4 studies and investigations were prominent in discussions and decision-making:

- Bakhsandeh and colleagues⁵⁹ (level 4) represents a cross-sectional study demonstrating that patients with diabetes have poor periodontal status and little knowledge concerning proper oral hygiene/oral health.
- Khader and colleagues⁵⁷ (level 2a) confirms this study, and represents a recent large meta-analysis of the Medline database from 1970-2003 that included 21 observational studies.
- Lalla and colleagues³⁷ (level 2b) represents a small prospective clinical study of subjects with type 1 and type 2 diabetes, demonstrating that periodontal therapy significantly reduces immune cell production of TNF- α and circulating levels of CRP. This result provides evidence for reduction of systemic inflammatory markers associated with atherosclerosis-related complications in diabetes.
- Mealey and Oates⁵⁸ (level 2a) conducted a meta-analysis from a broad PubMed search of studies in the last 20 years, including data from over 3,500 adults with diabetes. The analysis relied on original data from small studies of diverse patient populations and/or studies that variably define parameters of diabetes/glycemic control. This study demonstrated consistent findings that diabetes increases the risk for periodontal disease and increases the extent/severity of periodontal disease. Additionally, the analysis revealed evidence that periodontal disease initiates or exacerbates insulin resistance through elevations in serum levels of TNF- α .

Three recent comprehensive reviews emphasize the connection between periodontal disease, diabetes, systemic inflammation, and the potential for improved oral health to reduce diabetic complications:

- Nishimura and colleagues⁶¹ (level 5) demonstrated that exaggerated host immune responses are the fundamental mechanisms by which patients at risk for diabetes, those already diagnosed with diabetes, and obese patients are prone to severe periodontitis; and, that periodontal infection and inflammation further exacerbates host immune responses accelerating development of complications such as nephropathy and macrovascular disorders.
- Nassar and colleagues⁶⁰ (level 5) demonstrated that adjunctive anti-inflammatory therapies are highly effective for treatment of periodontal disease in patients with diabetes. This is significant because it confirms that therapies targeting the specific inflammatory mechanisms in diabetes may have value

in controlling diabetes-associated complications including periodontitis.

- Southerland and colleagues⁶² (level 5) demonstrated the bidirectional relationship between diabetes and periodontal disease, whereby diabetes represents a systemic disease predisposing to oral infection, and once that oral infection is established, periodontitis serves as a metabolic stressor that accelerates systemic disease progression. It appears that the incidence of CVD is increased in patients with diabetes, in part because diabetes and periodontal infections are both associated with a systemic inflammatory response leading to more extensive atherosclerosis that develops at an earlier age in diabetic patients. This study also provided suggestions for improving oral health outcomes and reducing complications of diabetes in this patient population.

Saremi and colleagues⁴² (level 2a) represents a moderate size prospective longitudinal study in Pima Indians. Results demonstrated that periodontal disease is a strong predictor of mortality from diabetic complications (ischemic heart disease and nephropathy) in patients with type 2 diabetes.

Focus #7 – Periodontal Diseases and Atherosclerosis-Induced Diseases

Evidence from 5 studies (2 [level 1b],^{28,32} 1 [level 2b],³⁰ and 2 [level 5]^{25,130}) supports a systemic effect of periodontitis (and possibly gingivitis) associated bacteremias/endotoxemias and entry of inflammatory mediators into the circulatory system. There is strong evidence from 2 studies (1 [level 1b]¹³¹ and 1 [level 2b]¹³²) that inflammation plays a dominant role in the pathogenesis of atherosclerosis and that atherosclerosis is a major component of cardiovascular and cerebrovascular diseases. Larsen and colleagues¹³³ (level 1b) recently indicated that control of inflammation improves glycemic control in diabetes; Bogaty and colleagues¹³⁴ (level 1b) suggested that anti-inflammatory therapies may be effective in reducing cardiovascular risk.

Several types of observational studies were prominent in discussions and decision-making:

- The first type consisted of 6 retrospective, cross-sectional, or case comparison designs (3 [level 2b]⁶⁴⁻⁶⁶ and 3 [level 3b]^{72,78,79}). Beck and colleagues⁶⁴ (level 2b) demonstrated that both moderate and severe periodontal disease were significantly associated with carotid intima-media wall thickness (a measure of preclinical atherosclerosis) suggesting that periodontal disease plays a role in atheroma formation. Deliagyris and colleagues⁷² (level 3b) demonstrated that periodontal therapy produces significant reductions in circulating inflammatory biomarkers (IL-6 and CRP) and that the association between CRP and periodontal disease in patients with acute myocardial infarction is independent of other risk factors. Hung and colleagues⁶⁵ (level 2b) demonstrated that there is an inverse relationship between the number of remaining teeth and CVD while Lee demonstrated this inverse association for

ischemic stroke. This supports that tooth loss is an important indicator of past history of periodontal disease and systemic inflammation.

- The second study type consisted of 7 randomized, prospective case-control designed (level 3b) studies.^{70,75,77,80,81,83,84} Dorfer and colleagues⁷⁵ (level 3b) conducted a large case-control study linking periodontal disease to cerebral ischemia. It was actually the largest study of its kind and shows the strongest association between these two entities. The study controlled for many confounding factors and used meticulous determination of dental status. Spahr and colleagues⁸³ (level 3b) conducted a moderate size case-control study linking periodontal disease to coronary heart disease, and demonstrated a dose-response relationship between oral microbial burden and heart disease severity. It was a well controlled study of consecutive patients with clinically confirmed coronary heart disease. Tabrizi and colleagues⁸⁴ (level 3b) conducted a small twin study of 10 monozygotic pairs (1 twin with coronary heart disease and 1 twin without coronary heart disease), confirming that poor periodontal status was comparable in both twins.
- The third study type consisted of 8 prospective cohort designs (2 [level 2b]^{67,68} and 6 [level 3b]^{71,73,74,76,82,87}). Desvarieux and colleagues⁷³ (level 3b) conducted a moderate sized study that demonstrated a significant association between tooth loss and carotid artery plaques; in another moderate sized study, Desvarieux and colleagues⁷⁴ (level 3b) demonstrated a significant association between oral microbial burden and carotid artery intima-media wall thickness. Slade and colleagues⁸² (level 3b) conducted a large study demonstrating a significant association between periodontal disease and CRP levels. Wu and colleagues⁶⁸ (level 2b) conducted a large National Health and Nutrition Estimate Studies (NHANES) cohort study that demonstrated a significant association between periodontal disease and ischemic stroke. This was a particularly strong study because it focused on PD measurements (not on tooth loss) in a national representative sample of the U.S. population (NHANES data). In addition, it provides some specificity to the observed association between PD and stroke because it shows the link between PD and ischemic stroke but not between PD and nonischemic stroke (exactly what one would expect from the hypothesized mechanisms).
- The fourth study type consisted of a prospective, randomized, controlled parallel arm intervention trial (level 1b);¹³⁵ and the fifth study type consisted of 2 (level 2a) meta-analyses^{63,85} and 1 (level 3a) systematic review.⁶⁹ D'Aiuto and colleagues¹³⁵ (level 1b) conducted a small study demonstrating that periodontal therapy significantly decreased circulating inflammatory biomarkers (IL-6 and CRP). Janket and colleagues⁶³ (level 2a) conducted a large meta-analysis that confirmed a significant association between periodontal disease and coronary heart disease as well as stroke. This study also demonstrated that the risk is higher for persons less than 65 years of age emphasizing the importance of prevention and early intervention for periodontal disease. Meurman and colleagues⁶⁹ (level 3a)

conducted a systematic review of published retrospective/prospective studies and meta-analyses, confirming that the preponderance of studies report significant associations between periodontal and coronary heart disease as well as stroke.

Three studies (1 [level 2b],⁸⁶ 1 [level 3b] observational study,⁸⁷ and 1 [level 2a] meta-analysis⁸⁵) failed to demonstrate significant associations (i.e., there were no associations or only very weak associations) between periodontal disease and coronary heart disease, or between periodontal disease and cerebrovascular disease. Howell and colleagues⁸⁶ (level 2b) conducted a prospective cohort study where periodontal disease was self-reported, potentially leading to misclassification and biasing the study to the null. Nakib and colleagues⁸⁷ (level 3b) conducted a prospective cohort study that found no association between periodontal disease and coronary artery calcification. The study was small and underpowered. Khader and colleagues⁸⁵ (level 2a) conducted a meta-analysis of observational studies (only 8 studies for periodontal disease and coronary heart disease, only 6 studies for periodontal disease and cerebrovascular disease). No significant associations were demonstrated; study selection complicated the analysis due to wide variability in study designs.

There are potential benefits of periodontal disease treatment as a method for reducing systemic inflammation and subsequently improving glycemic control in diabetes or reducing cardiovascular risk. Larsen and colleagues¹³³ (level 1b) represents a small multicenter randomized, double-blind, parallel group, controlled trial. This study demonstrated that blockade of IL-1 improves glycemia (as evidenced by significant reductions in HbA_{1c} levels), and significantly reduces circulating markers of systemic inflammation. Bogaty and colleagues¹³⁴ (level 1b) represents a small randomized, double-blind, parallel group, placebo controlled trial. This study demonstrated that COX-2 inhibition significantly reduces circulating markers of systemic inflammation associated with cardiovascular risk. However, it is important to consider that recent studies involving COX-2 inhibitors have been linked to increased risk of myocardial infarction.

Focus #8 – Potential of Periodontal Disease Interventions to Decrease Risk for CVD

In addition to evidence that periodontitis results in systemic inflammation,^{25,28,30,32,130} as discussed in Focus #7 above, there is strong evidence in 2 studies (1 [level 1b]¹³¹ and 1 [level 2b]¹³²) that inflammation plays a dominant role in the pathogenesis of atherosclerosis, and that atherosclerosis is a major component of cardiovascular and cerebrovascular diseases.

Four recent studies (1 [level 1b],⁴⁵ 1 [level 2b],⁸⁸ and 2 [level 4]^{89,90}) provide evidence for improved endothelial function after periodontal treatment:

- The study by Mercanoglu and colleagues⁸⁸ (level 2b) was a

small prospective controlled trial of cohorts with chronic periodontitis and without any atherosclerotic vascular disease. Brachial artery responses to reactive hyperemia (endothelium-dependent dilatation, EDD) and sublingual nitroglycerin (endothelium-independent dilatation, EID) were measured using high-resolution vascular ultrasound before and after initial periodontal therapy. At baseline, EDD and EID were significantly impaired in patients with chronic periodontitis. After nonsurgical periodontal therapy, EDD and EID improved significantly.

- The study by Tonetti and colleagues⁴⁵ (level 1b) was a moderate sized prospective trial of patients with moderate periodontal disease assessing endothelial function by measurement of the diameter of the brachial artery (flow-mediated dilatation, [FMD]) before and after treatment. FMD was greater within 60 days after treatment and the degree of improvement was associated with improvement in clinical measures of periodontal disease.
- The study by Elter and colleagues⁸⁹ (level 4) represented a small prospective trial of healthy adults with moderate to severe periodontitis who underwent complete mouth disinfection and were evaluated to determine if periodontal therapy would result in improved endothelial function using EDD and EID of the brachial artery. Periodontal treatment resulted in significant improvements in periodontal pocketing and EDD.
- The study by Seinost and colleagues⁹⁰ (level 4) was a small prospective controlled trial assessing the effects of treatment for severe periodontitis on FMD of the brachial artery. The groups were matched for age, sex, and cardiovascular risk factors. FMD was significantly lower in patients with periodontitis than in control subjects and periodontal treatment resulted in a significant improvement in FMD.

Taken together, these initial studies indicate that treatment of periodontitis reverses endothelial dysfunction. Randomized controlled trials are needed to determine if this is the case. Whether improved endothelial function will translate into a beneficial effect on atherogenesis and cardiovascular/cerebrovascular events needs further investigation.

CONCLUSIONS OF THE INDEPENDENT PANEL OF EXPERTS REGARDING APPROPRIATENESS OF GUIDELINE DEVELOPMENT

The answers to the focused questions and their companion recommendations provide the rationale for solidarity of expert opinion regarding whether sufficient evidence currently exists to support the development of guidelines.

KEY ISSUE I

Question: Is it appropriate to develop guidelines that assist dental providers in identifying patients who have or who are at risk for diabetes and/or CVD, or screening patients for

undiagnosed diabetes and/or CVD who need to be referred to physicians?

Consensus Statement: Yes, it is appropriate to develop guidelines to assist dental providers in identifying patients who are at risk for diabetes and/or CVD. A thorough search for patient-provided information that may lead to a diagnosis to improve oral and systemic health should be conducted by dental providers.

Recommendation (USPSTF Level A): The American Diabetes Association has established criteria for screening for diabetes.¹³⁶ With the epidemic increase of diabetes in the past 10 years, the dentist and dental hygienist have a greater responsibility than ever before in carefully screening patients. The expert panel of *The Scottsdale Project* recommends increasing awareness of the diabetic profile and these screening criteria within the dentist and dental hygienist communities.

The risk of having undiagnosed diabetes with newly diagnosed periodontal disease is unknown; however, periodontal disease is associated with diabetes. Indeed a very first attempt to explore the contribution of periodontal findings in assessing the probability for unrecognized diabetes in the dental office was reported by Borrell and colleagues.¹³⁷ The study suggested that the dental office could provide an important opportunity to identify individuals unaware of their diabetic status, and is the first step of the effort to develop a tool to assist dentists in such an endeavor. Although there was a spread of opinion among the panel's experts regarding how screening protocols should be incorporated into dental care settings, the expert panel was concordant in recommending the following:

1. Patients at risk for diabetes (information obtained from thorough family and personal medical history), regardless of oral presentation, should be referred by dentists to laboratories to have their fasting blood glucose levels checked and/or referred to the physician for further diagnostic evaluation.
2. Patients with severe periodontitis (severe for age, failure to respond to treatment, abscesses) or fungal infection should be considered for referral to the physician for screening for diabetes.
3. If laboratory testing for diabetes is performed in a dental care setting, it should be done in accordance with American Diabetes Association screening guidelines (fasting blood glucose) with appropriate follow up of laboratory data and communication with the physician.
4. For the patient who has been diagnosed with diabetes and/or CVD, dentists should work collaboratively with physicians to achieve the best possible patient care outcomes. A set of guidelines should be developed to define what is important for bidirectional interprofessional communication.
5. Patients at risk for CVD should be referred to the physician. There was a lack of consensus regarding the optimal screening method for coronary heart disease or stroke (e.g., risk assessment tools developed by the American Heart Association,

Framingham Risk Assessment). However, the expert panel recommended referral to a physician for additional assessment of CVD risk for those dental patients who have not had a medical evaluation within 2 years, and 2 or more of the following: older than 50 years of age, at risk for diabetes mellitus, hypertension, dyslipidemia with a family history of coronary heart disease or stroke, tobacco use, and/or a history consistent with CVD.

6. Patients already diagnosed with diabetes who do not have a treating physician are at high risk for cardiovascular events and should be seen by a physician.

KEY ISSUE II

Question: Is it appropriate to develop guidelines that assist medical providers in identifying patients who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists?

Consensus Statement: Yes, it is appropriate to develop guidelines to assist medical providers in identifying patients who are at risk for periodontal disease, or screening patients who may have undiagnosed periodontal disease who need to be referred to dentists. Medical providers' recognition of the signs and symptoms associated with periodontal disease may identify patients who are either at risk or are undiagnosed who should be

referred to the dental provider.

Recommendation (USPSTF Level A): The American Academy of Periodontology has developed guidelines^{4,6} for the diagnosis and assessment of patients with periodontal disease. The guidelines include periodontal probing and intraoral radiographic diagnosis, which are not feasible in most medical settings. Nevertheless, physicians can screen for signs and symptoms associated with periodontal disease based on patient history, symptoms, and a visual assessment of the patient's teeth and gums. Signs of periodontal disease include:

- red, sore, swollen, receding, or bleeding gums
- loose or sensitive teeth, separation of teeth
- presence or history of oral abscesses
- halitosis
- missing teeth
- accumulation of food debris or plaque around teeth

Accordingly, the expert panel of *The Scottsdale Project* recommended that medical providers screen and refer all patients suspected as having periodontal disease as outlined in Figure 4, as well as the following management plan for patients with diabetes.

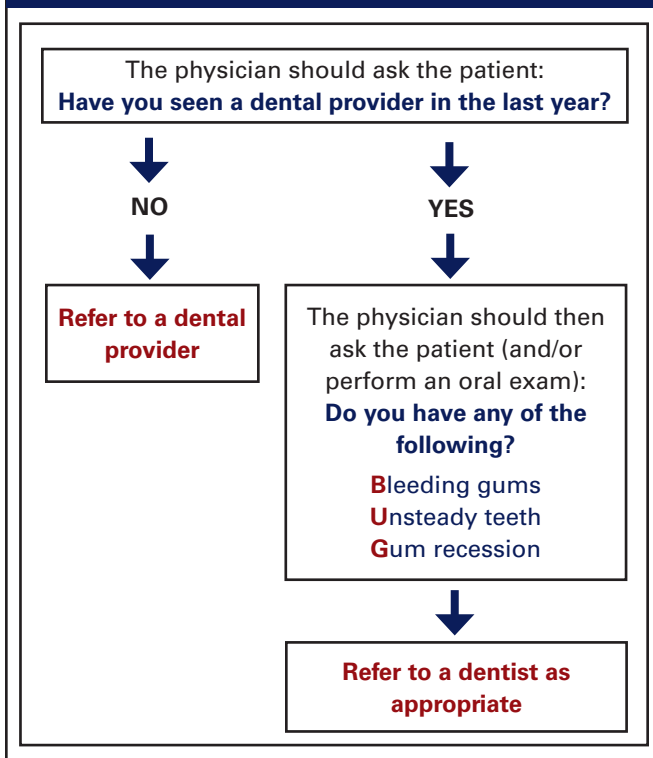
1. Patients with diabetes should be medically managed as recommended by the American Diabetes Association.
2. Patients with diabetes should have a dental exam at a minimum of twice a year, or more frequently if advised by the dental provider, and receive appropriate dental/periodontal care.
3. There should be close communication between the primary care physician and the dentist.
4. Medical providers should advise the patient with periodontal disease that it is a chronic infection of the gums and an important complication of diabetes.
5. Medical providers should also advise patients that periodontal disease has been associated with significant health problems, including worse metabolic control and other complications of diabetes, coronary artery disease, and stroke.
6. Medical providers should advise the patient that periodontal disease can be treated by the dentist and dental hygienist.
7. If the patient has not seen a dentist within the last year or if there are signs of periodontal disease, the patient should be advised to make an appointment to see the dental provider right away.

The currently available evidence was assessed in the formulation of these recommendations; the expert panel's recommendations for clinical guidelines should not be interpreted to mean that the scientific evidence is fully adequate.

SPECIAL NOTE

At the time the *Report of the Independent Panel of Experts of The Scottsdale Project* went to press, the American Diabetes Association suggested that the report be referred to its professional practice

Figure 4. Expert panel recommendations for physicians to screen and refer patients with signs of periodontal disease.



committee (guideline committee) to summarize the report's recommendations and reference the report in the 2008 Standards of Medical Care in Diabetes.

DISCLOSURE

Casey Hein received an honorarium for oversight of *The Scottsdale Project* and authorship of the *Report of the Independent Panel of Experts of The Scottsdale Project*.



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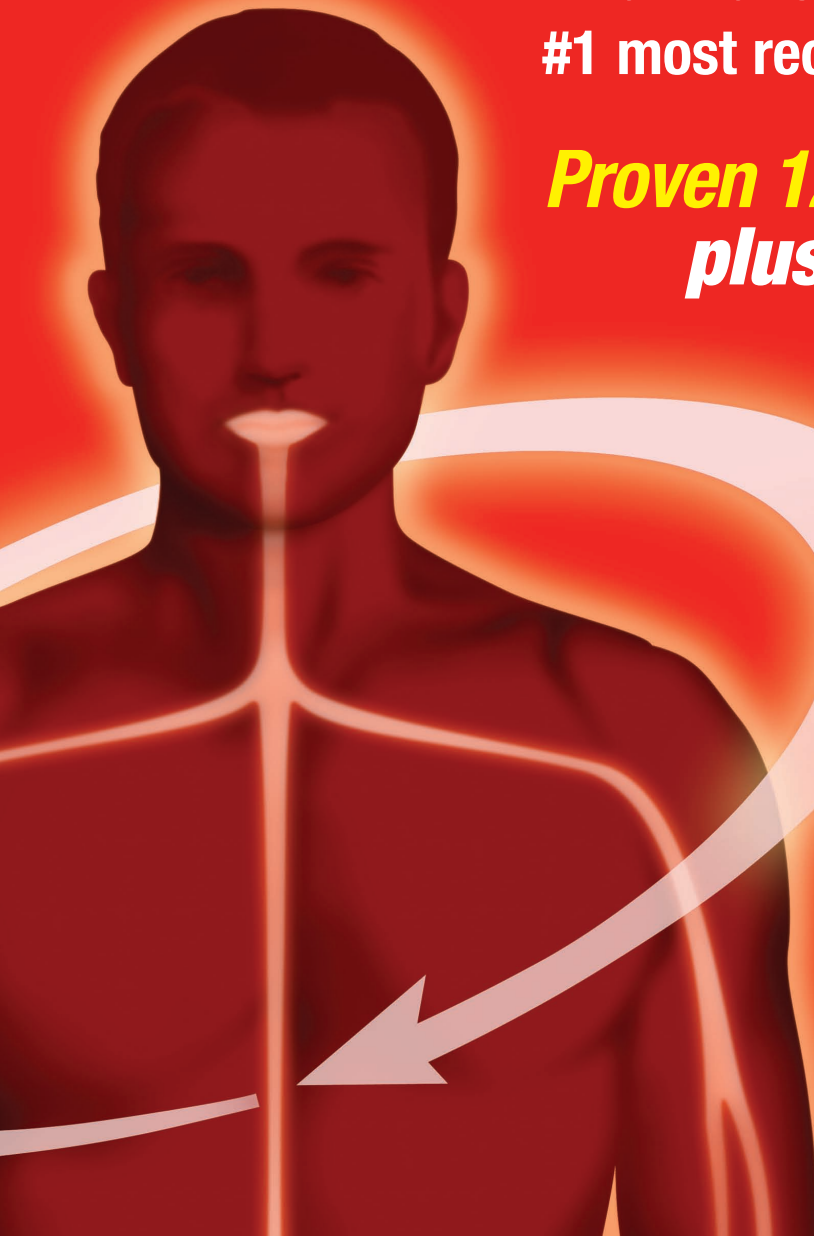
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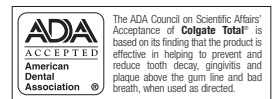
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¹. Data on file. Colgate-Palmolive, New York, NY. ². Panagakos FS, et al. *J Clin Dent*. 2005;16(suppl):S1-S19.