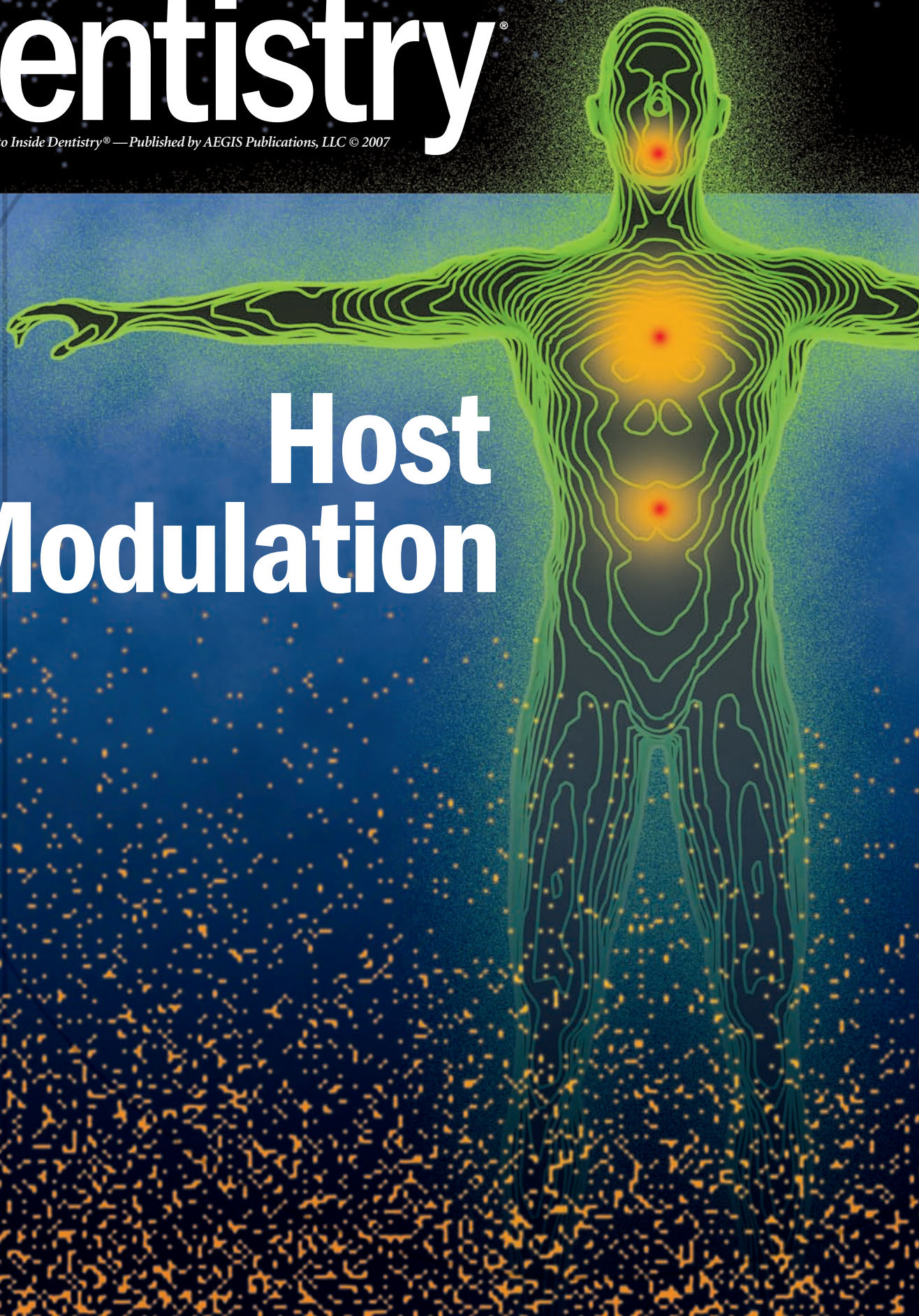


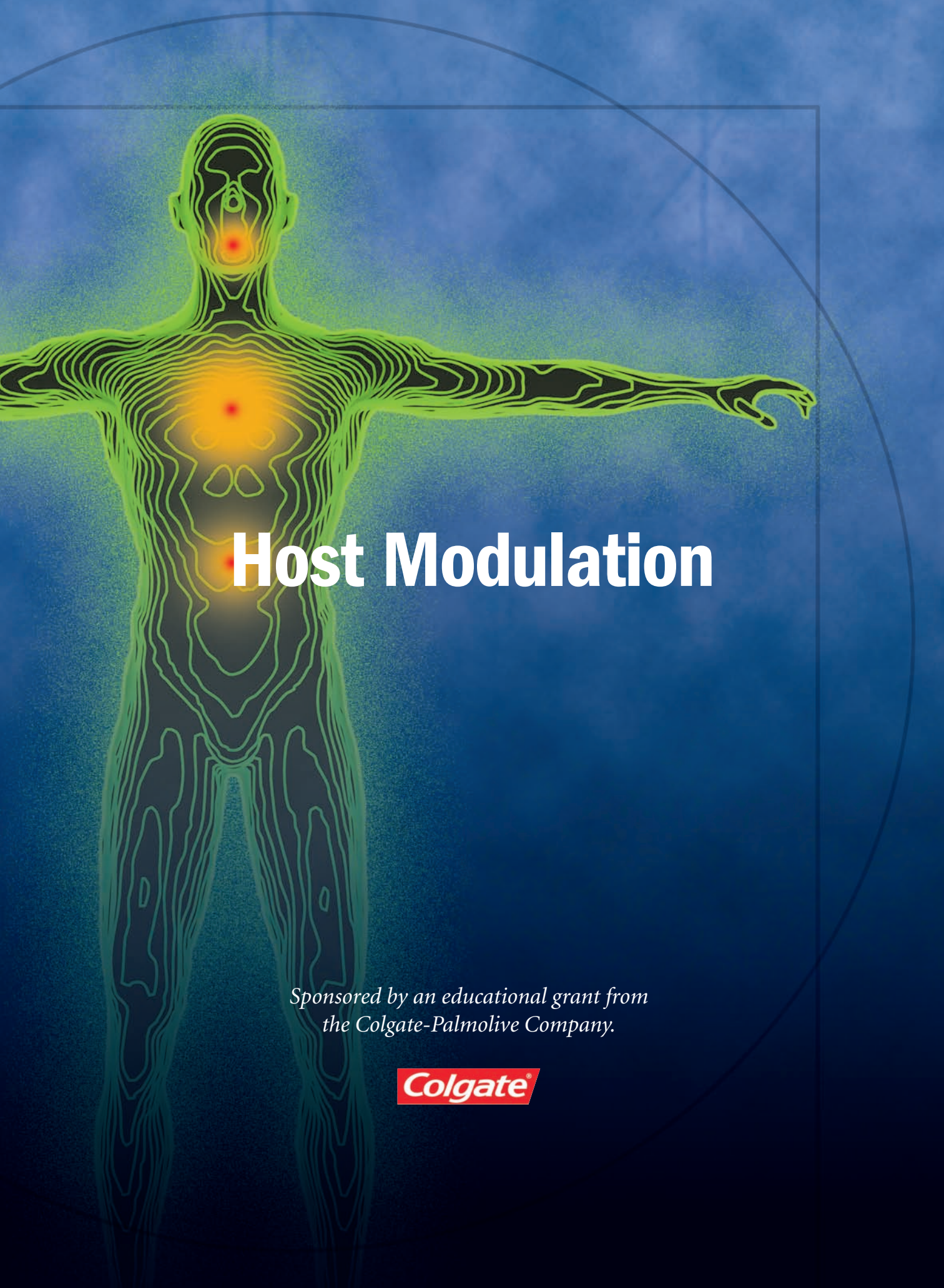
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## Host Modulation



# Host Modulation

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# Host Modulation for the Treatment of Periodontal Diseases

Ray C. Williams, DMD

## INTRODUCTION

Until the 1970s, treatment strategies for periodontal disease were primarily based on the understanding that plaque bacteria and their products mediated the tissue destruction in periodontal patients. This concept began to change, however, when investigators reported that host responses to the causative bacteria were a major contributor to disease pathogenesis. With a new understanding of host response and periodontal disease pathogenesis, it became apparent that inhibition of certain host response pathways might be an additional strategy, in addition to suppressing the causative bacteria, for treating periodontal diseases. The current understanding of periodontal disease etiology and pathogenesis emphasizes the role of the host in tissue destruction (Figure 1).

## INITIAL STUDIES OF HOST MODULATION

In the early 1970s, Paul Goldhaber and Max Goodson began to implicate arachidonic acid metabolites as important inflammatory mediators of the bone loss of periodontitis. The arachidonic acid metabolites include a variety of fatty acid-derived compounds that are enzymatically produced and released in response to local tissue injury. These metabolites, such as prostaglandins, were implicated as major mediators of tissue loss in periodontal diseases because they are potent stimulators of bone resorption, are present

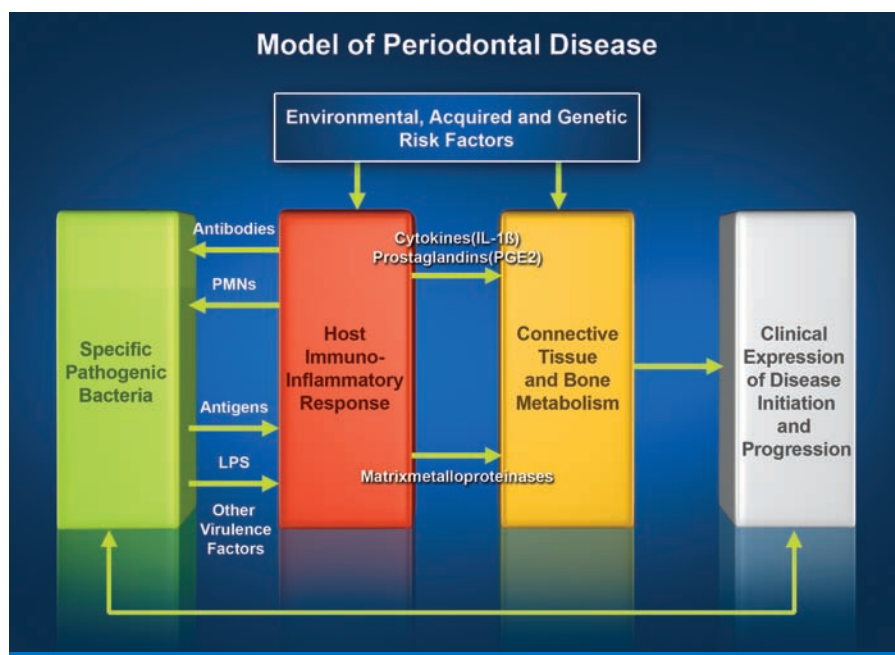
in gingival tissues, and are elevated in diseased individuals.<sup>1,2</sup>

In 1971 John Vane and colleagues reported that aspirin and aspirin-like drugs, also called nonsteroidal anti-inflammatory drugs (NSAIDs), interfered with the arachidonic acid metabolite pathway by blocking the enzyme cyclooxygenase, thus blocking the production of prostaglandins.<sup>3</sup> Soon thereafter periodontal investigations began asking the question: "Might the blocking of cyclooxygenase with NSAIDs, thus blocking prostaglandins, have an effect on the bone resorption of periodontitis (Figure 2)?"<sup>4</sup>

Utilizing the beagle experimental periodontitis model, Nyman et al examined the modulation of arachidonic acid metabolites with systemic indomethacin

and reported that the NSAID indomethacin, given by mouth, suppressed alveolar bone resorption and gingival inflammation in the beagle.<sup>5</sup> Weaks-Dybvig et al studied the effects of indomethacin in squirrel monkeys with ligature-induced periodontitis and reported that animals treated with systemic indomethacin had significantly less alveolar bone resorption (height and mass) and suppressed osteoclast density as compared with control animals.<sup>6</sup>

Williams and co-workers were the first to report in vivo data on the effect of NSAIDs on the progression of naturally occurring periodontal disease in an animal model. Over a 12-month treatment period, the effects of the NSAID flurbiprofen (Figure 3) were compared with a placebo in aged beagles with naturally occurring periodontitis. The investigators combined experimental agents with conventional nonsurgical and surgical treatment modalities. Their results indicated that daily administration of 0.02 mg/kg flurbiprofen by mouth significantly decreased the rate of radiographic alveolar bone loss at 3, 6, 9 and 12 months in both surgically and nonsurgically treated animal groups when compared to baseline levels. The rate of alveolar



**Figure 1** Diagram of the current concept of the etiology and pathogenesis of periodontal disease (Adapted from: Page RC, Kornman KS. The pathogenesis of human periodontitis: an introduction. *Periodontol* 2000. 1997;14:9-11).

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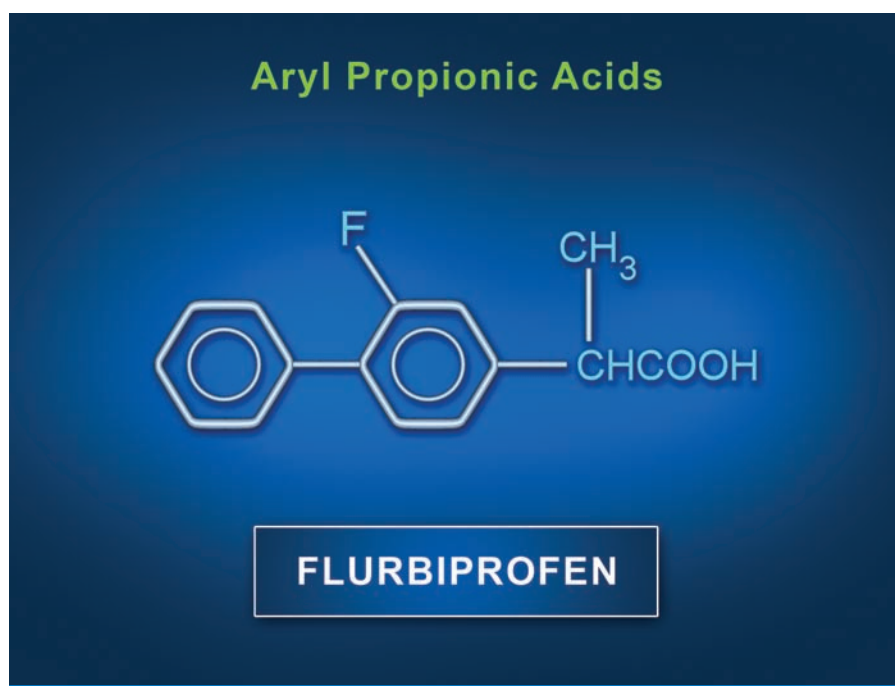
bone loss did not decrease significantly over the treatment period for placebo-treated animal groups.<sup>7</sup>

Other NSAIDs, either systemically or topically administered, also have shown efficacy in treating periodontal disease in animal models. The propionic acid-derived NSAID ibuprofen at 4.0 mg/kg and 0.4 mg/kg (sustained release and standard by mouth formulations) was effective in blocking alveolar bone loss in beagles with naturally occurring periodontitis.<sup>8</sup> Naproxen (2 mg/kg for one month and 0.2 mg for 6 months) reduced radiographic periodontitis progression in the beagles by 61% when compared to pretreatment levels.<sup>9</sup> Williams et al also reported a 71% suppression in radiographic bone loss rates for dogs treated with a topical flurbiprofen-propylene glycol gel (0.3 mg/ml daily).<sup>10</sup> Similarly, a topically applied substituted oxazopyridine derivative reduced histometric bone resorption, as well as clinical attachment loss and gingival inflammation, in squirrel monkeys with ligature-induced periodontitis.<sup>11</sup> Monitoring the effects of two topical NSAIDs, ibuprofen and meclofenamic acid, in cynomolgus monkeys over 20 weeks, Kornman et al reported significant inhibition in alveolar bone loss despite continuing signs of clinical gingivitis and plaque accumulation with either agent.<sup>12</sup> Over a 16-week period, Howell et al evaluated the anti-gingivitis effects of topical piroxicam in gel and liquid forms (2 mg/ml) on gingivitis in the beagle dog.<sup>13</sup> Gingival and bleeding indices were significantly reduced after 2 and 4 weeks in the piroxicam-treated dogs as compared with placebo controls; however, no significant differences in plaque scores among the groups were noted. The results of these latter 2 pre-clinical studies indicate that NSAIDs may act in the presence of significant local factors that would otherwise influence disease progression. Paquette et al have evaluated topical (S)-ketoprofen formulations in beagle dogs.<sup>14</sup> Following induction of experimental periodontitis, 16 beagles were randomized for (S)-ketoprofen dentifrices (0.1%, 1.0%), (S)-ketoprofen capsules (10.0 mg by mouth), or placebo dentifrice and assessed radiographically over a 2-month period. A

## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

- **Aryl Acetic Acids**
  - Indomethacin
  - Sulindac
  - Tolmetin
  - Diclofenac
- **Fenamates**
  - Meclofenamic Acid
  - Mefenamic Acid
  - Flufenamic Acid
- **Aryl Propionic Acids**
  - Flurbiprofen
  - Ibuprofen
  - Naproxen
  - Ketoprofen
  - Fenoprofen
  - Suprofen
  - Pirprofen
- **Enolic Acids**
  - Phenylbutazone
  - Oxyphenbutazone
  - Piroxicam
  - Tenoxicam
- **Pyrrolopyrrole Carboxylic Acids**
  - Ketorolac

**Figure 2** List of nonsteroidal anti-inflammatory drugs.

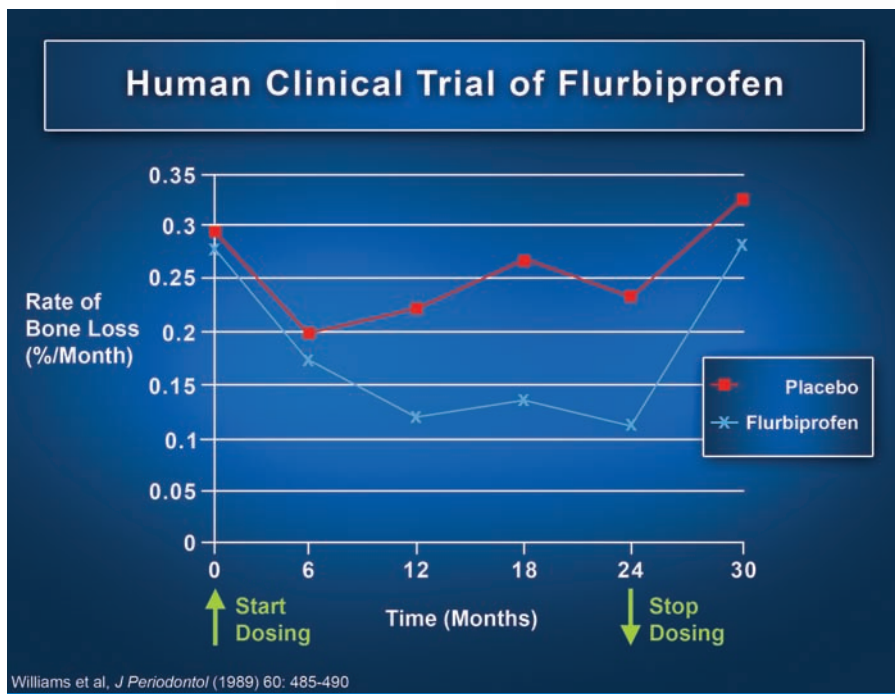


**Figure 3** Formulation of the aryl propionic acid flurbiprofen.

significant reduction in gingival inflammation was reported with (S)-ketoprofen treatments.

There are also compelling data from human cross-sectional and cohort studies indicating periodontal disease inhibition with NSAIDs. Waite et al evaluated the periodontal status among 22 subjects taking NSAIDs for arthritis or ankylosing

spondylitis and 22 age-matched controls not taking such medications.<sup>15</sup> Subjects taking NSAIDs had lower gingival index scores and shallower periodontal pocket depths than individuals not taking NSAIDs. In a retrospective cohort study, 75 patients who had taken aspirin or aspirin plus indomethacin for at least 5 years for arthritis had significantly fewer sites with



Williams et al, *J Periodontol* (1989) 60: 485-490

**Figure 4** Rate of alveolar bone loss over a 2-year period in patients taking either a placebo capsule twice daily or flurbiprofen 50 mg twice daily. The rate of bone loss was significantly less in flurbiprofen treated patients at 12, 18, and 24 months.

proximal bone loss ( $\geq 10\%$ ) as compared with 75 healthy control subjects.<sup>16</sup>

In a 3-year clinical trial, Williams et al followed 44 patients with advanced adult periodontitis to radiographically assess long-term and post-treatment effects.<sup>17</sup> After a 6-month pretreatment period, patients were stratified according to disease progression rates and randomized for 50 mg flurbiprofen or placebo capsules. Patients took study medications by mouth twice daily over a 24-month treatment period. Patients dosing with flurbiprofen demonstrated significantly lower bone loss rates at 12 and 18 months as compared with patients dosing with placebo. A subsequent analysis of 33 compliant patients monitored for the 6-month post-treatment period indicated significantly depressed bone loss rates also at 24 months with flurbiprofen treatment and a return to baseline rates upon withdrawal of the agent (Figure 4).<sup>18</sup>

Jeffcoat et al subsequently evaluated the short-term effects of systemic flurbiprofen (50 mg twice daily) in 15 refractory periodontitis patients. Standardized radiographs indicated significantly less alveolar bone loss over 2 months with flurbiprofen treatment relative to the placebo treatment.<sup>19</sup> Jeffcoat and co-workers later

tested the bone-preserving effects of systemic naproxen as an adjunct to mechanical periodontal therapy in patients with rapidly progressive periodontitis.<sup>20</sup> In 7 patients taking 500 mg naproxen twice daily for 3 months, a significant decrease in bone loss was detected when compared with the placebo group. This research group also reported significant bone gains with the NSAID meclofenamate sodium (50 mg or 100 mg twice daily perorally) combined with scaling and root planing (SRP) in patients with rapidly progressive periodontitis over a 6-month placebo-controlled clinical trial.<sup>21</sup> Flemming and co-workers questioned whether aspirin (acetylsalicylic acid) taken by mouth could provide added benefit with mechanical scaling.<sup>22</sup> Thirty patients with untreated moderate to severe adult periodontitis were recruited for this paired design trial. Participants received supragingival and subgingival scaling in one quadrant after the baseline examination and in 2 additional randomly selected quadrants after the 6-week examination. Additionally, patients were given placebo (4 times daily) between the baseline and the 6 weeks and acetylsalicylic acid (500 mg 4 times daily) between 6 and 12 weeks. The findings of this study indicated that mechanical

scaling plus acetylsalicylic acid result in synergistic reductions in gingival inflammation, probing pocket depth, and clinical attachment loss.<sup>22</sup>

In the mid-1990s, investigators began to examine the effect of topical NSAID formulations on periodontal disease in human clinical trials. Heasman et al clinically and radiographically studied 49 adult periodontitis patients randomized for adjunctive topical flurbiprofen or placebo gels.<sup>23,24</sup> All patients received conventional nonsurgical periodontal therapy at baseline. Over the subsequent 12 months of topical dosing, no clinical effects of flurbiprofen on plaque and bleeding scores, probing depths, and attachment levels were observed; however, significantly more sites in the flurbiprofen-treated group exhibited bone gain when compared with the placebo group. In a 55-patient clinical trial, Jeffcoat and co-workers assessed the efficacy of a topical NSAID rinse, ketorolac tromethamine, for treating adult periodontitis.<sup>21</sup> At baseline, patients were randomized for 0.1% ketorolac rinse plus peroral placebo capsule, placebo rinse plus peroral 50-mg flurbiprofen capsule, or placebo rinse and peroral capsule. Patients were monitored radiographically, clinically, and biochemically over a 6-month period during which they administered rinses and capsules twice daily. Although no significant differences among the groups were detected for clinical parameters, patients treated with topical ketorolac or systemic flurbiprofen exhibited significantly reduced alveolar bone loss rates and depressed prostaglandin  $E_2$  levels in gingival crevicular fluid as compared with patients treated with placebo. Paquette and co-workers conducted a 12-month clinical trial evaluating the clinical efficacy of topical (S)-ketoprofen dentifrices.<sup>25</sup> Ninety-six patients participated and applied randomized dentifrice formulations (0.3%, 1.0% or 3.0% ketoprofen versus placebo) twice daily. Although inter-group differences in bone loss rates approached significance ( $P=0.06$ ) in the trial, significant strata-by-treatment interactions were detected such that patients with advanced periodontitis dosing with 1.0% or 3.0% S-ketoprofen demonstrated comparatively greater improvements in disease progression.<sup>25</sup> In summary, a great deal of evidence gathered from

preclinical and clinical studies since the late 1970s indicates that it is possible to inhibit periodontal disease progression via the local modulation of arachidonic acid metabolites with NSAIDs. Serhan et al have described a novel series of oxygenated arachidonic acid derivatives called “lipoxigenase interaction products” or “lipoxins”.<sup>26</sup> These derivatives (eg, lipoxin A<sub>4</sub> and lipoxin B<sub>4</sub>) arise via 15- or 5-lipoxygenase activities and by cell-to-cell interactions and appear to serve as endogenous anti-inflammatory mediators.<sup>26</sup> Hasturk et al have reported that these aspirin induced lipoxins block ligature induced bone loss in New Zealand rabbits.<sup>27</sup>

### MODULATION OF HOST CYTOKINES IN THE TREATMENT OF PERIODONTAL DISEASE

Host cytokines are another group of inflammatory mediators highly implicated in periodontal disease pathogenesis and intensely investigated as potential chemotherapeutic targets. Cytokines, literally “cell proteins” in etymology, transmit information from one cell to another via autocrine or paracrine mechanisms. Following specific binding to their complementary receptors, pro-inflammatory cytokines like interleukin-1 (IL-1) and tumor necrosis factor (TNF) trigger intracellular signaling events and catabolic cell behaviors.

Assuma et al have explored the inhibition of periodontal disease using cytokine receptor antagonists.<sup>28</sup> In an initial experiment, periodontitis was induced in 14 *Macaca fascicularis* monkeys with subgingivally placed, *P. gingivalis*-soaked silk ligatures. Animals were randomized to one of 3 groups. The experimental group received gingival injections of soluble human recombinant IL-1 receptor type I plus soluble TNF receptor, each at 6.6 µg/injection over a 6-week period (3 times per week). Two other groups served as controls and received either gingival injections of vehicle alone at the same schedule or no treatment. The results from this study indicated that the soluble receptors of IL-1 and TNF inhibited roughly 80% of the inflammatory cell numbers (ie, polymorphonuclear leukocytes, mononuclear leukocytes, and plasma cells)

proximal to the bone relative to control animals. Similarly, the cytokine receptor antagonist therapy significantly reduced osteoclast cell numbers by 67% and alveolar bone resorption by 60%. A second report included specimens from 11 *M. fascicularis* monkeys with experimental periodontitis and treated as described above.<sup>29</sup> Here, the investigators quantified the average distance from the inflammatory front (ie, a field containing ≥10 inflammatory cells per field at high magnification) to the alveolar crest. Whereas the inflammatory front distance at 6 weeks measured 0.12 mm in control animals, the distance measured 0.59 mm in the IL-1 receptor- and TNF receptor-treated animals, suggesting inhibition of inflammatory cell extravasation and migration with the antagonists. The data from these experiments suggests that IL-1 and TNF are important mediators of periodontal disease progression and that specific inhibition may slow or alter the disease process.

### MODULATION OF MATRIX METALLOPROTEINASES IN PERIODONTAL DISEASE TREATMENT

There is also intense interest in the ability to block or modulate matrix metalloproteinases (MMPs) as a strategy to modulate the progression of periodontal disease. In the 1980s, Golub and co-workers reported that tetracyclines were beneficial in the management of periodontal disease.<sup>30,31,32</sup> It had traditionally been assumed that the beneficial actions of tetracyclines reflected their antimicrobial effects. However, in a series of novel experiments, Golub demonstrated that tetracyclines could inhibit connective tissue breakdown and bone loss in periodontitis, arthritis, and osteoporosis by mechanisms unrelated to tetracycline’s antimicrobial effect. Rather, it was tetracycline’s inhibition of MMPs that could explain the effect of this drug on inhibiting periodontal disease progression.

To further examine the role of tetracycline in blocking periodontal disease progression through host modulation, several human clinical studies were initiated to determine the efficacy of subantimicrobial doses of tetracyclines in the treatment of periodontitis. Treatment

with subantimicrobial doses of doxycycline (SDD, 20 mg twice daily) in conjunction with subgingival and/or supragingival scaling and dental prophylaxis improved attachment levels in patients with adult periodontitis when administered for 2-month cycles during a 6-month period and as part of a series of 3-month treatment cycles for 9 months.<sup>33</sup>

In a large double-blind, placebo-controlled, multicenter clinical trial involving 437 patients with adult periodontitis, adjunctive SDD significantly improved clinical parameters relative to placebo when used in conjunction with supragingival and subgingival scaling and prophylaxis for a 12-month period. In this study, treatment with adjunctive doxycycline (20 mg twice daily) resulted in significant reductions in pocket probing depths and bleeding on probing. It also showed significant gains in clinical attachment levels relative to treatment with adjunctive placebo. Mean attachment gains were shown to be comparable to those reported for SRP.<sup>34</sup>

In another placebo-controlled clinical study of 190 patients with adult periodontitis, adjunctive treatment with low dose doxycycline during a 9-month period improved the efficacy of SRP. Treatment with adjunctive SDD significantly augmented the attachment gains that followed a single course of SRP. A clinically significant benefit was realized as early as 3 months after the initiation of treatment. These human clinical trials of SRP plus low dose doxycycline indicate that when the destructive host response mediated by MMPs is blocked, it is possible to block the tissue destruction of periodontitis.<sup>35</sup>

### TRICLOSAN AS A HOST MODULATORY THERAPEUTIC AGENT

There is much interest recently in the discovery that the anti-infective agent triclosan is also anti-inflammatory. Beginning in 1995 with a report by Gaffar and co-workers, several studies have demonstrated the anti-inflammatory properties of triclosan.<sup>36</sup> They used enzyme assays to measure the ability of triclosan to inhibit 4 enzymes known to regulate arachidonic acid metabolism and prostaglandin production. Subsequently, Modeer and

co-workers reported the stimulatory effect of IL-1 $\beta$  in gingival fibroblasts in cell culture.<sup>37</sup> The investigators further reported that triclosan reduces the production of IL-1 $\beta$  in gingival fibroblasts.<sup>38</sup> **The findings greatly extend our view of triclosan, the active ingredient in Colgate® Total® toothpaste, and suggest that the dentifrice—in addition to being anti-infective—is host modulatory.**

## SUMMARY

The concept of modulating host destructive pathways as a strategy for treating periodontal disease has come a long way since the 1970s. Studies by a number of researchers and clinicians world-wide clearly demonstrate that blocking specific inflammatory mediators and/or enzymes can be efficacious in slowing periodontal disease progression. As new mediators and pathways of periodontal tissue destruction are identified, so will new host modulating strategies for blocking tissue destruction evolve, which is something exciting to envision for the future.

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# Oral Inflammation and Cardiovascular Disease

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## ABSTRACT

*Cardiovascular and periodontal diseases are common inflammatory conditions in patients. With periodontal disease, oral inflammatory events culminate in the destruction of soft tissues around teeth. Similarly, with cardiovascular disease (CVD), inflammation plays a role in the development and rupture of atheromatous plaques. Observational studies and meta-analyses consistently demonstrate a modest but statistically significant increased risk for CVD among persons with periodontal disease. These findings support the hypothesis that exposure to periodontal disease may promote atherogenesis via direct bacterial effects on platelets, autoimmune responses, invasion, and/or uptake of bacteria in endothelial cells and macrophages, and endocrine-like effects of proinflammatory mediators. While available pilot data in patients suggest that interventions aimed at reducing oral or periodontal inflammation can improve surrogate markers associated with CVD, the effect of these interventions on true outcomes of CVD—such as myocardial infarction and stroke—is presently unknown. Nevertheless, clinicians should be aware of the association between cardiovascular and periodontal diseases, the importance of identifying patients at risk who exhibit oral inflammation, and the potential preventive benefits of periodontal interventions.*

## INTRODUCTION

Cardiovascular disease (CVD) accounts for 29% of deaths worldwide and is the second leading cause of death.<sup>1</sup> Atherosclerosis, a major component of CVD, affects one in 4 persons and contributes to 39% of deaths annually in the United States.<sup>2</sup> In atherosclerosis, large to medium sized muscular and large elastic arteries become occluded with fibro-lipid lesions called atheromas. End stage complications or events associated with atherosclerosis

include coronary thrombosis, acute myocardial infarction (MI), and stroke. Interestingly, traditional CVD risk factors related to behaviors, diet, lifestyle, and family history do not appear to fully account for the development of atherosclerosis. Furthermore, despite continued preventive efforts addressing modifiable risk factors, mortality rates from CVD have remained virtually unchanged over the past decade in developed countries. Clinicians and investigators currently appreciate that inflammation plays a central role in the pathogenesis of atherosclerosis, including endothelial cell expression of adhesion molecules (eg, vascular cell adhesion molecule-1 or VCAM-1), development of the fatty streak, progression to a complex plaque, and rupture of plaques.<sup>3</sup> Clinicians and investigators also understand that exposures to infections may promote some of these inflammatory

changes in vessels. Implicated infections include cytomegalovirus, herpes simplex virus, *Chlamydia pneumoniae*, *Helicobacter pylori*, and periodontal disease.<sup>4</sup> The objectives of this review are to present the latest and cumulative evidence supporting a relationship between cardiovascular and periodontal diseases, explain the biological plausibility for this association, and advise clinicians how to integrate these findings into practice.

## OBSERVATIONAL EVIDENCE RELATING PERIODONTAL AND CARDIOVASCULAR DISEASES

Periodontal disease (oral inflammation) and CVD have several common risk factors, such as advanced age, male gender, lower socioeconomic status, stress, and smoking.<sup>5</sup> Additionally, many patients with periodontal disease also exhibit CVD.<sup>6</sup> These observations suggest that periodontal disease and atherosclerosis share similar or common etiologic pathways. Scannapieco and colleagues conducted a recent systematic review of the observational evidence supporting a relationship between periodontal disease and CVD.<sup>7</sup> The investigators asked the focused question: “Does periodontal disease influence the initiation/progression of atherosclerosis and therefore CVD, stroke and peripheral vascular disease?” Although the investigators did not perform any meta-analysis of data from 31 identified human studies because of heterogeneity in study outcomes, the authors noted relative consistency in the findings and concluded: “Periodontal disease may be modestly associated with atherosclerosis, myocardial infarction and cardiovascular events.” An accompanying consensus report approved by the American Academy of Periodontology recommends: “Patients and health care providers should be informed that periodontal intervention may prevent the onset or progression of atherosclerosis-induced diseases.”

Since this review and consensus report, other meta-analyses on the cardiovascular-periodontal disease association have been conducted and published. Meurman and coworker reported a 20% increase in the risk for CVD among patients with periodontal disease (95% CI 1.08-1.32) and an

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**TABLE 1:**  
**Select Evidence from Human Observational Studies** **Linking**  
**Periodontal and Cardiovascular Diseases.**

Reference	Study Design	Population	Periodontal Outcome or Exposure	Cardiovascular Outcome
Matilla et al. 1989 (11)	Case control	100 cases and 102 controls	Dental Severity Index (sum of scores for caries, periodontal disease, periapical pathosis and pericoronitis)	Evidence of MI from EKG and elevated enzyme levels (creatinine phosphokinase isoenzyme MB)
Matilla et al. 1993 (12)	Case control	100 cases	Dental Severity Index	Clinical diagnosis or radiographically confirmed MI
Arbes et al. 1999 (13)	Case control	5,564 subjects (NHANES III)	Percent attachment loss of all teeth (>3mm) and categorized according to four levels	Self-reported MI
DeStefano et al. 1993 (14)	Cohort	9,760 subjects (NHANES I)	Subjects classified with no periodontal disease, with gingivitis, periodontitis ( $\geq 4$ probing depth) or edentulous	Hospital admission or death due to CHD
Beck et al. 1996 (15)	Cohort	1,147 males (Normative Aging Study)	Percent radiographic alveolar bone loss	Incidence of total and fatal CHD and stroke
Beck et al. 2001 (16)	Cohort	6,017 subjects (ARIC Study)	Severe periodontitis defined as clinical attachment loss $\geq 3$ mm at $\geq 30\%$ of sites	Carotid artery intima-media wall thickness (IMT) $\geq 1$ mm
Beck et al. 2005 (17)	Cohort	15,792 subjects (ARIC Study)	Serum antibodies to periodontal pathogens	Carotid artery intima-media wall thickness (IMT) $\geq 1$ mm
Hung et al. 2004 (19)	Cohort	41,407 males from the HPFS and 58,974 females from the NHS	Self-reported tooth loss at baseline	Incident fatal and nonfatal MI or stroke
Joshiyura et al. 1996 (20)	Cohort	44,119 subjects (Health Professionals Follow-up Study)	Self-reported number of teeth and history of periodontal disease	Fatal and nonfatal MI or sudden death (revascularization cases excluded)
Engelbretson et al. 2005 (21)	Cohort	203 subjects from INVEST	Radiographic alveolar bone loss	Carotid plaque thickness via ultrasonography
Desvarieux et al. 2005 (22)	Cohort	1,056 subjects from INVEST	Subgingival bacterial burden	Carotid artery intima-media wall thickness (IMT) $\geq 1$ mm
Pussinen et al. 2004 (24)	Cohort	6,950 Finnish subjects in the Mobile Clinic Health Survey	Serum antibodies to <i>P. gingivalis</i> or <i>A. actinomycetemcomitans</i>	Incident fatal or nonfatal stroke
Abnet et al. 2005 (26)	Cohort	29,584 rural Chinese subjects	Tooth loss	Incidence of fatal MI or stroke

## Findings and Conclusions

Dental health significantly worse in patients with MI versus controls after adjusting for smoking, social class, serum lipids, and diabetes

Significant association between dental infections and severe coronary atheromatosis in males (but not females)

Positive association between periodontal disease and CHD (OR=3.8 for severe attachment loss) after adjusting for age, gender, race, etc.)

Periodontitis is associated with small increased risk for CHD (RR=1.7) among males

Periodontal disease associated with moderate risk for CHD (OR=1.5-1.9) and stroke after adjusting for age and CVD risk factors (OR=2.9)

Periodontitis may influence atheroma formation (OR=1.3)

Presence of antibody to *C. rectus* was associated with carotid atherosclerosis (OR=2.3)

For males with tooth loss, the relative risk for coronary heart disease was 1.36. For females with tooth loss, the relative risk was 1.64.

A small association between tooth loss and CHD risk for men (RR=1.7)

Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR=3.64)

Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR=3.64)

Seropositive subjects had an OR of 2.6 for stroke

Tooth loss was associated with an increased odds for death from MI (RR=1.29) and stroke (RR=1.12)

even higher risk ratio for stroke, varying from 2.85 (95% CI 1.78-4.56) to 1.74 (95% CI 1.08-2.81).<sup>8</sup> Similarly, Vettore and Khader et al reported relative risk estimates of 1.19 (95% CI 1.08-1.32) and 1.15 (95% CI 1.06-1.25), respectively.<sup>9,10</sup> Cumulatively, these meta-analyses support a modest but statistically significant increase in the risk for CVD for patients with periodontal disease.

Several case-control and cohort studies (Table 1) conducted over the past two decades and pooled in these meta-analyses warrant detailed discussion. In 1989, Matilla et al first reported that poor oral health (including periodontal disease) was a predictor for MI among 202 Finnish subjects.<sup>11</sup> Accordingly, the investigators found that individuals with evidence of oral infection were 30% more likely to present with MI compared to subjects without oral infections. This association was significant after adjusting for known risk factors like age, total cholesterol levels, hypertension, body mass index, and cigarette smoking. In a follow-up publication based on the same population, these investigators documented a significant and specific association between dental infections and severe coronary atheromatosis for males.<sup>12</sup> More recently, Arbes et al evaluated cross-sectional data from the Third National Health and Nutrition Survey (NHANES III).<sup>13</sup> They found that for cases with severe clinical attachment loss (CAL) and periodontitis, the odds ratio (OR) for self-reported MI was 3.8 (95% CI 1.5-9.7) compared to periodontally healthy controls. An early cohort study conducted by DeStefano et al reviewed data from 9,760 US adults followed for 14 years and found that individuals with pre-existing clinical signs of periodontitis were 25% more likely to develop coronary heart disease (CHD) compared to those with minimal periodontal disease after adjusting for other known risk factors.<sup>14</sup> In this study, males younger than 50 years with periodontitis were 72% more likely to develop CHD compared to their periodontally healthy counterparts.

Beck and co-workers assessed the periodontal status of 1,147 males aged 21-80 years enrolled in the Normative Aging Study and free of CHD at baseline.<sup>15</sup> Odds ratios adjusted for age and established cardiovascular risk factors were 1.5 (95%

CI 1.0-2.1), 1.9 (95% CI 1.1-3.4), and 2.8 (95% CI 1.5-5.5) for periodontal bone loss and total CHD, fatal CHD, and stroke, respectively. When the investigators graphed the cumulative incidence of coronary heart disease or events versus baseline mean alveolar bone loss, they noted a linear relationship such that increasing severities of periodontitis were accompanied by increasing occurrences of CVD.

Beck and coworkers also collected and analyzed data on a larger population (6,017 persons ages 52-75 years) participating in the Atherosclerosis Risk in Communities (ARIC) study.<sup>16-18</sup> Here they explored clinical CHD (MI or revascularization procedure) and subclinical atherosclerosis [carotid artery intima-media wall thickness (IMT) using B-mode ultrasound] as dependent variables in logistic regression analyses. Individuals with both high attachment loss ( $\geq 10\%$  of sites with attachment loss  $\geq 3$  mm) and high tooth loss exhibited elevated odds of prevalent CHD as compared to individuals with low attachment loss and low tooth loss (OR=1.5, 95% CI 1.1-2.0 and OR=1.8, CI 1.4-2.4, respectively).<sup>18</sup> A second analysis indicated a significant association between severe periodontitis and thickened carotid arteries after adjusting for covariates such as age, gender, diabetes, lipids, hypertension, and smoking.<sup>16</sup> Accordingly, the OR for severe periodontitis (ie, 30% or more of sites with  $\geq 3$  mm clinical attachment loss) and subclinical carotid atherosclerosis was 1.31 (95% CI 1.0-1.7). In a third report, the investigators quantified serum IgG antibody levels specific for 17 periodontal organisms using a whole bacterial checkerboard immunoblotting technique.<sup>17</sup> Analyzing mean carotid IMT ( $\geq 1$  mm) as the outcome and serum antibody levels as exposures within the ARIC population, the investigators noted that the presence of antibody to *Campylobacter rectus* increased the risk for subclinical atherosclerosis two-fold (OR=2.3, 95% CI 1.8-2.8). In particular, individuals with both high *C. rectus* and *Peptostreptococcus* microorganism antibody titers had almost twice the prevalence of carotid atherosclerosis as compared to those with only a high *C. rectus* antibody (8.3% versus 16.3%). Stratification by smoking indicated that all

microbial models significant for smokers were also significant for never smokers except for *Porphyromonas gingivalis*. Hence, clinical signs of periodontitis are associated with CHD and subclinical atherosclerosis in the ARIC population, and exposures to specific periodontal pathogens significantly increase the risk for atherosclerosis in smoking and nonsmoking subjects.

Several other recent population studies further support the association between periodontal disease and CVD. Joshipura and coworkers assessed self-reported periodontal disease outcomes and incident CVD in two extant databases: the Health Professional Follow-up Study (HPFS, n=41,407 males followed for 12 years) and the Nurses Health Study (NHS, n=58,974 females followed for 6 years).<sup>19</sup> After controlling for important cardiovascular risk factors, males with a low number of reported teeth ( $\leq 10$  at baseline) had a significantly higher risk of CHD (OR= 1.4, 95% CI 1.1-1.7) as compared to males with a high number of teeth ( $\geq 25$ ). For females with the same reported extent of tooth loss, the relative risk for CHD was 1.64 (95% CI 1.3-2.1) as compared to women with at least 25 teeth. The relative risks for fatal CHD events increased to 1.8 (95% CI 1.3-2.4) for males and 1.7 (95% CI 1.1-2.5) for females with tooth loss, respectively. In a second report, the investigators evaluated the association between self-reported periodontal disease and serum elevations in CVD biomarkers cross-sectionally in a subset of HPFS participants (n=468 males).<sup>20</sup> Serum biomarkers included C-reactive protein (CRP), fibrinogen, factor VII, tissue plasminogen activator (t-PA), low-density lipoprotein (LDL) cholesterol, von Willebrand factor, and soluble tumor necrosis factor (TNF) receptors 1 and 2. In multivariate regression models controlling for age, cigarette smoking, alcohol intake, physical activity, and aspirin intake, self-reported periodontal disease was associated with significantly higher levels of CRP (30% higher among periodontal cases compared with non-cases), t-PA (11% higher), and LDL cholesterol (11% higher). These analyses reveal significant associations between self-reported measures of periodontal disease and not only CHD, but also serum biomarkers of endothelial dysfunction and dyslipidemia.

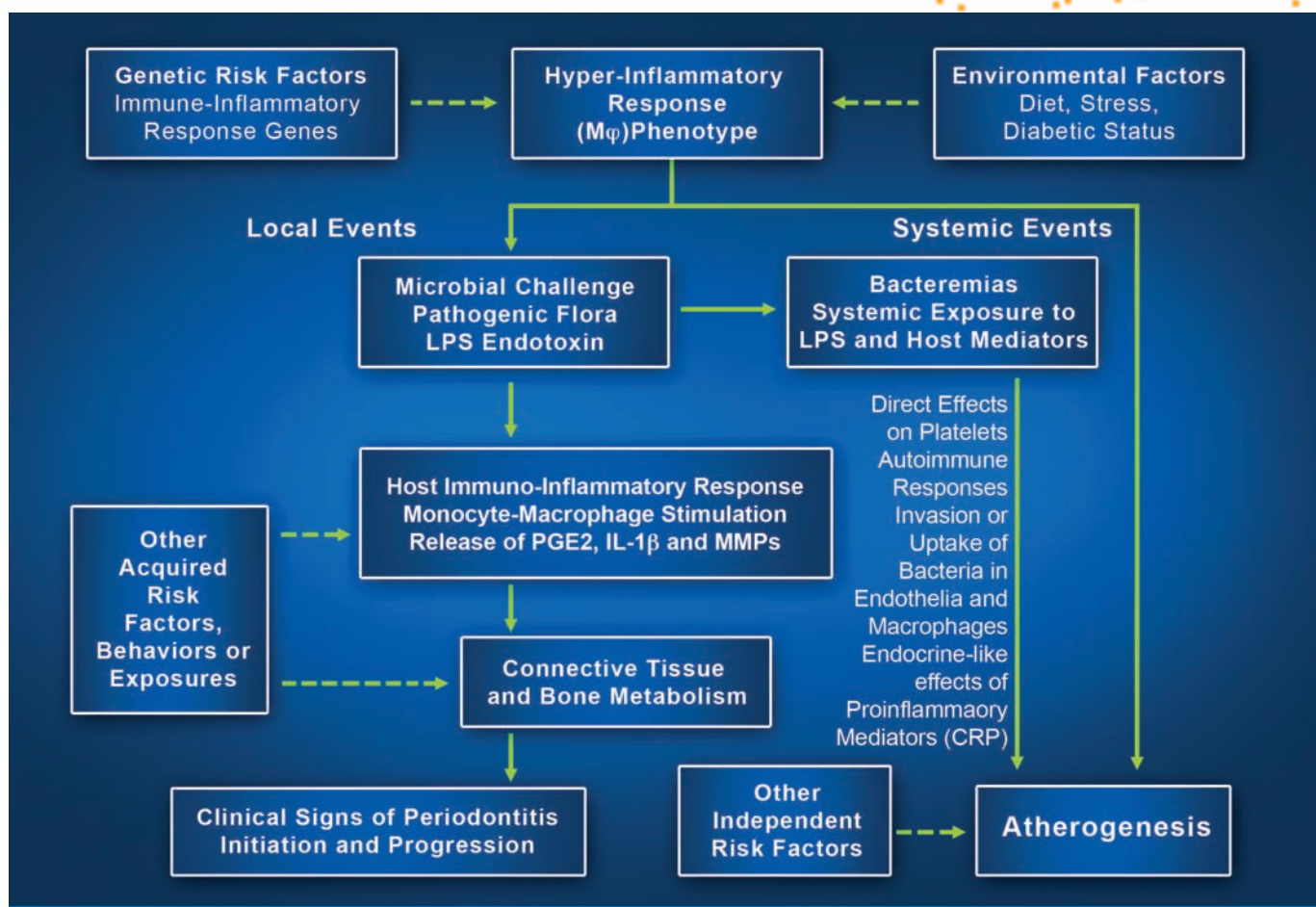
Another US population study called Oral Infections and Vascular Disease Epidemiology Study (INVEST) was designed to further evaluate the association between atherosclerosis and periodontal outcomes. Desvarieux and coworkers first reported that for a group of 203 stroke-free subjects (ages 54 -94) at baseline, mean carotid plaque thickness (measured with B-mode ultrasound) was significantly greater among dentate subjects with severe periodontal bone loss ( $\geq 50\%$  measured radiographically) as compared to those with less bone loss ( $< 50\%$ ).<sup>21</sup> The group noted a clear dose-response relationship when they graphed subject tertiles of periodontal bone loss versus carotid plaque thickness. The investigators then collected subgingival plaque from 1,056 subjects and tested for the presence of 11 known periodontal bacteria using DNA techniques.<sup>22</sup> The investigators found that cumulative periodontal bacterial burden was significantly related to carotid IMT after adjusting for CVD risk factors. Whereas mean IMT values were similar across burden tertiles for putative (orange complex) and health-associated bacteria, IMT values rose with each tertile of etiologic bacterial burden (*Actinobacillus actinomycetemcomitans*, *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythensis*). Similarly, white blood cell values but not serum CRP increased across these burden tertiles. These data from INVEST provide evidence of a direct relationship between oral infective organisms and subclinical atherosclerosis.

Consistent associations between periodontal and CVD outcomes have also been demonstrated for European and Asian populations. For 131 adult Swedes, mean carotid IMT values were significantly higher in subjects with clinical and/or radiographic evidence of periodontal disease as compared to periodontally healthy controls.<sup>23</sup> Multiple logistic regression analysis identified periodontal disease as a principal independent predictor of carotid atherosclerosis with an OR of 4.6 (95% CI 1.6-13.1). Pussinen et al monitored antibody responses for *A. actinomycetemcomitans* and *P. gingivalis* among 6,950 Finnish subjects for whom CVD outcomes over 13 years were available (Mobile Clinic Health Survey).<sup>24</sup> Compared with the subjects who were

seronegative for these pathogens, seropositive subjects had an OR of 2.6 (95% CI 1.0-7.0) for a secondary stroke. In a second report on 1,023 males (Kuopio Ischemic Heart Disease Study), Pussinen and coworkers observed that cases with MI or CHD death were more often seropositive for *A. actinomycetemcomitans* than those controls who remained healthy (15.5% versus 10.2%).<sup>25</sup> In the highest tertile of *A. actinomycetemcomitans* antibodies, the relative risk for MI or CHD death was 2.0 (95% CI 1.2-3.3) compared with the lowest tertile. For *P. gingivalis* antibody responses, the relative risk was of 2.1 (95% CI 1.3-3.4). Abnet and coworkers recently published findings from a cohort study of 29,584 healthy rural Chinese adults monitored for tooth loss and CVD for 15 years or less.<sup>26</sup> Individuals with greater than the age-specific median number of teeth lost exhibited a significantly increased risk of death from MI (OR=1.3, 95% CI 1.2-1.4) and stroke (OR=1.1, 95% CI 1.0-1.2). These elevated risks were present in males and females irrespective of smoking status. Collectively, these findings indicate consistent and generalizable associations for periodontal disease and pathogenic exposures with CVD in worldwide populations.

## MECHANISMS EXPLAINING BIOLOGICAL PLAUSIBILITY

Since periodontal infections result in low-grade bacteremias and endotoxemias in affected patients, systemic effects on vascular physiology via these exposures appear biologically plausible.<sup>27,28</sup> Four specific pathways have been proposed to explain the **plausibility of a link between CVD and periodontal infection** (Figure 1). These pathways include: (1) direct bacterial effects on platelets, (2) autoimmune responses, (3) invasion and/or uptake of bacteria in endothelial cells and macrophages, and (4) endocrine-like effects of proinflammatory mediators. In support of the first pathway, two oral bacteria, *P. gingivalis* and *Streptococcus sanguis*, express virulence factors called collagen-like platelet aggregation associated proteins (PAAP) that induce platelet aggregation in vitro and in vivo.<sup>29,30</sup> Secondly, autoimmune mechanisms may play a role since antibodies that cross-react with periodontal bacteria, and human



**Figure 1** Model explaining the biological plausibility for the association between periodontal and cardiovascular diseases.

heat shock proteins have been identified.<sup>31,32</sup> Thirdly, Deshpande and coworkers have demonstrated that *P. gingivalis* can invade aortic and heart endothelial cells via fimbriae.<sup>33</sup> Several investigative groups have independently identified specific oral pathogens in atherosclerotic tissues.<sup>34</sup> In addition, macrophages incubated in vitro with *P. gingivalis* and LDL uptake the bacteria intracellularly and transform into foam cells.<sup>35</sup> In the last potential pathway, systemic proinflammatory mediators are upregulated for endocrine-like effects in vascular tissues, and studies consistently demonstrate elevations in C-reactive protein and fibrinogen among periodontally diseased subjects.<sup>36-38</sup>

### EFFECT OF PERIODONTAL INTERVENTIONS ON CVD OUTCOMES

Human evidence demonstrating beneficial effects of periodontal therapy on CVD outcomes presently is limited and indirect.

D'Aiuto and coworkers recently demonstrated that periodontitis patients treated with scaling and root planing (SRP) exhibited significant serum reductions in the CVD biomarkers, CRP, and interleukin-6 (IL-6).<sup>39</sup> In particular, patients who clinically responded to periodontal therapy in terms of pocket depth reductions were 4 times more likely to exhibit serum decreases in CRP relative to patients with a poor clinical periodontal response. Elter and colleagues also report decreases in these serum biomarkers plus improved endothelial function (ie, flow-mediated dilation of the brachial artery) for 22 periodontitis patients treated with “complete mouth disinfection” (ie, SRP, periodontal flap surgery, and extraction of hopeless teeth within a 2-week interval).<sup>40</sup> Similarly, Seinost and coworkers tested endothelial function in 30 patients with severe periodontitis versus 31 periodontally healthy control subjects.<sup>41</sup> At baseline (prior to treatment), flow-mediated dilation was significantly lower

in patients with periodontitis than in control subjects. Periodontitis patients with favorable clinical responses to non-surgical periodontal therapy (ie, SRP, topical and peroral antimicrobials plus mechanical retreatment) exhibited concomitant improvements in flow-mediated dilation of the brachial artery and serum CRP concentrations. While the effects of periodontal therapy on CVD events in patients have yet to be determined, the available data suggest that periodontal therapies can improve surrogate CVD outcomes such as serum biomarkers and endothelial dysfunction.

### CONCLUSIONS AND INTEGRATING FINDINGS INTO CLINICAL PRACTICE

Inflammation plays a central role in the pathogenesis of periodontal disease and CVD. Human observational studies consistently implicate periodontal infection and the resulting oral inflammatory burden as systemic exposures that may

perpetuate these inflammatory events in vessels. **Although treatments aimed at decreasing periodontal therapy can reduce serum inflammatory biomarkers predictive of CVD and improve vascular responses, the clinical relevance of these surrogate changes to reduced risks for MI or stroke are not known at this time.**

Nevertheless, clinicians should be knowledgeable about this consistently observed association and integrate these findings into clinical practice. Physicians, dentists, and other health care providers should appreciate that the presence of oral inflammation at least indicates an increased likelihood of CVD or events in patients who otherwise exhibit the traditional risk factors. While medicine and dentistry currently lack the definitive evidence establishing causality, clinicians should identify patients exhibiting signs of oral inflammation, appropriately educate them about the current level of evidence on the risk relationship, and implement preventive strategies that can improve oral health and systemic well being.

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# Control of the Oral Microbial Flora to Prevent Pneumonia in Special Patient Populations

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## INTRODUCTION

There is ever-increasing interest in the potential influence of oral diseases and conditions on systemic health outcomes. The primary cause of the most frequent oral diseases (eg, dental caries and inflammatory periodontal diseases) is dental plaque, the microbial biofilm that forms on teeth.<sup>1</sup> This biofilm hosts a remarkable diversity of microbial species, some of which are known etiologic agents of systemic disease. Since the oral cavity is proximal and contiguous with the trachea and lungs, it should not be surprising that oral microflora may influence lung infections such as pneumonia, the inflammation of the lungs resulting from bacterial or viral infection (Figure 1).

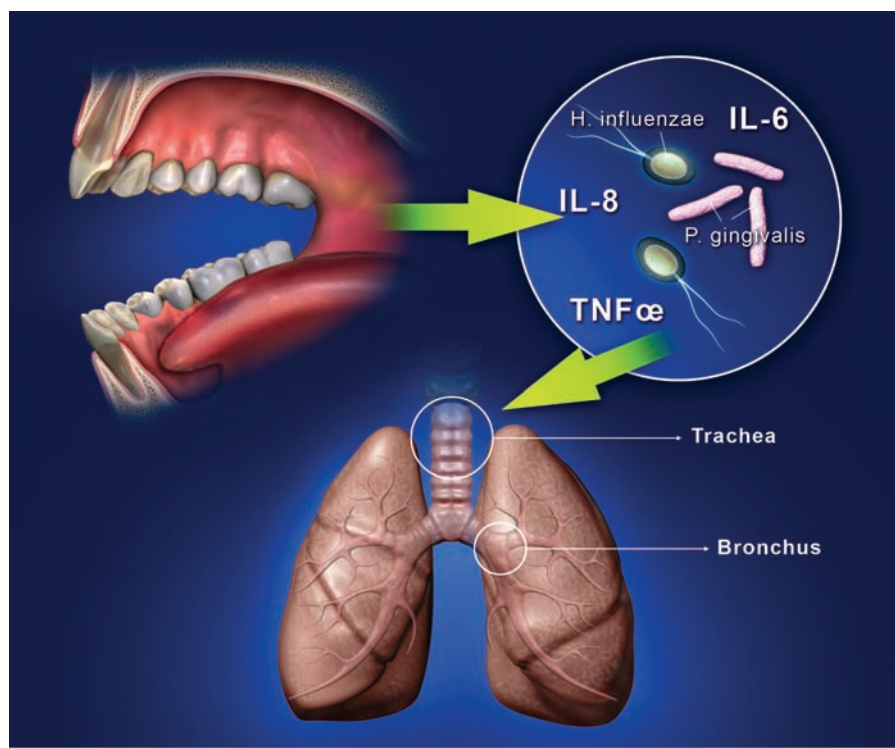
Cases of pneumonia may be divided into 2 major types: community-acquired and hospital-acquired (nosocomial). Community-acquired pneumonia results in more than 10 million visits to physicians, 64 million days of restricted activity, and 600,000 hospitalizations each year.<sup>2</sup> This disease results in significant

mortality, morbidity, and economic cost. Bacteria that often colonize the oropharynx and upper airway, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Mycoplasma pneumoniae*, are the common causes of community-acquired pneumonia.<sup>3</sup>

Hospitalization for community-acquired pneumonia is especially problematic for the elderly and is associated with a high mortality and high rate of

readmission within the following year.<sup>4</sup> Aspiration pneumonia occurs following aspiration of oropharyngeal contents and is frequent in the elderly, especially those with swallowing difficulties or depressed consciousness. It has been shown that 20% of organisms implicated in aspiration pneumonia are anaerobic and 80% aerobic, most of the latter being gram-negative *Enterobacteriaceae*. It is becoming more appreciated that poor oral hygiene increases subsequent risk for pneumonia and that dental plaque likely serves as a reservoir for pathogens implicated in pneumonia.

Hospital-acquired (nosocomial) pneumonia (HAP) represents 13% to 18% of hospital-acquired infections and occurs in 0.4% to 0.7% of all hospitalizations; mortality is about 30%.<sup>5,6,7</sup> Pulmonary complications, including various forms of pneumonia, are common in the post-operative period and affect a substantial fraction of patients following surgery with general anesthesia. Ventilator-associated pneumonia (VAP) is the second most common hospital-acquired infection<sup>8,9</sup> and is a leading cause of death in critically-ill patients in the intensive care unit (ICU), with estimated prevalence rates



**Figure 1** Illustration demonstrating the manner in which oral microflora may influence lung infections.

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**AN EPISODE  
OF HAP ADDS  
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HOSPITAL STAY  
AND THOUSANDS  
OF DOLLARS  
IN COST TO  
MEDICAL CARE.**

of 10% to 65% and mortality rates of 25% to 60%, depending on the study. VAP and other forms of HAP are independent risk factors for mortality in hospitalized patients irrespective of the severity and type of underlying illness.<sup>10</sup> An episode of HAP adds approximately 5 to 6 days to the length of hospital stay and thousands of dollars in cost to medical care.<sup>11</sup>

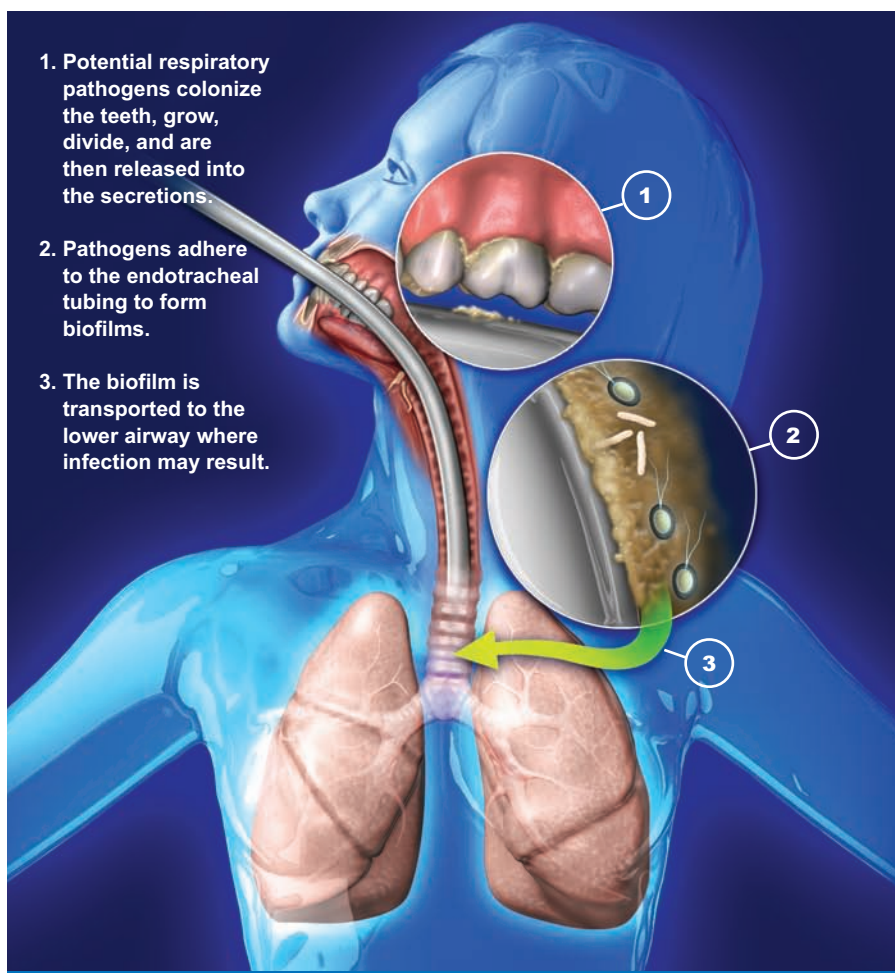
A number of risk factors have been implicated for initiation and progression of pneumonia, most importantly the placement of an endotracheal tube (ET) and mechanical ventilation. The incidence of respiratory tract infections in patients requiring an endotracheal tube is substantial, and the risk of acquiring VAP increases by as much as 1% to 5% per hospital day.<sup>12</sup> The ET provides an inert, nonshedding surface to which bacteria adhere and grow to form biofilms, from which bacteria are shed and aspirated into the lower airway. Furthermore,

the ET induces mechanical abrasion, irritation of the respiratory mucosa, impairment of normal laryngeal function, and increased sedation, all of which lead to an increased risk of aspiration of upper respiratory tract secretions.

Other identified risk factors include patient age greater than 70 years, altered mental status (particularly closed-head injuries with placement of intracranial pressure monitors), thoracoabdominal procedures, underlying chronic lung disease, history of large-volume aspiration, trauma, perioperative use of antibiotics, supine position, use of neuromuscular paralysis, and obesity.<sup>13,14</sup> Additional risk factors include 24-hour ventilator circuit changes, acute respiratory distress syndrome, contaminated anesthesia or respiratory therapy equipment, and recent bronchoscopy.

It is clear that bacterial pathogens that first colonize the oral cavity and upper airway are subsequently aspirated into the lower airway where they then induce inflammation and infection. A person with teeth or dentures has nonshedding surfaces on which oral biofilms form. These biofilms are susceptible to colonization by respiratory pathogens.<sup>15,16</sup> Poor oral hygiene may predispose high-risk patients to oral colonization by respiratory pathogens. Subsequent aspiration would deposit these bacteria into the lower airway, thereby increasing the risk of infection (Figure 2). The potential respiratory pathogens identified in the oral flora of hospital patients include *S. aureus*, *P. aeruginosa*, and a number of enteric species. It has been reported that the relative risk for pneumonia is increased 9.6-fold when the dental plaque is colonized by a potential respiratory pathogen between days 0 and 5 following admission to an ICU. In some cases, the pathogen causing pneumonia appeared to first colonize the dental plaque.<sup>17</sup> The ET offers another nonshedding surface that is vulnerable to colonization by pathogenic bacteria, with subsequent biofilm formation.

The association between oral bacteria and pneumonia has also been suggested in studies of those living in nursing homes or hospitals for extended periods of time. People in these situations are more often exposed to pathogens, are less likely to pay close attention to oral hygiene, and are



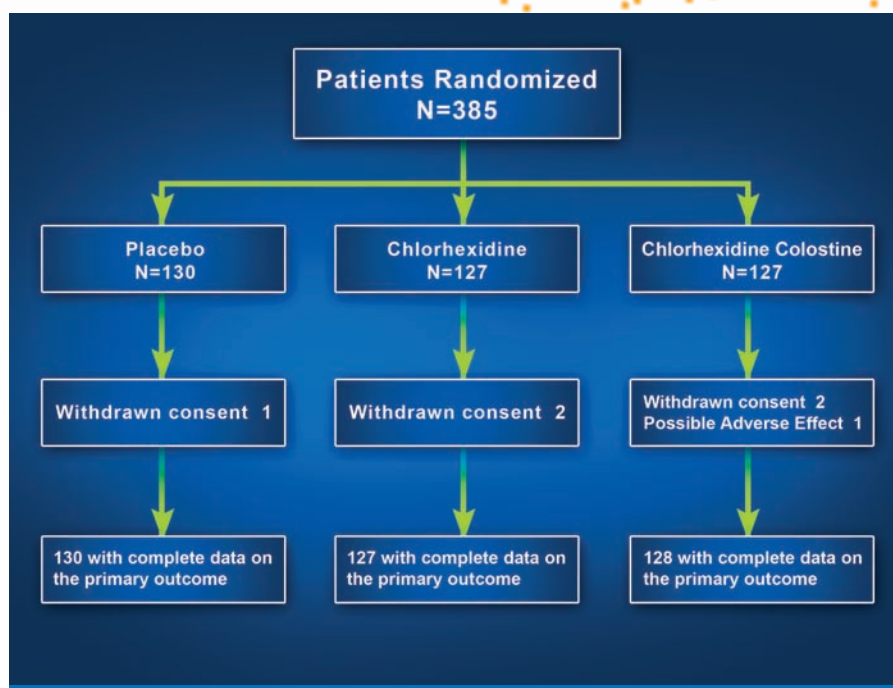
**Figure 2** Biofilms are susceptible to colonization by respiratory pathogens; subsequent aspiration deposit bacteria into the lower airway and increase the chances of infection.

more likely to have poor general health. Institutionalized subjects appear to have more dental plaque and be more prone to oral colonization by respiratory pathogens than community dwelling subjects.<sup>18-22</sup> Diminished salivation and salivary pH may also promote oral colonization by respiratory pathogens; these conditions occur in ill patients and those receiving various medications.<sup>18</sup> One study found the dental plaque of 43% of elderly patients recently admitted to a hospital to be colonized by gram-negative pathogens.<sup>23</sup> More recently, the relationship between oral hygiene status, the number of oral bacteria in saliva, and pneumonia experience in 145 Japanese nursing home subjects was explored.<sup>24</sup> Dentate patients with poor oral hygiene showed significantly higher salivary bacterial counts than those with good oral hygiene. Interestingly, the number of febrile days was significantly higher—and the number of patients developing pneumonia more numerous—in dentate patients with poor oral hygiene. Taken together, these studies show that institutionalized patients represent a high-risk group for pneumonia related to oral bacteria.

Evidence has also been presented that demonstrates the genetic identity of respiratory pathogen isolates recovered from bronchoalveolar lavage fluid of hospitalized institutionalized elders and isolates from the dental plaques of the same patients.<sup>25</sup> These results confirm that dental plaque serves as an important reservoir of respiratory pathogens in this patient cohort.

### EVIDENCE THAT ORAL INTERVENTION PREVENTS VAP

The oral cavity likely serves as an important reservoir for the growth of respiratory pathogens in patients admitted to hospital ICUs and the elderly who are debilitated, hospitalized, or living in a nursing home. Inpatients of hospitals and nursing homes often have poorer oral hygiene than community-dwelling individuals, and poor oral hygiene and periodontal inflammation may foster respiratory pathogen oropharyngeal colonization. Therefore, oral hygiene interventions may reduce the rate of oral colonization by respiratory pathogens



**Figure 3** Distribution of trial participants and method of oral decontamination.

and, subsequently, the risk for pneumonia in these special patient populations.

Several trials have evaluated the effectiveness of oral decontamination to prevent pneumonia.<sup>26</sup> Most of these trials, while varying in setting (eg, ICU, nursing homes), design, and intervention [including topical application of non-absorbable antibiotics, antiseptics such as chlorhexidine gluconate (CHG) rinse, and mechanical debridement such as tooth brushing], showed reductions in oral colonization by respiratory pathogens and/or incidence of pneumonia (Figure 3). The combined data from five controlled oral hygiene intervention trials was analyzed.<sup>27-31</sup> In all cases the intervention reduced the rate of pneumonia in these populations by approximately 40%. A more recent systematic review and meta-analysis corroborate these findings.<sup>32</sup> Thus, oral decontamination appears to hold promise for reducing carriage of respiratory pathogens on the oropharynx and, therefore, the rate of pneumonia in high-risk populations.

Heightened interest in the possibility that improved oral hygiene could prevent VAP has resulted in recognition of oral care as a possible modifiable risk factor for VAP by the Centers for Disease Control,<sup>33</sup> the American Thoracic Society, and the Infectious Disease Society of

America.<sup>34</sup> Some hospitals have implemented formal, organized oral care programs to reduce VAP in high-risk subjects. For example, a retrospective study reported on the impact of implementing such a program that involved nurse administered tooth brushing every 2 to 4 hours, swabbing with an alcohol-free antiseptic oral rinse, frequent suctioning of oral and pharyngeal secretions, and application of a water-based mouth moisturizer on VAP-ICU rates.<sup>35</sup> Results showed that the VAP rate decreased by 3.4 per 1000 ventilator days (from 9.9 per 1100 ventilator days) following institution of this program, resulting in an estimated cost savings of about \$30,000 per incident of VAP.

### IMPEDIMENTS TO ORAL CARE PRACTICES TO PREVENT PNEUMONIA

Several obstacles impede progress toward formulation and adoption of universal standards for the use of oral care to prevent pneumonia in special patient populations. Regarding research, it is sometimes difficult to obtain informed consent from patients to participate in trials, especially those who are unconscious or otherwise rely on surrogates for such decisions. All hospital patients, especially those admitted

## General Guidelines for Managing Intensive Care and Ventilated Patients

- Remove all dental appliances upon admission to the unit
- Conduct oral examination initially, then daily by a registered nurse
- Brush teeth 2 to 3 times per day; floss if possible
- Rinse all oral surfaces with antimicrobial rinses
- Frequent deep suction of oral and pharyngeal secretions as needed, as well as prior to repositioning the tube or deflation of the cuff
- If possible, remove hard deposits (eg, tartar/calculus) from the teeth
- For elective procedures, have teeth professionally cleaned before admission to the hospital

## “How To” Provide Oral Intervention to Reduce the Risk of Oral Colonization by Respiratory Pathogens in Ventilated Patients

1. Position patient's head to the side or place in semi-fowlers.
2. Provide deep suction as needed in intubated patients to remove oropharyngeal secretions that can migrate down the tube and settle on top of the cuff.
3. Brush teeth using a wet soft toothbrush for approximately 1 to 2 minutes.
4. Brush tongue and vestibular surfaces.
5. Apply mouth moisturizer inside the mouth and lip balm if needed to reduce the risk of oral ulceration.

**IN-SERVICE TRAINING TO IMPROVE  
HOSPITAL AND NURSING HOME STAFF  
KNOWLEDGE REGARDING THE  
IMPORTANCE OF ORAL CARE FOR  
PREVENTING PNEUMONIA WOULD  
NO DOUBT PAY DIVIDENDS**

to ICUs, are considered vulnerable; consent typically must be obtained from the legally authorized representative (LAR). Any individual who is not competent or able to comprehend and understand verbal and written information and provide informed consent (eg, due to trauma, surgery, sedation, etc.) must have a LAR to sign the informed consent on his or her behalf.

Buy-in by nursing staff may also impose an obstacle. Nurses are often overworked and burdened by severe time limitations, staffing shortfalls, etc. Severe limitations may also be presented based on the nature of oral hygiene care. There are often physical barriers to oral care, such as limited access to the oral cavity (eg, due to ET placement, need to reposition tubing, soft tissue edema from trauma, etc.), agitation of the patient from neurological impairment, or other medical limitations. These obstacles are often compounded by the fact that in many ICUs, many of the patients admitted are trauma patients with myriad other confounding problems, including oral and head trauma and edema. Patients who are intubated may also have an oral airway/bite block to prevent him/her from biting on the ET tube and an oral-gastric tube in place. The patient may also clench the jaw and preclude free access to the posterior aspect of the teeth, hard and soft palate, and tongue. These restrictions often limit access for providing hygiene to the entire oral cavity.

In some cases, certain trauma patients or those withdrawing from drug or alcohol abuse are on “minimal stimulation” due to the severity of the head/spinal cord injury. In these cases, even minor stimulation can set off untoward events (eg, elevated intracranial or blood pressure, agitation, fighting, etc.).

However, despite these obstacles, after possibly initial resistance, most nursing staff members have been found to be interested, involved, and helpful with all aspects of research on the effects of oral care in the prevention of pneumonia.

## PRESENT STANDARDS OF CARE AND PRACTICE

Most nursing texts suggest that routine dental care should be provided according to a routine schedule (once or twice daily)

and include brushing, flossing, rinsing, and other appropriate interventions to maintain oral health. However, given the obstacles described above, it is not surprising that these standards may not be uniformly met in all health care settings. One recent study observed and recorded actual daily practices used by nurses to render oral care to nursing home residents in the United States.<sup>36</sup> A set of oral care standards developed and validated by an expert panel of dentists, dental hygienists, and registered nurses was compared to observed practices. Adherence to these standards was found to be low. For example, teeth were brushed and mouths rinsed with water in only 16% of resident observations. Interestingly, actual oral care provided to residents contrasts sharply with self-reported practices in the literature and suggests that nursing home residents who need assistance receive inadequate oral health care.

What can be done to enhance compliance to oral care standards in hospital and nursing home settings? An important task is to increase exposure of dental, medical, and nursing students to better appreciate the importance of oral care in the prevention of medical diseases such as pneumonia in vulnerable populations. In addition, in-service training to improve hospital and nursing home staff knowledge regarding the importance of oral care for preventing pneumonia would no doubt pay dividends as well. Recognition by the insurance industry regarding reimbursement for oral care will likely make a dramatic impact on preventing such diseases in these populations.

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# Diabetes and Periodontitis: The **Links**, The Risk, and The Need for Optimal Control

**Maria Emanuel Ryan, DDS, PhD**

## INTRODUCTION

The bridge between systemic and oral health has been strengthened over the past decade by multiple publications in medical and dental journals. The oral focus of these publications has been on periodontal diseases, which are the most common dental conditions. The strongest data supporting an oral-systemic **link** exists for diabetes and periodontitis.

Despite multiple published reports of this connection, which date back to the 1920s<sup>1</sup> and 1930s,<sup>2</sup> many practitioners in the medical and dental fields have been unable to convert these findings into clinical actions. A recent survey of general dentists and periodontists revealed that the dental practitioner's rates of proactive management of diabetic patients (eg, willingness to change/adjust treatment plans) and referring patients for evaluation of suspected diabetes or screening for diabetes with a finger-stick test may actually be quite low.<sup>3</sup>

There is no doubt that poor control of diabetes increases the risk for developing a number of oral manifestations of the disease, including periodontitis. In addition, an uncontrolled oral infection such

as periodontitis increases the risk for poor metabolic control and certain long-term complications of the diabetes, particularly nephropathy<sup>4</sup> and cardiovascular disease (CVD).<sup>5</sup> Recent research has shown that improving oral health is important to optimizing metabolic control of diabetes. This **link** has led to the belief that not only is metabolic control key to the proper management of the diabetic patient, but we can now conclude that the treatment of periodontal diseases should not be considered an option or elective, but instead a necessary and integral part of a patient's overall health care program. Just as the bar has been raised for the proper management by the physician of diabetic patients requiring tighter control (ie, lower hemoglobin A1c levels), so too must dentists raise the bar for the level of oral care provided to diabetic individuals because periodontal evaluation and therapy appear to be necessary for the physician and patients to achieve their ultimate goal of preventing the long-term complications of diabetes.

## THE AMERICAN MEDICAL ASSOCIATION (AMA) AND AMERICAN DENTAL ASSOCIATION (ADA)

A joint press conference was held in February 2006 between the AMA and the ADA entitled "Oral and Systemic Health: Exploring the Connection" to address the emerging data linking periodontitis to diabetes, heart disease, stroke, respiratory infections, and adverse pregnancy

outcomes.<sup>6</sup> The esteemed speakers from the dental and medical professions who participated in this media briefing emphasized the need for collaborative efforts to achieve optimal overall care for patients. Studies supporting these relationships were presented, as well as the results of some pilot intervention studies demonstrating that periodontal therapy can improve metabolic control in diabetes, reduce pre-term birth in high-risk pregnant females, and reduce pneumonia in patients in intensive care units.

However, despite the strong data confirming the relationship between diabetes and periodontitis, oral health was barely addressed in the Clinical Practice Recommendations of the American Diabetes Association for the Standards of Medical Care in Diabetes.<sup>7</sup> There was a brief mention in its components of the comprehensive diabetes evaluation (Table 1) under medical history, where current or prior infections include dental infection, yet periodontitis is not listed below as a complication associated with diabetes. It is interesting that an oral examination is suggested as part of the physical examination, but dentists are not listed as one of the referrals to be considered.

Hopefully the joint media briefing between the AMA and the ADA will help to forge an alliance between the medical and dental professions, as well as among all other allied health providers, to incorporate the mounting findings connecting oral and systemic health into the respective management of patients with diabetes. It is also important that the ADA—representing the dental profession—and the American Diabetes Association—which is actively involved in the development and dissemination of diabetes care standards and guidelines—recognize the synergy that can be achieved by working together to inform patients and practitioners of the importance of good oral health to the overall well-being of the diabetic patient.

## THE IMPORTANCE OF KNOWLEDGE TRANSFER

It is the practitioner's charge to empower their patients with the knowledge necessary to combat their disease. Practitioners should inform their patients about the

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**links** between diabetes and other diseases, such as periodontitis. Interaction with many patients and diabetes support groups reveals that the dissemination of this information to patients is lagging behind the publication of significant supporting studies. Sharing information such as that presented in this publication will enable patients to better assess their risk for developing certain long-term complications of diabetes, as well as motivate them to determine—through appropriate evaluations—what preventive measures can be taken and whether or not they require active therapy and follow-up care.

Diabetes and periodontitis are diseases that cannot currently be cured, but with appropriate therapy, regular follow-up, and a motivated patient, they can be kept under control. Successful management of these diseases requires frequent monitoring of the patient and careful attention to therapeutic responses. A team effort is truly necessary for the proper management of the diabetic patient: the physician, nurse, diabetes educators, dietitians, dentists, hygienists, and a number of other specialists should work collaboratively in the patient's best interest.

## DIABETES

Diabetes mellitus is a disease of metabolic dysregulation, primarily carbohydrate metabolism. It is characterized by hyperglycemia or elevated blood glucose levels. Hyperglycemia is due to defects in insulin secretion and/or impaired insulin action. Alterations in lipid and protein metabolism are also hallmarks of the disease. In 2004, 18.2 million Americans (ie, 6.3% of the population) were believed to have diabetes, with 13 million diagnosed and an estimated 5.2 million not diagnosed. From 1980 to 2004, the number of Americans with diabetes more than doubled.<sup>8</sup> In 2004, about 1.4 million adults between 18 and 79 years of age were diagnosed with diabetes.<sup>9</sup> The reasons for such an increase include increasing longevity, change in demographics, and genetic predispositions. Rising urbanization and changes in lifestyle also play a role, in addition to an increased prevalence of obesity. In the United States, obesity is known to play a major role, with more than 60% of the adult population considered either overweight or obese.

**TABLE 1:**  
**Components of the comprehensive diabetes evaluation.**

### MEDICAL HISTORY

- Symptoms, results of laboratory tests, and special examination results related to the diagnosis of diabetes
- Prior A1C records
- Eating patterns, nutritional status, and weight history; growth and development in children and adolescents
- Details of previous treatment programs, including nutrition and diabetes self-management education, attitudes, and health beliefs
- Current treatment of diabetes, including medications, meal plan, and results of glucose monitoring and patients' use of data
- Exercise history
- Frequency, severity, and cause of acute complications such as ketoacidosis and hypoglycemia
- Prior or current infections, particularly skin, foot, dental, and genitourinary infections
- Symptoms and treatment of chronic eye, kidney, nerve, genitourinary (including sexual), bladder, and gastrointestinal function (including symptoms of celiac disease in type 1 diabetic patients); heart; peripheral vascular; foot; and cerebrovascular complications associated with diabetes
- Other medications that may affect blood glucose levels
- Risk factors for atherosclerosis: smoking, hypertension, obesity, dyslipidemia, and family history
- History and treatment of other conditions, including endocrine and eating disorders
- Assessment for mood disorder
- Family history of diabetes and other endocrine disorders
- Lifestyle, cultural, psychosocial, educational, and economic factors that might influence the management of diabetes
- Tobacco, alcohol, and/or controlled substance use
- Contraception and reproductive and sexual history

### PHYSICAL EXAMINATION

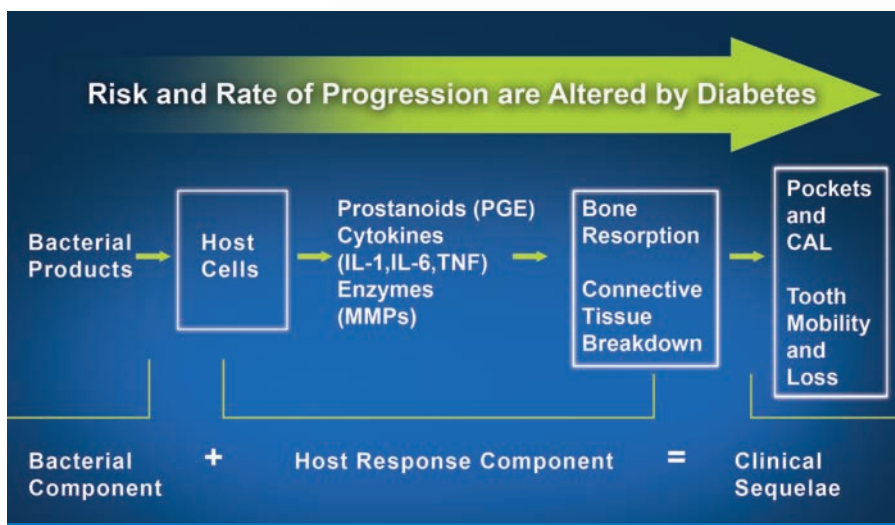
- Height and weight measurement (and comparison to norms in children and adolescents)
- Sexual maturation staging (during pubertal period)
- Blood pressure determination, including orthostatic measurements when indicated, and comparison to age-related norms
- Fundoscopic examination
- Oral examination
- Thyroid palpation
- Cardiac examination
- Abdominal examination (eg, for hepatomegaly)
- Evaluation of pulses by palpation and with auscultation
- Hand/finger examination
- Foot examination
- Skin examination (for acanthosis nigricans and insulin-injection sites)
- Neurological examination
- Signs of diseases that can cause secondary diabetes (eg, hemochromatosis, pancreatic disease)

### LABORATORY EVALUATION

- A1C
- Fasting lipid profile, including total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol, liver function tests with further evaluation for fatty liver or hepatitis if abnormal
- Test for microalbuminuria in type 1 diabetic patients who have had diabetes for at least 5 years and in all patients with type 2 diabetes; some advocate beginning screening of pubertal children before 5 years of diabetes
- Serum creatinine and calculated GFR in adults (check creatinine in children if proteinuria is present)
- Thyroid-stimulating hormone (TSH) in all type 1 diabetic patients; in type 2 if clinically indicated
- Electrocardiogram in adults, if clinically indicated
- Urinalysis for ketones, protein, sediment

### REFERRALS

- Eye exam, if indicated
- Family planning for women of reproductive age
- MNT, as indicated
- Diabetes educator, if not provided by physician or practice staff
- Behavioral specialist, as indicated
- Foot specialist, as indicated
- Other specialties and services as appropriate



**Figure 1** Simplified schematic depicting etiologic factors and cascade of events contributing to periodontitis that are altered by the systemic disorder, diabetes.

There are a number of long-term complications that result as chronic hyperglycemia persists and leads to dysfunction and damage of numerous organs. These include complications related to angiopathy, nephropathy, retinopathy, neuropathy, wound healing, and periodontitis. Periodontitis was identified as the sixth long-term complication of diabetes by Dr. Harold Loe, the former director of the National Institute for Dental and Craniofacial Research.<sup>10</sup> Ninety percent to 95% of all cases of diabetes in the United States are type 2. Half of all people with type 2 diabetes

are unaware that they even have the disease because it is possible to have mild symptoms that would not lead to a timely diagnosis.

This presents a substantial health care problem considering the long-term complications of the disease. Diabetes is the leading cause of blindness in adults. End-stage renal disease, cardiovascular complications, and nontraumatic amputations are additional complications, and the health care costs are immense: \$132 billion annually.<sup>11</sup> In 1997, 159,720 deaths were attributed to diabetes and its complications, with cardiovascular complications

accounting for the majority (92,557) of the fatalities.<sup>12</sup>

There are an additional 41 million adults aged 40-74 who are considered to be pre-diabetic. There is evidence to suggest that chronic inflammation may play a role in converting these pre-diabetic individuals to diabetics, and there are criteria for testing for diabetes in asymptomatic adult individuals (Table 2).<sup>7</sup> The presence of significant periodontitis with no evident risk factors (eg, smoking or poor oral hygiene) can sometimes be a sign that systemically the patient may have an underlying disease such as diabetes.

Dentists should be very suspicious of rapidly progressing cases of periodontitis with no apparent risk factors. Risk assessment needs to be conducted on a regularly basis because a patient's risk will change based on environmental and systemic factors. Suspicious cases of periodontitis should be referred from the dentist/hygienist to a physician for evaluation of underlying systemic contributions, such as those seen in diabetics.

## PERIODONTITIS

The [link](#) between periodontal and systemic health is a two-way street, particularly when it comes to periodontitis and diabetes mellitus. A number of systemic diseases and conditions can increase a patient's susceptibility to periodontitis, with significant data supporting the contribution of diabetes mellitus. Furthermore, poor metabolic control of diabetes may not only make an individual more susceptible to developing periodontitis but can lead to more aggressive periodontitis once it has developed. However, it is generally accepted that adults whose diabetes is well-controlled do not have more destructive periodontitis than non-diabetics. Conversely, periodontal infections can have an impact on systemic health, particularly for diabetes, where untreated periodontitis can impede metabolic control. Periodontitis can impair a diabetic's ability to process and/or utilize insulin, which obviously leads to less optimal diabetic control. To prevent this vicious cycle of events from occurring, it is important for diabetics to be aware of their periodontal status.

Understanding the pathway to periodontitis is important to understanding these connections because it helps health-

**TABLE 2:**  
**Criteria for testing diabetes in asymptomatic adult individuals**

1. Testing for diabetes should be considered in all individuals at age 45 years and older, particularly in those with a BMI 25 kg/m<sup>2</sup>\* and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI 25 kg/m<sup>2</sup>\*) and have additional risk factors, such as:
  - are habitually physically inactive
  - have a first-degree relative with diabetes
  - are members of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
  - have delivered a baby weighing > 9 lb or have been diagnosed with GDM
  - are hypertensive (≥ 140/90 mmHg)
  - have an HDL cholesterol level < 35 mg/dl (0.90 mmol/l) and/or a triglyceride level > 250 mg/dl (2.82 mmol/l)
  - have PCOS
  - on previous testing, had IGT or IFG
  - have other clinical conditions associated with insulin resistance (eg, PCOS or acanthosis nigricans)
  - have a history of vascular disease

care professionals consider the possible mechanisms by which oral and systemic diseases—such as periodontitis and diabetes—are linked. It is the microbial challenge that initiates periodontal disease. The presence of endotoxins, antigens, and other virulence factors stimulate the host immuno-inflammatory response. Neutrophils are recruited to the site of infection to address the pathogenic microbes, which invokes an antibody response. In more resistant individuals, the development of gingivitis is observed, but without the breakdown of the bone and connective tissue that's seen in periodontitis. However, in susceptible individuals, very high levels of proinflammatory mediators, known as cytokines and prostanoids, as well as enzymes such as matrix metalloproteinases, will be secreted into the tissues. These are the factors that lead to connective tissue destruction and bone metabolism changes. In the clinical setting, this presents as the sign of periodontal disease: increases in probing pocket depths, loss of clinical attachment, and radiographic evidence of bone loss. Unfortunately for diabetic patients, their diabetic condition leads to an overproduction of proinflammatory mediators, which in turn can cause more aggressive periodontal disease.

Diabetics may also experience decreased or diminished flow of saliva and increases in sugars in the saliva and the fluid between the teeth and gums, known as gingival crevicular fluid. All of these factors can lead to increased plaque and calculus formation, thereby increasing the chance of not only developing periodontal disease but also a higher risk for caries. Xerostomia or dry mouth can also contribute to the development of candidiasis (eg, burning mouth and tongue). The administration of anti-fungal agents may be necessary for the management of candidiasis. The management of oral burning symptoms can include the maintenance of adequate oral hydration and restrictions on the intake of caffeine and alcohol.

In addition, preventive measures for infection and delayed wound healing need to be taught at all levels because diabetics are at greater risk for infection, and delayed wound healing is a well-known complication of diabetes. Preventive measures include frequent dental visits to assess plaque control, risk assessment profiles to identify

risk—particularly preoperatively, as well as postoperative antibiotic therapy, if necessary, and the avoidance of compounding risk factors such as smoking.

### THE SYSTEMIC IMPACT OF ORAL INFECTION AND INFLAMMATION IN DIABETES

The surface area of the pocket epithelium is estimated to be the equivalent of the surface area of the palm of one or even two hands, depending on the severity of periodontal disease.<sup>13</sup> In a poorly controlled diabetic patient, the extent of the oral challenge to the patient once identified may be clearly evident (Figure 2). If a patient had an equivalent challenge anywhere else on the body, such as a non-healing ulcer on the leg of a diabetic patient (Figure 3), it certainly would be of concern as it is easily visible. A bacterial infection of the gingival tissues and the ensuing inflammation resulting in periodontitis can complicate the management of diabetes in the same manner as any other unresolved infection in the body, such as a chronic foot ulcer.

Periodontal disease is very often a silent disease, with few obvious signs and symptoms, similar to type 2 diabetes. Periodontitis, if left untreated, often increases in severity, making it a leading cause of adult tooth loss in the United States. Juvenile diabetic patients are just as susceptible to periodontal disease as adult diabetics. Early detection could prevent unnecessary tooth loss.

Individuals with diabetes who have periodontal disease are more prone to develop abscesses or areas around certain teeth that, in addition to being inflamed and infected, may swell and become painful. Periodontitis must be treated regularly through professional care to halt the progress of the disease and prevent tooth loss. Just as a patient works closely with their physician to monitor the status of their diabetes to keep it under control, so too must they work closely with their dentist to monitor their periodontal status, which may have a significant impact on the control of their diabetes.

It is important for dental practitioners to explain the dangers of a hidden oral infection not only to their patients but also to physicians. Many physicians are often unaware of the significant challenge that oral infection and inflammation can



**Figure 2** Dentition of a diabetic with poor metabolic control.



**Figure 3** Non-healing ulcer in a diabetic with poor metabolic control.

present to the entire body. If periodontitis is left untreated, bacteria will eventually enter the bloodstream, attracting platelets and putting patients at greater risk for a number of systemic diseases, including CVD, which is the number one killer of people with diabetes.<sup>12</sup> The systemic exposure to periodontal pathogens is a result of the loss of the epithelial integrity within the periodontal pockets in people with periodontal disease, allowing for bacterial penetration into the tissues and eventually the blood stream, resulting in a bacteremia. Recurrent transient bacteremias can occur every time a person with untreated periodontitis eats.

Oral pathogens have been found throughout the body, even in atheromatous plaques.<sup>14</sup> Endotoxins from these pathogens can also penetrate into the tissues, resulting in endotoxemia. In addition, many of the proinflammatory mediators present in patients with periodontitis can be found not only locally within the gingival crevicular fluid—flowing out of their pockets—but also within the gingival tissues, alveolar bone, and eventually in the blood stream, resulting in systemically elevated levels of interleukins (IL-1 and IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and prostanoids. When there is gingival inflammation, there is much more vascularity in these tissues and, therefore, a

greater chance for bacteremia and endotoxemia to occur, and more chances for the inflammatory mediators to enter into the bloodstream. Once all of these factors are introduced into systemic circulation, they can have a profound effect on the patient, particularly the diabetic patient, leading to insulin resistance and resulting in difficulties in achieving metabolic control of the diabetes.

### PERIODONTITIS, C-REACTIVE PROTEIN (CRP), AND DIABETES

The persistent chronic inflammation related to untreated periodontitis ultimately results in elevations of the systemic inflammatory marker CRP that is produced by the liver in response to bacterial challenge and chronic inflammation.<sup>15-19</sup> High sensitivity or hsCRP is one of the best indicators for risk of CVD and, along with cholesterol levels, provides the most accurate risk assessment for future cardiovascular events.<sup>20</sup> Regarding CVD risk, a cross-sectional study of 3,873 subjects from the National Health and Nutrition Examination Survey (NHANES) reported odds ratio for CVD of 1.99 (95% CI 1.10-3.59) for subjects without diabetes with high CRP levels.<sup>21</sup> For those with diabetes and low CRP levels, the reported odds ratio for CVD jumped to 3.21 (1.27-8.09). Finally, the data demonstrate that the likelihood of CVD was highest in those with diabetes and either intermediate or high CRP levels, with reported odds ratios for CVD of 6.01 (2.54-14.20) and 7.73 (3.99-14.95), respectively.

The Insulin Resistance Atherosclerosis Study (IRAS) provided evidence demonstrating that inflammation is associated with insulin sensitivity, even in patients without diabetes.<sup>22</sup> The study found a strong independent association between the levels of CRP and insulin sensitivity. Higher levels of CRP are associated with a greater degree of insulin resistance. Serum concentrations of CRP and other markers of inflammation were significantly related to the development of type 2 diabetes in 1,047 non-diabetic subjects followed for 5 years in the IRAS.<sup>23</sup> The IRAS investigators concluded that chronic inflammation has emerged as a new risk factor for type 2 diabetes. In the context of this paper, this could imply that untreated periodontitis, which is a well-known chronic

inflammatory condition, might increase a person's risk for the development of type 2 diabetes. Therefore, future studies should be designed to address this issue, and appropriate management of chronic oral inflammation in patients should be a priority for all dental professionals.

### METABOLIC CONTROL (HbA1c) AND PERIODONTITIS

Prospective randomized clinical trials such as the Diabetes Complication and Control Trial (DCCT)<sup>4</sup> and the U.K. Prospective Diabetes Study (UKPDS)<sup>24,25</sup> found that improved control of blood glucose reduces the risk of a number of long-term complications, particularly retinopathy, nephropathy, and neuropathy. The potential for intensive glycemic control to reduce CVD is emerging, as supported by epidemiological studies<sup>4,24-28</sup> and a meta-analysis<sup>29</sup> but has not yet been demonstrated in a randomized clinical trial. The major marker of metabolic control for physicians is the level of glycosylated hemoglobin (HbA1c), which is a long-term marker of control measuring the patient's average glycemia over the past 2 to 3 months<sup>30</sup> (unlike blood glucose, which fluctuates daily and as we eat). HbA1c levels of 4% to 6% are normal; < 7% is considered good diabetes control; 7% to 8% is moderate control; and with > 8%, action is suggested to improve control. Clinical Practice Recommendations of the American Diabetes Association for the Standards of Medical Care in Diabetes<sup>7</sup> suggest that the A1c goal for patients in general is < 7%, but that for the individual patient, < 6% is preferred if this can be accomplished without significant hypoglycemia. The less stringent goals are for patients with a history of severe hypoglycemia, patients with limited life expectancies, very young or old individuals, and those with comorbid conditions. Aggressive glycemic management may reduce morbidity in patients with severe acute illness, perioperatively, following acute myocardial infarction, and in pregnancy.

It is the primary objective of most physicians to keep these levels low to prevent long-term complications. HbA1c testing is recommended at least twice a year for patients with stable glycemic control and quarterly for those not meeting glycemic goals.<sup>7</sup> It is interesting that similar recommendations exist for periodontal

maintenance visits for patients who are well-controlled versus those who require more careful monitoring. The use of point-of-care testing for HbA1c enables timely decisions on therapy changes, when needed, which may not only apply to physicians but also dental practitioners considering more invasive surgical procedures.

Poorly controlled diabetic patients are at greater risk for developing periodontitis and, for this reason, the patient's physician should be contacted to determine the level of the patient's glycemic control and help the poorly controlled patient achieve better control of his or her diabetes in order to facilitate an optimal response to periodontal therapy. Patients who are unable to control their diabetes are much more difficult for dental professionals to manage and may require the use of adjunctive therapeutics, in addition to traditional mechanical therapy, such as either systemically administered or locally applied antimicrobials and/or host modulatory therapy, as part of the treatment regimen. The consequence of poor periodontal management of a diabetic patient is that an unresolved infection and a significant proinflammatory response can lead to insulin resistance, making it difficult for the diabetic patient and their physician to achieve optimal glycemic control. In the future, dentists will most likely develop a closer relationship with physicians to monitor patients for changes in oral health. Improvements in biochemical diagnostics for periodontitis might allow physicians, nurses, and even patients to send samples to a centralized laboratory for evaluation and preliminary detection of periodontal inflammation and breakdown, with subsequent referral to the oral health care provider for a complete oral evaluation and treatment.

### THE IMPORTANCE OF MANAGING PERIODONTAL DISEASE IN THE DIABETIC

Two studies have demonstrated that diabetic subjects with severe periodontitis are at greater risk for developing nephropathy and CVD which can both affect mortality in this patient population. Thorstenson et al<sup>5</sup> in an 11-year follow-up of subjects demonstrated that diabetics with severe periodontitis had a greater prevalence of proteinuria indicative of nephropathy and a greater number of

cardiovascular complications. These oral-systemic connections in diabetics have been confirmed most recently by Saremi et al,<sup>14</sup> who reported that periodontal disease is strongly predictive of mortality from ischemic heart disease and diabetic nephropathy in a population of Pima Indians with type 2 diabetes. In an 11-year follow-up, the age and sex-adjusted death rates of the type 2 diabetics increased with their severity of periodontitis. There is no doubt that optimal oral health is essential to the medical management of the diabetic patient.

### PRACTICAL STEPS FOR THE DENTAL PROFESSIONAL

Instructions to diabetic patients on how to help prevent or keep periodontal disease under control should include twice daily brushing and flossing at least once a day to remove the bacterial plaque from the teeth. The use of powered toothbrushes may be necessary, and mouth rinses or toothpastes with antiseptic agents may be recommended as adjuncts to mechanical plaque removal to provide optimal home care. Triclosan is present in a toothpaste (Colgate® Total®), currently available in the United States. Triclosan is a substantive antibacterial agent that adheres to the oral mucosa and hard and soft tissues for up to 12 hours. It is approved by the FDA and accepted by the ADA for treatment of gingivitis, plaque, caries, calculus, and oral malodor. Placebo controlled studies in higher risk subjects such as smokers<sup>31</sup> and subjects with recurrent periodontitis<sup>32</sup> suggest that an oral hygiene regimen including a triclosan/copolymer dentrifice may sustain the short-term effect of non-surgical therapy in smokers and improve healing after non-surgical treatment of recurrent periodontitis, as measured by improvements in gingival inflammation, probing depths, and probing attachment levels. Triclosan in vitro has anti-inflammatory effects inhibiting cytokine (IL-1 $\beta$  and TNF- $\alpha$ ) stimulated production of prostanoids (PGE2) from monocytes and reducing the activity of an enzyme, cyclooxygenase (COX-2), which is responsible for the production of prostanoids in culture, as well as inhibiting bone resorption in a parathyroid-hormone-induced release of calcium from bone cultures.<sup>33</sup>

Regular visits to the dentist are necessary to assess the patient's periodontal

status and to determine the frequency needed for professional cleanings to remove any plaque missed and to remove and prevent calculus from forming that can no longer be removed by home care. Assessment of all risk factors for periodontitis with risk reduction strategies is important for the optimal management of the diabetic patient. This is especially true of smoking, which is not only a significant risk factor for periodontal disease but also for CVD, which has an increased risk for mortality in diabetics. Smoking cessation should be encouraged. Eating a balanced diet, weight loss strategies, exercise, and compliance with medical and dental treatments should be encouraged to maintain control of blood glucose levels, since this will help the patient to be more resistant to periodontal infection and promote improved wound healing and therapeutic responses.

If the patient visiting the dental practitioner has been diagnosed with periodontitis, appropriate treatment should be initiated as soon as possible to control or prevent further destruction of tooth-supporting tissues and tooth loss. The most common procedure to reduce the bacterial load is scaling and root planning (SRP). Depending on the severity of a patient's condition, they may need more visits and the use of a local anesthetic. Another consideration may include the adjunctive use of systemic antimicrobial agents or the adjunctive use of locally applied antimicrobials, such as Arestin®, Atridox® or PerioChip®. More advanced cases may require a surgical therapy, which should be preceded by optimal metabolic control because the healing response is critical for optimal post-surgical responses.

The first case series to demonstrate that periodontal therapy could affect glycemic control in people with diabetes was published in 1960.<sup>34</sup> This report indicated that type 1 diabetics with periodontitis had a reduction in required insulin doses following a variety of therapies: SRP, localized gingivectomy, selected tooth extraction, and systemic use of antibiotics. A recently published meta-analysis<sup>35</sup> of 10 intervention trials including 456 patients revealed that periodontal therapy resulted in a decrease in absolute HbA1c of ~0.4% and that the addition of systemic antibiotics resulted in an average absolute reduction of 0.7%.

In addition to reducing the bacterial challenge, another important treatment modality, known as host modulatory therapy, involves reducing the levels of proinflammatory mediators and inhibiting the enzymes that are destroying the periodontal tissues. To date, the only available adjunctive medication aimed specifically at modulating the host response is a pharmaceutical product called Periostat® (a subantimicrobial dose of doxycycline hyclate). Studies have shown that when used during and after SRP, Periostat significantly improved the result of the standard treatment, helped to prevent further progression of the periodontal disease, and resulted in less tooth loss. Although the initial studies did not include diabetic patients, recently reported pilot clinical studies using this two-pronged approach in the treatment of diabetic patients demonstrated similar clinical results,<sup>36</sup> with improvements in the diabetic control of patients as assessed by significant reductions in HbA1c levels.<sup>36,37</sup> It is interesting to note that this same dental host modulatory therapy was used in a pilot medical trial to assess its usefulness as an agent to prevent acute coronary syndromes.<sup>38</sup> In this study it significantly reduced systemic levels of the cytokines IL-6, consequently reducing hsCRP levels, and it also inhibited the enzymes responsible for the disruption of atheromatous plaques.

### CONCLUSION

Periodontitis is the sixth complication of diabetes, an important risk factor that needs to be controlled in order to improve overall health. It is known that the more complications a diabetic individual may have, the more likely they are to develop other complications of diabetes. Periodontitis has been linked to other well-known complications such as retinopathy,<sup>4</sup> angiopathy,<sup>39</sup> and nephropathy.<sup>40</sup> A recent study in type 2 diabetics has linked periodontitis to mortality in diabetic patients from nephropathy and CVD.<sup>5</sup> Just as physicians closely monitor diabetic patients for control, compliance, and overall systemic health, it is incumbent upon dental care providers to do the same because periodontal disease can be monitored and controlled with careful attention to home care and regular visits to the dentist who, with newly developed

treatments, can manage periodontal disease better than ever before.

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# Working Together to Manage Oral-Systemic Conditions

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## ABSTRACT

*Evidence for oral disease as a risk factor for systemic disease has been increasing in the last decade. Relationships between oral health and cardiovascular disease (CVD), diabetes, pulmonary disease, adverse pregnancy outcomes, and Alzheimer's disease and dementia have been noted. Given these relationships, oral health care providers must consider approaches that foster comprehensive care, including risk assessment, patient education, and updated treatment protocols. This article discusses guidelines for treating individuals at risk for or who present with systemic conditions. Particular emphasis is placed on those with CVD and diabetes.*

## INTRODUCTION

The relationship between periodontal inflammatory disease and systemic diseases such as cardiovascular disease (CVD), diabetes mellitus (DM), respiratory disease, adverse pregnancy outcomes, and Alzheimer's disease and dementia has been examined.<sup>1-28</sup> The basis for the biological mechanism of this relationship is beginning to emerge. Research has demonstrated that the association between oral inflammation and systemic inflammation may be the key to understanding the significant and deleterious effects on multiple organ systems.<sup>29</sup> Although further study is indicated to determine whether or not a causal relationship exists, current

understanding is that when periodontal treatment is performed and clinical inflammation decreases, the serum levels of inflammatory mediators also decrease.<sup>30</sup> Therefore, improvement in oral health may offer improvement in total health.

Given the connections between oral health and systemic conditions such as CVD and DM, dentists and dental hygienists have an opportunity to reframe their practice to provide comprehensive care utilizing principles of oral medicine. Based on a recent forum concerning oral health and systemic health, a consensus statement has been developed that defines opportunities for knowledge transfer from

research to practice, collaborations among health care providers, and treatment considerations.<sup>31</sup> In addition, both the American Dental Hygienists' Association (ADHA) and the American Academy of Periodontology (AAP) have recently published clinical practice guidelines and referral guidelines for managing patients with periodontal diseases, respectively.<sup>32-33</sup> These documents provide the foundation for promoting dental and dental hygiene care that is based on current and relevant scientific evidence and a process focused on collaborative patient-centered care.

## COMPREHENSIVE ASSESSMENT

Providing comprehensive treatment for patients with oral and systemic diseases begins with thorough assessment procedures. This assessment should include a medical history, vital signs, risk factor identification, and clinical examination using a variety of screening and diagnostic procedures.

With respect to the medical and dental histories, many forms are available for use. However, they tend to be limited in terms of delineating details related to systemic conditions. For example, some popular forms have only one question related to DM. Simply asking a patient if he/she has DM and which type is insufficient for identifying and documenting the parameters of this condition. Further, this question does not help to identify the 33 million individuals in the United States who have either DM or prediabetes but are unaware they have these conditions. A review of systems is recommended to allow for specific questioning about each major body system, including integumentary, immune, respiratory, cardiovascular, gastrointestinal, genitourinary, endocrine, musculoskeletal, neurologic,

**GIVEN THE CONNECTIONS BETWEEN ORAL HEALTH AND SYSTEMIC CONDITIONS, DENTISTS HAVE AN OPPORTUNITY TO PROVIDE COMPREHENSIVE CARE UTILIZING PRINCIPLES OF ORAL MEDICINE.**

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**TABLE 1:**  
**Review of Systems Medical History Form**

**GENERAL INFORMATION**

- change in appetite  weight gain / loss  fatigue  chills  fever  sweats  "feeling sick"  
 other (specify)

**SKIN**

- itching  rash  hives  bruise easily  psoriasis  bleed easily  skin cancer  
 varicose veins  skin discoloration  poor wound healing  dryness  flushing  excessive perspiration  
 changes in nail beds  unusual hair distribution  changes in color of skin  other (specify)

**IMMUNE SYSTEM**

- seasonal allergies  hives or rash  persistent infections  HIV exposure  cancer  other (specify)

**EARS, NOSE, MOUTH, THROAT**

- hearing problem  ringing in ears  discharge from ears  nose bleeds  difficulty swallowing  nasal congestion  
 hoarseness  sore throat  other

**EYES**

- wear glasses  blindness  cataracts  glaucoma  vision loss  "halos" around eyes  double vision  discharge  
 eye irritation or pain  light sensitivity  other (specify)

**RESPIRATORY**

- asthma  wheezing  shortness of breath  frequent coughing  sleep disturbances due to breathing  
 coughing up blood  excessive sputum  chest discomfort  excessive snoring  other (specify)

**CARDIOVASCULAR**

- high blood pressure  heart attack  chest pains  blood clotting disorder  difficulty breathing at night  
 racing/skipping heart beats  shortness of breath with exertion  difficulty breathing while lying down  
 bluish discoloration of lips or nails  near fainting  fatigue  palpitations  fainting  weight gain  lightheadedness  
 swelling of hands or feet  leg cramps with exertion  other (specify)

**GASTROINTESTINAL**

- frequent nausea  indigestion  heartburn  vomiting  diarrhea or constipation  
 hemorrhoids  blood in stools  difficulty controlling bowels  excessive appetite  loss of appetite  
 yellowish skin color  bloating  change in bowel habits  nausea  gas  indigestion  abdominal pain  
 other (specify)

**GENITOURINARY**

- pain or burning with urination  frequent urination  blood in urine  kidney stones  difficulty controlling urine  
 enlarged prostate  venereal disease  pelvic infection  irregular periods  painful periods  post menopause  
 pregnant  vaginal discharge  lack of sexual drive  unusual urinary color or smell  inability to empty bladder  
 excessively heavy periods  blood in urine  genital sores  missed periods  other (specify)

**ENDOCRINE**

- diabetes  enlarged thyroid  hyperthyroid  hypothyroid  steroid use  heat intolerance  weight change  
 cold intolerance  excessive thirst  excessive hunger  excessive urination  other

**MUSCULOSKELETAL**

- difficulty walking  arthritis  deformities  gout  osteoporosis  joint pain  joint swelling  stiffness  back pain  
 muscle aches or cramps  presence of joint fluid  muscle weakness  loss of strength  other

**NEUROLOGIC**

- frequent headaches  seizures  dizziness  memory loss  fainting  paralysis  stroke  balance problems  
 speech problems  coordination problems  numbness or tingling  tremors  difficulty with concentration  
 falling down  visual disturbances  sensation of room spinning  excessive daytime sleeping  other (specify)

**PSYCHIATRIC**

- nervousness  difficulty sleeping  depression  considered suicide  anxiety  emotional problems  
 thoughts of violence  sense of great danger  frightening visions or sounds  other (specify)

**BLOOD OR LYMPHATIC**

- anemia  bruise easily  swollen lymph nodes  reaction to blood transfusion  fevers  skin discoloration  
 bleeding  other (specify)

Please detail any other problems or concerns as well as symptoms and treatment associated with medical conditions:

psychiatric, and blood or lymphatic systems (Table 1).

In addition, risk factor assessment for CVD and DM should be performed routinely. Risk factors for CVD include modifiable and non-modifiable components. Non-modifiable risk factors are age, sex, and family history of premature CVD. Modifiable risk factors include smoking, blood pressure control, blood lipid management, physical activity, dietary intake, weight management, diabetes management, and C-reactive protein level. There also are multiple risk factors for DM.

Risk factor forms for CVD and DM can be provided to patients either prior to their appointment or when they arrive (Tables 2 and 3). Each form requires little time to complete and provides the clinician the opportunity to begin discussion of the oral health-systemic health relationship.

Once risk factors are identified, the dental hygienist or dentist can begin to develop a treatment plan and patient education program that includes parameters for risk factor modification. Lifestyle changes such as weight loss, smoking/alcohol cessation, and exercise may be recommended. In addition, medication management and methods for improving oral health and lowering serum inflammatory markers can be discussed.

Next, a comprehensive oral health assessment should be completed that consists of a head and neck examination, intraoral and extraoral examination, and dental and periodontal examinations. Depending on clinical findings, radiographs and other diagnostic tools may be indicated. Once these assessments have been performed, the oral health provider can create a picture for the patient that compares the oral health findings with systemic health findings. This information can be used for further treatment planning and patient instruction.

In some cases, referrals to other providers may be indicated. If the patient presents with a significant history of heart disease or risk factors for DM, it is important to refer that individual for further evaluation. Referrals can be made to a family physician or nurse practitioner, diabetes educator, wellness center, or to other specialists as appropriate, including cardiologists, endocrinologists, and pharmacists. Sending a formal referral

## TABLE 2: Risk Assessment for Cardiovascular Disease

This risk assessment is designed to identify patients who are at risk of developing Cardiovascular Disease. If two or more risk factors are identified, refer the patient to an appropriate medical provider for further evaluation. Use only as a screening tool and not to make a diagnosis of cardiovascular disease.

1. Age? \_\_\_\_\_ higher risk: Women >55 yrs, Men >45 yrs
2. Do you smoke or live or work with others who smoke tobacco daily?
3. Have you been told your blood pressure is too high (>140/90mm Hg)?
4. Is your cholesterol level 240 mg/dL or higher?
5. Is your diet high in saturated fats, trans fat and/or cholesterol?
6. Is your fasting blood sugar level 126 mg/dL or higher?
7. Do you have diabetes or have a family history of diabetes?
8. Are you or have you ever been under care for heart problems?
9. Do you have a family history of heart disease?
10. Are you fairly inactive? Do you exercise fewer than 3 times a week?
11. Are you overweight according to the Body Mass Index?

Adapted from: Risbek CA. Case study: identifying risk factors for systemic disease. Access. 2004;18:20-25.

## TABLE 3: Risk Assessment for Diabetes Mellitus

To find out your risk for type 2 diabetes, check each item that applies to you:

- Age greater than 45 years
- Obesity
- Family history of type 2 diabetes
- Racial descent
- History of GDM or a history of delivering a baby > 9 lbs.
- History of impaired glucose tolerance or impaired fasting glucose
- Hypertension (>140/90)
- Dyslipidemia (HDL cholesterol < 35mg/dL or triglyceride level >250mg/dL)
- History of cardiovascular disease
- Inactivity, exercises < 3x/week
- Other clinical conditions associated with insulin resistance (acanthosis nigricans)
- Polycystic Ovary Syndrome (PCOS)

(If there are two or more risk factors, refer to a medical provider for further evaluation.)

Adapted from: National Diabetes Information Clearinghouse. National Institute of Diabetes and Digestive and Kidney Diseases.

Am I at risk for type 2 diabetes? Taking steps to lower your risk of getting diabetes. Accessed October 2, 2006 at <http://diabetes.niddk.nih.gov/dm/pubs/riskfortype2/index.htm>.

**THE ORAL HEALTH PROVIDER CAN CREATE  
A PICTURE FOR THE PATIENT THAT  
COMPARES THE ORAL HEALTH FINDINGS  
WITH SYSTEMIC HEALTH FINDINGS.**

**TABLE 4:**  
**Sample Referral Letter for Patients with Cardiovascular Disease**

Dear Dr. **(Physician name)**:

**(Patient name)** is a mutual patient who was examined in my office on (date) and a diagnosis of **(diagnosis to include extent [localized or generalized] and severity [slight, moderate, or advanced loss of periodontal support])** was determined.

As you know, **(patient name)** has a history of **(cardiovascular disease [CVD], risk factors like smoking, familial history of CVD, hypertension, high LDL cholesterol, low HDL cholesterol, diabetes, obesity, physical inactivity, stress, alcohol)**. For your perusal, I have taken the liberty of attaching a list of published articles that, when considered collectively, appear to indicate that moderate to severe periodontal disease and the associated bacteria play a role in elevation of the systemic inflammatory response and promote atherosclerosis. Obviously, this would make periodontal disease a risk factor in both cardiovascular and cerebrovascular disease.

**(Patient name)**'s periodontal therapy will involve **(list treatment like nonsurgical, surgical, or nonsurgical and surgical)** treatment modalities and adjunctive therapies that include **(list therapies adjunctive to instrumentation, such as locally applied antimicrobials, subantimicrobial dose doxycycline, systemic antibiotics)**. In addition, we have recommended counseling for **(list therapeutic counseling for risk reduction elimination like smoking cessation, stress management, and nutrition)** to help this patient eliminate, modify or reduce **his/her** risk for CVD and periodontal disease. To track this patient's periodontal status with their systemic health, I am requesting periodic confirmation of **(patient name)**'s level of diabetic control (ie, HbA1c values) and hsCRP values. If these laboratory tests have been performed on this patient within the last 2 months, I would appreciate receiving a copy of **(patient name)**'s lab report (patient signed release of information document is attached). If these tests have not been performed within the last 2 months, please advise me of such and I will order HbA1c and hsCRP tests and have copies of the results sent to your office.

Should you have any questions or concerns regarding **(patient name)**'s periodontal therapy or the possible interactions of **his/her** periodontal condition and systemic diseases, please feel free to give me a call at your convenience. I appreciate this opportunity to collaborate with you to provide **(patient name)** with comprehensive treatment that may preempt greater risk for any potential systemic consequences of periodontal disease.

Adapted from: Sample referral letter for patients with cardiovascular disease. *Grand Rounds*. Accessed September 10, 2006 at [www.thesystemiclink.com](http://www.thesystemiclink.com).

**IF THE PATIENT PRESENTS WITH  
 A SIGNIFICANT HISTORY OF HEART  
 DISEASE OR RISK FACTORS FOR DM,  
 IT IS IMPORTANT TO REFER THAT  
 INDIVIDUAL FOR FURTHER EVALUATION.**

letter to the medical practitioner is appropriate and should include references to justify the basis of the referral (Table 4).<sup>34</sup>

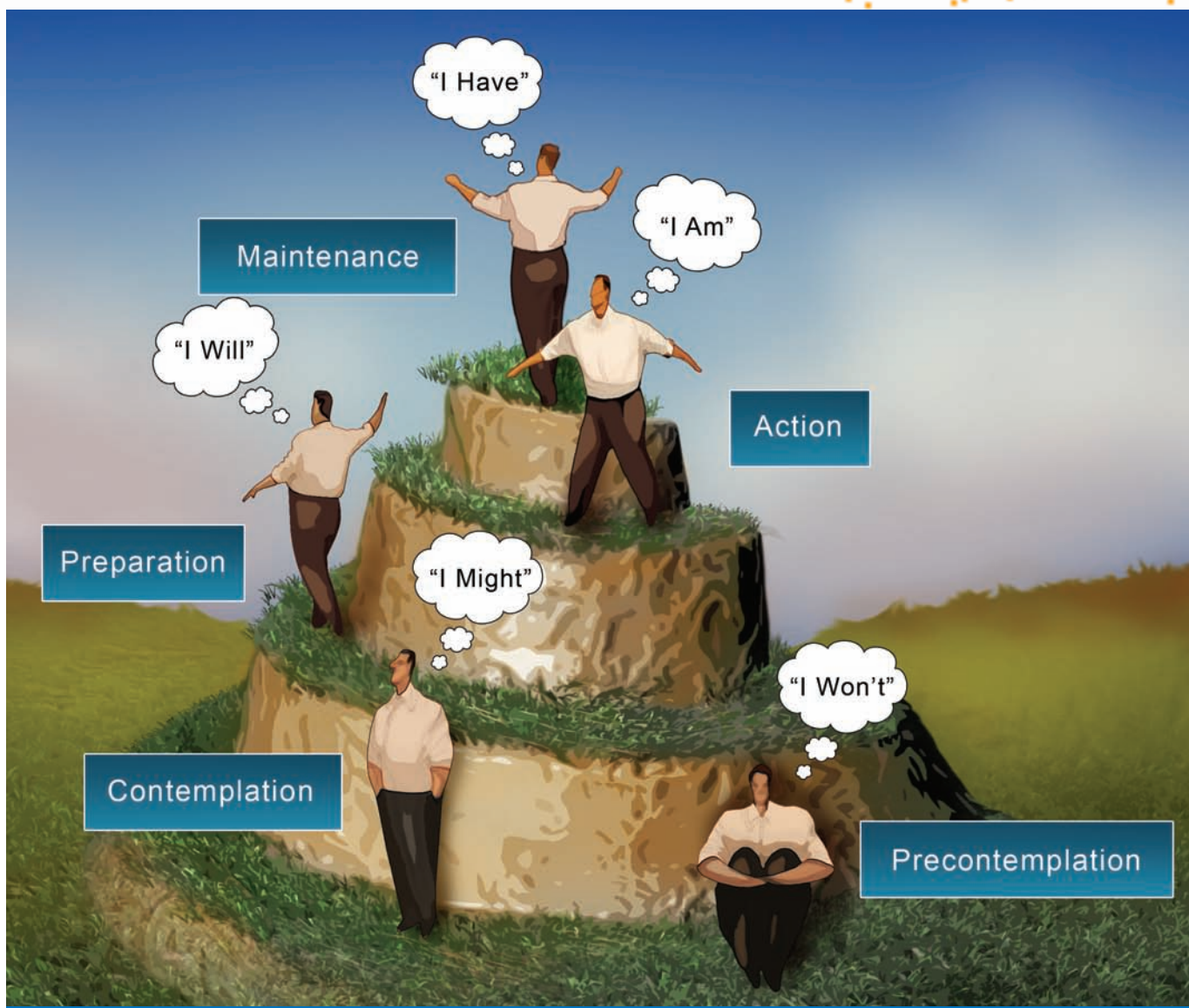
For those patients who present with systemic disease as well as challenging periodontal conditions, co-management with a periodontist may be appropriate. The AAP guidelines for the management of periodontal diseases include 3 referral levels for consideration.<sup>33</sup>

## PATIENT EDUCATION

Once the treatment plan has been developed, preventive education programs can be provided to the patient. Ideally, time should be devoted to discussing the patient's systemic and oral health and the connections between oral findings and risk factors for systemic disease. Daily brushing, interproximal cleaning, and use of a chemotherapeutic mouth rinse to reduce bacterial plaque and susceptibility to gingivitis should be proposed. Where appropriate, the dental hygienist or dentist may suggest nutritional counseling for healthy eating and weight loss, exercise, smoking cessation, medication management, and monitoring of blood glucose levels.

Products should be recommended based on sound research that documents safety and efficacy. While there are many products available, not all have received approval from the American Dental Association Council on Scientific Affairs (ADA Council). For example, Peridex® and Listerine® Antiseptic Mouth Rinse are the only 2 chemotherapeutic mouth rinses approved by this organization. Their effectiveness has been well established.

Similarly, it is important to recommend a toothpaste that will provide the most benefit to the patient. A dentifrice containing triclosan/copolymer (Colgate® Total®) has been shown to be effective in reducing plaque and gingivitis, controlling caries and bacterial infection, and preventing or slowing the progression of periodontal disease.<sup>35</sup> In addition, triclosan has been shown to possess anti-inflammatory properties. In vitro studies have demonstrated that triclosan has inhibited inflammatory mediators including prostaglandin, interleukin-1 (IL-1), and collagenases. The combined antibacterial and anti-inflammatory properties of triclosan are reasons to recommend



**Figure 1** Transtheoretical Model (Adapted from: Prochaska JO, Norcross JA, DiClemente CC. *Changing for Good*. New York: Avon;1994).

the use of Colgate® Total® to patients with periodontal diseases and those demonstrating compromised systemic health.<sup>36</sup>

It is important to recognize that not all patients will switch products to those recommended or embrace the advice offered for oral and general health improvement. Models exist that explain the change process and an individual's readiness to adhere to patient education recommendations. For example, the transtheoretical model provides a framework for appreciating behavior change (Figure 1). Developed by Prochaska and DiClemente,<sup>37-38</sup> this model of change recognizes that individuals move through consecutive and predictable stages. To successfully help a patient adopt a practice such as

flossing, exercising regularly, or checking blood glucose levels routinely, the oral health provider must assess which stage of change the patient is in and apply the necessary processes to help that person progress to the next stage. Listening carefully to the patient's feelings about readiness, importance, and confidence to make a change is critical to tailoring preventive education messages and interventions.<sup>39-40</sup> Likewise, it is important to recognize that the practice in which one works may not be ready to adapt to multiple changes that are components of practicing oral medicine. Providing comprehensive assessments, modifying treatment plans to incorporate improvement in systemic health, and promoting

total health—while ideal—may be difficult to accomplish if clinicians are at different stages of change in their practice philosophy.

### **GUIDELINES FOR PROVIDING CARE**

Patients who present with CVD or DM require particular attention during oral health care appointments. General recommendations for caring for patients with CVD and guidelines for providing care to individuals with DM can be helpful (Tables 5 and 6). Such care includes collaboration and consultation with other health care providers, preventive protocols to avoid emergency situations in the office, and treatment considerations.

**TABLE 5:**  
**Guidelines for Providing Oral Health Care to Patients with Cardiovascular Disease**

**Consult with cardiologist**

- Especially if recent history of Myocardial Infarction
- If taking anticoagulants
- If recent history of cardiovascular surgery
- Determine if patient is stable to receive oral health care
- Determine if antibiotic prophylaxis is indicated
- If taking warfarin or other anticoagulant therapy, discuss INR and need for dosage adjustments

**Take careful medical history**

- Note cardiovascular disease condition, treatment rendered, complications, medications used, interactions, and adverse effects of medications
- Determine if patient requires oxygen supplementation and/or premedication with nitroglycerin depending on circumstances
- Encourage patient to bring medications to appointment for accurate record documentation and potential emergency management

**Utilize stress reduction protocol**

**Seat patient in semi-reclined position if pulmonary edema is present**

**Monitor vital signs throughout appointment**

**Use caution with local anesthetics with vasoconstriction**

- Maximum of 2 carpules of local containing 1:100,000 epinephrine
- Use less potent vasoconstrictor if possible
- Avoid vasoconstrictors in patients who are taking digitalis preparations

**Avoid using gingival retraction cord with epinephrine**

**Allow patient to remain seated upright several minutes at completion of treatment to avoid hypotension**

**Evaluate patient for signs of xerostomia due to medications**

- Stress protocols for managing xerostomia, maintaining plaque control, and reducing caries risk

**Evaluate patient for gingival hyperplasia and bleeding, a common side effect of using calcium channel blockers**

**Stress importance of plaque control and frequent continuing care appointments to reduce periodontal inflammation and bacteremia; discuss role of inflammation in oral health and cardiovascular health**

**Advise patient to follow prevention protocols: blood pressure management, weight reduction, regular exercise, smoking cessation, psychological health, and prevention drug interventions**

For specific clinical recommendations for women, consult: Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation*. 2004;109:672-693 or at <http://circ.ahajournals.org/egi/content/full/109/5/672>. Accessed September 4, 2005.

Adapted from: Little JW, Falace DA, Miller CS, Rhodus NL. *Dental management of the medically compromised patient*. 6<sup>th</sup> ed. St. Louis: Mosby; 2002.

## CHANGING PRACTICE PARADIGMS

Implementing an oral medicine approach to care for patients with systemic challenges requires a change in practice philosophy and procedures. Consideration must be given to modifying appointment timeframes for these patients. Patients will require a longer initial appointment to allow for comprehensive assessment and treatment plan development. A re-evaluation appointment should be sched-

uled to assess improvement in oral health and determine whether or not further treatment is indicated. Further, a continuing care schedule should be individualized based on the patient's oral and systemic health. The 6-month "recall" will likely not be appropriate for many patients with systemic health conditions and significant periodontal problems. It is important for patients to recognize and value the additional time and attention being devoted to the health needs of these

patients. Therefore, the practice must consider the impact of this additional time and care investment and establish a fee that reflects the comprehensive assessment and treatment provided.

Additionally, oral health care providers must be prepared to promote health practices beyond the traditional brushing and flossing reminders. Key preventive messages to promote a healthy lifestyle and better manage systemic conditions should be offered (Table 7).

**TABLE 6:**  
**Guidelines for Providing Oral Health Care to Patients with Diabetes Mellitus**

**Front Office Staff Preparation**

- Prepare a telephone script to screen for diabetes and customize first appointment
- Advise patients to bring list of medications used, physician contact information, and arrive early to complete health history forms
- If ample time, mail forms in advance to patient
- Inform patient that initial appointments will be lengthy to allow for comprehensive examinations and education
- Offer morning appointments; schedule periodic breaks if long procedures planned

**Recognize early signs and symptoms of uncontrolled DM in an unsuspecting patient**

**Perform thorough medical history**

- Document medications taken
- Document frequency of blood glucose screenings and results
- Document frequency of hypoglycemic episodes

**Evaluate oral complaints/findings that appear due to abnormal neutrophil function, microangiopathy, and altered oral microflora:**

- Dry, burning mouth
- Gingival proliferation, gingivitis, periodontitis
- Abnormal wound healing
- Multiple carious lesions
- Candidal infection - denture sore mouth, angular cheilitis, median rhomboid glossitis
- Periodontal abscesses
- Acetone breath
- Increased salivary viscosity
- Asymptomatic parotid gland swelling

Based on above findings in known DM but uncontrolled, or suspected DM case, medical referral is warranted

**Frequent oral prophylaxis/debridement is needed to minimize periodontal infection**

- Periodontal infections should be managed aggressively with antibiotic therapy
- Cultures recommended
- Monitor wound healing and response to therapy
- Prophylactic antibiotics recommended for poorly controlled patients with DM
- Inform patient that periodontal treatment improves disease control

**Utilize stress reduction strategies**

- Patient may require additional insulin during appointment
- Short morning appointments are usually best
- If patient is taking insulin, know type, how often it's taken, and when peak insulin activity occurs to avoid hypoglycemia medical emergency
- If long appointment, allow for short break or snack
- Use semi-supine position if GI side effects are problematic

**Reinforce proper nutrition, exercise, medication regimens, monitoring of blood glucose, need for regular eye exams, foot exams, oral health exams, and medication management and review**

**Use local anesthetics containing vasoconstrictors with caution**

- Epinephrine antagonizes the action of insulin and in large doses can cause hyperglycemia
- Make certain patient has taken daily dose of insulin prior to treatment

**Monitor vital signs and evaluate for signs of hypoglycemia and insulin shock**

- Weakness, trembling, hunger, sweating, tachycardia, confusion, anxiety
- Progresses to combativeness and incoherence
- Leads to unconsciousness, sweating, hypotension, and hypothermia
- Treat with rapid administration of glucose; keep sugar source available chairside for hypoglycemia reversal
- If patient is taking alpha glucosidase inhibitors (Precose® or Glyset®), must use glucose, not sucrose or fructose

**Stress meticulous plaque control and regular periodontal maintenance appointments (every 1 to 2 months until well controlled); discuss relationship between DM and periodontal disease**

Adapted from: Vernillo AT. Dental considerations for the treatment of patients with diabetes mellitus. *JADA*. 2003;134:24S-33S.

Levin RP. How treating your patients with diabetes can enhance your practice: recommendations for practice management. *JADA*. 2003;134:49S-53S.

Gurenlian JR. Diabetes mellitus: overview and guidelines for providing oral health care. *Cont Oral Hyg*. 2001;1:14-16, 18-20.

Gurenlian JR. *Diabetes mellitus: strategies for providing comprehensive care*. Continuing Education for the Healthcare Professional (CEHP).

Distributed by Sullivan-Schein, a Henry Schein Company: Course reference #05AS2904; 2005.

When providing preventive and control messages, it is important to consider that not all messages can be delivered at one appointment. Messages should be prioritized and customized according to the patient's needs. Key messages can be offered in the form of computer generated

reminder notes or prescriptives that are handwritten. Further, the clinician should document which messages were provided and the patient's response.

To establish a broader base for communicating health prevention and control messages, the dentist and dental hygienist

can offer this information in office newsletters or health awareness programs for patients with particular systemic conditions. Oral health care providers also can establish a broad referral base that includes other health professionals such as optometrists, podiatrists, pharmacists, diabetes educators, nurse practitioners, endocrinologists, family practitioners, and cardiologists. These individuals may not be aware of oral considerations and connections with systemic diseases and may welcome the opportunity to collaborate and participate in continuing education programs, study clubs, and health awareness programs. Further, oral health professionals must develop a presence within the community to create greater awareness of the relationship between oral health and systemic health. Offering health education programs to the community, sponsoring wellness fairs, and conducting screening programs may help the public view dentists and dental hygienists as partners in promoting improved overall health.

**TABLE 7:**  
**Key Prevention Messages for Individuals with Diabetes**

#### EYE CARE

- Recent changes in eyesight: blurred vision, blindness, floaters, flashlights, signs of infections (red, painful eyes)
- Remind patient to seek annual dilated eye examination or immediate examination if above eye changes occur
- Remind patient to keep eye glasses/contact lens prescriptions current

#### FOOT CARE

- Remind patient to inspect feet daily for signs of infection of neuropathy (foot ulcers, redness, burning, tingling, numb or cold feet)
- Remind patient to have periodic exams (every 3 to 4 months) with foot care specialist and not to cut toe nails or self-treat foot problems
- Remind patients to remove their shoes every time they see a medical primary care provider

#### PHARMACY

- Take all medications as prescribed
- Ask the pharmacist if any prescribed medications, vitamins, or herbal products will affect diabetes

#### ORAL CARE

- Encourage patient to maintain daily mouth care, brushing teeth after eating to remove plaque and flossing at least once each day
- Remind patient to conduct a monthly self-examination and to contact the dental hygienist or dentist if they notice signs of infection, such as sore, swollen, or bleeding gums or mouth ulcers
- Encourage patient to eat healthy snacks, choosing foods that are low in sugar and fat
- Remind patients to have periodic dental and periodontal examinations, every 3 months or more frequently, as recommended by their oral health professional
- Encourage patients to achieve their best glycemic control possible; controlled diabetes improves oral health and maintaining good oral health helps to control diabetes

#### OTHER HEALTH MESSAGES

- Do not smoke or chew tobacco
- Have blood pressure and cholesterol checks performed regularly
- Exercise regularly
- Reduce stress
- Eat a healthy diet
- Get vaccinated to protect against pneumonia and flu

## CONCLUSION

As evidence continues to mount demonstrating a relationship between oral health and systemic health, dentists and dental hygienists have an opportunity to effect change in targeted population groups by focusing on early identification of disease and providing preventive interventions. Incorporating oral medicine in dental and dental hygiene practice may help to optimize treatment and improve outcomes for those patients with systemic health challenges.

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## Resources and References for Professionals & Patients

### ALCOHOL CESSATION

National Institute on Alcohol Abuse and Alcoholism  
[www.niaaa.nih.gov](http://www.niaaa.nih.gov)

### DIABETES

American Diabetes Association  
[www.diabetes.org/home.jsp](http://www.diabetes.org/home.jsp)

### Diabetes

[www.diabetesincontrol.com/index.php](http://www.diabetesincontrol.com/index.php)

### National Diabetes Education Program

<http://ndep.nih.gov>  
1-800-438-5383

### HEALTHY LIFESTYLE HABITS

American Cancer Society—  
Food and Fitness

[www.cancer.org/docroot/PED/ped\\_3.asp?sitearea+PED&level+1](http://www.cancer.org/docroot/PED/ped_3.asp?sitearea+PED&level+1)

American Heart Association—  
Healthy Lifestyle

[www.americanheart.org](http://www.americanheart.org)

### Healthy People 2010

[www.healthypeople.gov](http://www.healthypeople.gov)

National Institutes of Health—  
Wellness and Lifestyle

<http://health.nih.gov/search.asp/34>

### NUTRITION

American Dietetic Association  
[www.eatright.org](http://www.eatright.org)

### SMOKING AND SPIT TOBACCO CESSATION

American Cancer Society—  
Prevention and Early Detection  
[www.cancer.org/docroot/PED/PED\\_10\\_4\\_Great\\_American\\_Smokeout.asp](http://www.cancer.org/docroot/PED/PED_10_4_Great_American_Smokeout.asp)

Centers for Disease Control and  
Prevention—Tobacco Information  
and Prevention Source

[www.cdc.gov/tobacco/spit.htm](http://www.cdc.gov/tobacco/spit.htm)

National Spit Tobacco  
Education Program  
[www.nstep.org/index.htm](http://www.nstep.org/index.htm)

Smoking Cessation: Ask. Advise. Refer.  
[www.askadviserefer.org](http://www.askadviserefer.org)

### Quitline Information

[www.cancer.org](http://www.cancer.org)

### WEIGHT LOSS

Department of Health and Human  
Services—Aim for a Healthy Weight:  
Information for Professionals  
[www.nhlbi.nih.gov/health/public/heart/obesity/lose\\_wt/index.htm](http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/index.htm)

### OTHER RESOURCES

American Dental Association  
[www.ada.org](http://www.ada.org)

American Dental Hygienists Association  
[www.adha.org](http://www.adha.org)

National Institutes of Health  
[www.nih.gov](http://www.nih.gov)