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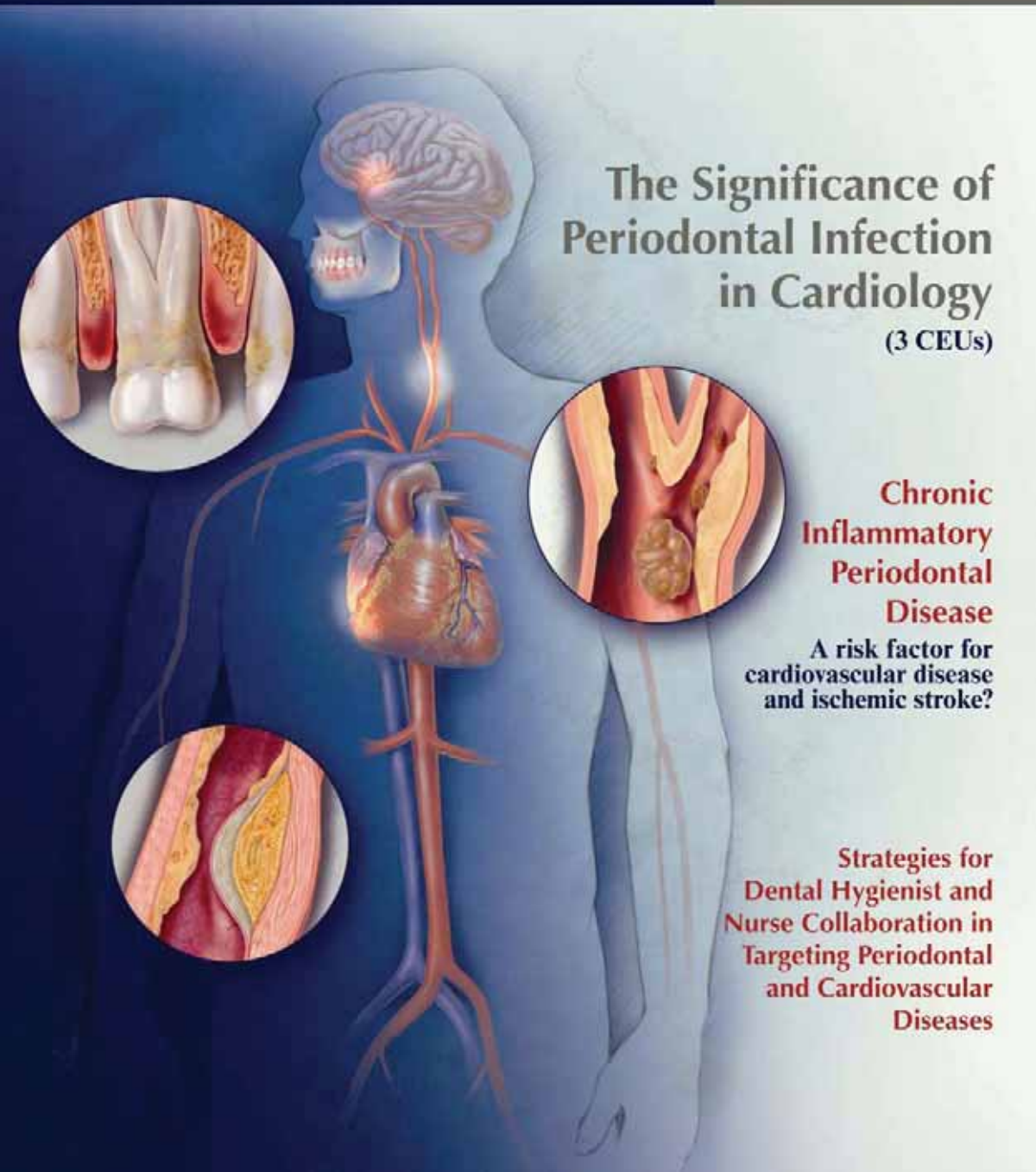

The Significance of Periodontal Infection in Cardiology
(3 CEUs)

Chronic Inflammatory Periodontal Disease
A risk factor for cardiovascular disease and ischemic stroke?

Strategies for Dental Hygienist and Nurse Collaboration in Targeting Periodontal and Cardiovascular Diseases

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THE SIGNIFICANCE OF PERIODONTAL INFECTION IN CARDIOLOGY

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Most of us have heard the refrain from an old song, “The ankle bone is connected to the leg bone.” Can we now sing, “The gums are connected to the heart?” As unlikely as this may sound, researchers and clinicians may have ample evidence to support this claim. Pilot intervention studies are now underway, but should we wait for those final answers before we consider periodontal disease as a risk correlate for CVD? And, if we move ahead now, how do health-care providers implement the current evidence?

Cardiologists and dental professionals appear to have a common enemy - chronic inflammation and its potential to accelerate the process of atherosclerosis, a widely recognized prelude to cardiovascular diseases. Science is beginning to revealthat destructive inflammatory periodontal diseases release substances that are involved in arterial wall inflammation, development of atherosclerosis, and rupture of established atheromas which result in myocardial infarction (MI) and stroke.[1,2] It is the atherosclerotic lesion that amplifies the risk for CVD.

Is human atherosclerosis an inevitability of aging? The hypothesis that human atherosclerosis is not an absolute consequence of aging and can be reversed was put forth in the 1980s by Malinow’s pioneering work aimed at halting the progression of atherosclerosis and promoting its regression.[3,4] Mounting evidence appears to strengthen Malinow’s hypothesis that old age may not necessarily equate to atherosclerosis. A recent study of more than 1,000 participants with a mean age of 73 found that for older adults, periodontal disease, which is one of the infections implicated as a cause of endothelial injury leading to atherosclerosis, is a modifiable risk indicator for elevated levels of systemic inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and hsCRP.[5] All three of these markers are widely recognized as being associated with periodontal infection.[6-8]The question becomes, “Could treatment of periodontal disease in patients both at an earlier stage and age translate into greater longevity?”

Challenges in Decreasing the Incidence and Severity of CVD -

More than 20 years have passed since Malinow tackled CVD. With an array of therapeutic strategies at hand, many health-care providers hoped that CVD would be eliminated by the end of the 20th century. At the beginning of the 21st century, despite cardiologists’ recommendations to patients for therapeutic lifestyle changes targeting classic risk factors - a diet restricted in calories to reach a body mass index of <25 kg/m^2; a waist circumference <105 cm in men and <90 cm in women; physical exercise, smoking cessation, and blood pressure control; and the widespread use of statins in treating hypercholesterolemia - CVD still accounts for 38% of all deaths in North America.[2] Largely because of its rapidly increasing prevalence in Eastern Europe and developing countries, and the obesity trends and rising incidence of diabetes in the West, coronary heart disease (CHD) is expected to be the main cause of death globally.[9] However, about half of patients presenting with MI do not have classic risk factors for CVD.[10] CVD was once thought of as a disease primarily induced by accumulation of lipid-laden cells. What we now know is that high cholesterol is important in only 50% of patients with coronary artery disease (CAD).[1] “Even with intensive statin therapy, the best current evidence-based treatment available, many patients will still have recurrent cardiovascular events.”[11] Although statin therapies have been successful for a large segment of the population, it appears that the medical community may need to pursue approaches beyond statins to modify the course of vascular diseases.[11]

Hardly daunted by the most progressive disease-management strategies, the prediction, prevention, and treatment of CVD represents one of the greatest challenges facing all of us in the health-care arena. This dismal revelation begs an important question: “If we are to implement the recommendations made by the Surgeon General in the Oral Health in America report,[12] already five years old, and achieve the target goals set by the Centers for Disease Control and Prevention,[13] should we include in risk assessments for CVD those factors associated but that, at present, are not proven to be causative, independent, or quantitative?

The answer may be “yes,” but this level of comprehensive care will require medical and dental professionals who are willing to champion this message and initiate models of collaborative care. The intervention trials necessary to prove a cause-and-effect relationship between periodontal disease and CVD are currently underway or about to be funded. Accumulation of that evidence will take years. In the meantime, do we not have enough evidence to support periodontal disease at least as a risk correlate for CVD?

The prevalence of both periodontitis and atherosclerosis is rampant. Periodontal disease is a “preventable [and treatable] contributor to the burden of cardiovascular disease,”[14] and as such, is a modifiable risk factor - a fact that may be escaping the attention of both medical and dental professionals. If only a marginal association between these two diseases is found, prevention and treatment of periodontal disease may

have an impact on the prevalence of CVD. It is not premature to include periodontal disease as a risk correlate for CVD, and failure to do so may forfeit an important therapeutic opportunity to reduce or eliminate a modifiable risk factor for CVD.

Quantifying Risk for CVD -

Table 1 on page 26 classifies various risk factors according to their quantitative association with CVD as elucidated by the Framingham Heart Study, which estimates risk for people without clinical manifestations of CVD. Scores derived from the Framingham risk assessment only apply to the primary prevention of CVD.[15] Once coronary atherosclerosis is clinically manifested, the risk for future coronary events is much higher than that for patients without CVD, regardless of other risk factors.[15]Therefore, the Framingham scores no longer apply.[15]

When considering the various risk factors for CHD (Table 1), it is important to understand that major risk factors are additive in predictive power in that total risk can be estimated by the summation of the individual risks related to each factor.[15]However, the major risk factors for CVD as identified in Table 1 do not account for all the variations in the incidence and severity of CVD. Accordingly, it is important to point out that other, less well documented risk factors for CVD may play a significant role.[16]

A strong argument may be made that periodontal disease should be considered both a predisposing and a conditional risk factor for CVD. Predisposing risk factors are agents that worsen independent risk factors.[15]The bidirectional relationship between periodontal disease and diabetes would seem to qualify periodontal disease as a predisposing risk factor for diabetic complications.[17-21] Conditional risk factors are associated with an increased risk for CVD, although their causative contributions to CVD have not been well documented.[15]Such is the case for the correlation between periodontal disease and increased risk for atherosclerosis. The presence of predisposing and conditional risk factors in the assessment of risk for CVD may confer greater risk than revealed from the summation of the major risk factors.[15]Although their contribution has not been quantified, this does not mean that they do not make an independent contribution to risk when they are present.[15]Accordingly, what may be left off this list of risk factors in Table 1 is the contribution of periodontal infection in accelerating atherosclerosis eventuating in CVD.

During the last 20 years there has been significant progress in understanding the link between periodontal infections and risk for CVD such as heart disease[22], stroke, and peripheral vasculature disease, all of which share atherosclerosis as a common feature.[16,23] Recent research found bacterial levels were elevated in only those patients with a history of myocardial infarction, suggesting that increased loads of subgingival bacteria present a danger for systemic health.[24]

The growing research to support the contribution of periodontal infection to the inflammatory burden is theorized to be through both a direct action on blood vessel walls, and by indirectly inducing the liver to produce acute phase proteins (e.g., CRP) (Figure 1).[25] Until recently, DNA footprints comprised the bulk of evidence suggesting that periodontal bacteria were directly involved in atherosclerosis. However, research at the University of Florida has demonstrated that Porphyromonas gingivalis (P. gingivalis) and Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans) are capable of adapting to the vasculature to live in human atherosclerotic lesions.[26] On the medical side, a study recently reported in the American Heart Journal found that periodontal disease is common in patients with MI and associated with elevated hsCRP levels typical of an enhanced systemic inflammatory response.[27] These associations were found to be independent of other contributing factors.[27] Other studies indicate an association between periodontal disease and elevated hsCRP and IL-6, and, conversely, that periodontal treatment lowered hsCRP and IL-6 with a simultaneous improvement in endothelial function.[28] As compelling as this research may be, the truth is that the evidence only supports, but does not prove, a causal association between periodontal disease and atherosclerosis-related diseases. Until this etiological mystery is decoded, we are faced with the dilemma of how to implement treatment strategies that are supported by the existing body of evidence.

Although a combination of risk factors may contribute to the progression of an atherosclerotic lesion, researchers now consider infection to be a significant inflammatory stimulus.[28] Inflammation is directly implicated in destabilization of atherosclerotic plaque in the carotid artery[1] and may lead to aneurism and embolism.[1] Seeding of live periodontal bacteria from the oral cavity to vessel walls,[26] a hyperinflammatory response to those periodontal pathogens,[29] and activation of proinflammatory mediators are three biological mechanisms implicated in the induction of a systemic inflammatory response.[26] This chain of events may describe the link between periodontal disease and CVD.

To fully understand the significance of periodontal disease in the cascade of events implicated in the formation of an atherosclerotic lesion, it is important that dental practitioners understand that infection is a well-established risk factor for atheroma formation and thromboembolic events.[16] To that end, discussion and illustration of the role of infection in the developing atherosclerotic lesion may help readers gain a more comprehensive understanding of this cascade of pathological events.

It is known that atherosclerosis is the main cause of CVD.[1,2] Possible causes of the endothelial dysfunction that lead to atherosclerosis include elevated and modified low density lipoprotein (LDL); free radicals caused by cigarette smoking; hypertension and diabetes; genetic alterations; and elevated plasma homocysteine concentrations.[1] Most germane are the studies that have also linked infection to atherosclerotic-induced diseases. What has become apparent is that several types of microbial pathogens may contribute to atherosclerosis, making it highly unlikely that a single microbe causes atherosclerosis.[2]It is now thought that the cumulative burden of infection at various sites is what affects the progression of atherosclerosis and its clinical manifestations of CVD.[2]

There are many studies to support the specific correlation of periodontal infection and atherosclerosis, and a few more recent pieces of evidence merit mention. Various studies have implicated P. gingivalis, a virulent periodontal pathogen, as part of a transient bacteremia that

can lead to the direct invasion of blood vessels.[30] In addition, P. gingivalis is implicated in several steps involved in the formation of the atherosclerotic lesion.[31,32] In 2003, it was reported that subjects with advanced periodontal disease exhibited endothelial dysfunction and evidence of systemic inflammation (elevated serum CRP levels), placing them at increased risk for CVD.[33] More recently, there is serological evidence that an infection caused by P. gingivalis increases the risk for MI; high P. gingivalis antibody levels have been shown to predict MI independently of classical cardiovascular risk factors,[34] and infection caused by major periodontal pathogens may be associated with future stroke.[35] Periodontal disease was found to be a treatable, independent risk factor for cerebral ischemia in male subjects (<60 years of age). Those with severe periodontitis had a 4.3 times greater risk of cerebral ischemia than subjects with mild periodontitis or healthy subjects.[36] Gingivitis and severe radiological bone loss were also independently associated with the risk of cerebral ischemia while tooth decay was not.[36]

A recent investigation demonstrated a direct relationship between microorganisms from periodontal infection and subclinical (undetected) atherosclerosis.[37] This relationship was found to be independent of hsCRP.[37]The same research found that bacteria causally related to periodontitis are related to increased carotid intima-media thickness (IMT),[37] an important marker of early atherosclerosis. This was true even after adjusting for conventional risk factors (i.e., age, race/ethnicity, body mass index (BMI), smoking, diabetes, systolic blood pressure, LDL, and high-density lipoprotein [HDL] cholesterol),[37] providing even more evidence of a direct role of certain infections in the pathogenesis of atherosclerosis. The same study found that white blood cell values tend to rise with both increasing levels of periodontopathic bacteria and increased carotid IMT.[37] Similar research findings continue to accumulate, strengthening the evidence that inflammation, either direct or from a distance (as in periodontal disease) is a primary etiology for affecting alterations in endothelial function which, left untreated, eventually develops into an atherosclerotic lesion.

An atheroma forms in the arterial wall as a result of inflammation.[1] The atheroma is made up of smooth muscle proliferation in the media of the arterial wall.[1] Other inflammatory changes in the media are seen distorting the anatomy of the arterial wall.[1] This is covered by a fibrous cap on the luminal surface narrowing the lumen to a greater or lesser extent, depending on the circumstances.[38] Some feel that distortion is more dangerous than luminal stenosis.[38] Over time, the fibrous cap thins and ruptures with matrix metalloproteinases (MMPs) playing a role in the degradation of the collagen within the fibrous cap.[38] This presents a rough surface to flowing blood in the lumen.[38] Platelets adhere to this surface under the influence of adhesion factor activity, causing a coagulation cascade leading to an occluding clot, cutting off all blood flow.[38] This results in stroke or MI, depending on the location.[38]

Ross wrote a 1999 review article in the New England Journal of Medicine titled “Atherosclerosis - An Inflammatory Disease,” which is used in teaching institutions to provide a step-by-step description of the development of the atherosclerotic lesion.[1] In this review, Ross detailed the atherosclerotic process beginning with endothelial dysfunction, the formation of the fatty streak, and then the formation of the advanced complicated atherosclerotic lesion, ending with how unstable fibrous plaque can rapidly lead to thrombosis. Illustrations and accompanying explanations of the contribution of infection in the atherosclerotic process are provided in Figures 2 to 5 on page 29 to help readers better understand the pathobiological cascade of events implicated in the formation of an atherosclerotic lesion.

It is becoming increasingly clear that the variety of cardiovascular events cannot be explained by a single pathobiological pathway. The relationship between novel biological markers of inflammation and traditional risk factors, such as high blood pressure, smoking, obesity, diabetes, low levels of physical activity, and use of hormone-replacement therapy, may be of variable importance for individual patients.[39]This has spawned a search for other factors that may be implicated and, when present, help to identify patients at greater risk for MI and other cardiovascular events.[10] Certain markers of inflammation (systemic and local) appear to play a central role in the development and progression of atherosclerosis.[10] HsCRP, one of the acute-phase proteins produced by the liver in response to infection, is a specific systemic marker of vascular inflammation that appears to have a strong association with adverse vascular events.[39]

Both hsCRP and LDL cholesterol levels are elevated in people at risk for cardiovascular events. However, hsCRP and LDL cholesterol measurements tend to identify different high-risk groups.[39] Researchers have found that independent effects were observed for hsCRP in analyses adjusted for all components of the Framingham risk score[39] (i.e., traditional risk factors for CVD). Specifically, hsCRP and LDL cholesterol levels are minimally correlated and hsCRP has been found to be a stronger predictor of future cardiovascular events than LDL cholesterol.[39] This advantage persisted after adjusting for all traditional cardiovascular risk factors and included the effect of hormone-replacement therapy at baseline.[39] The researchers further concluded that the combined evaluation of both hsCRP and LDL cholesterol proved to be a superior method of detecting risk for cardiovascular events than measurement of either biological marker alone.[39]

What is the normal range of hsCRP level? [40]

- If hsCRP level is lower than 1.0 mg/L, a person has a low risk of developing cardiovascular disease.
- If hsCRP is between 1.0 mg/L and 3.0 mg/L, a person has an average risk.
- If hsCRP is higher than 3.0 mg/L, a person is at high risk.

Low-grade chronic inflammation as measured by hsCRP predicts future risk of acute coronary syndromes independent of traditional cardiovascular risk factors.[41] Because periodontal infection appears to be a source of low-grade chronic infection, the use of hsCRP testing in dental practices provides an excellent opportunity for identifying patients at risk for acute coronary syndromes.

Along with monitoring blood pressure, which has long been routine in practice, the addition of chairside hsCRP testing in dental practices has the potential to become a significant tool for identification of patients at risk for CVD. This may be especially valuable in primary prevention of CVD. Current research considers subclinical (undetected) inflammation to be an accelerant of vascular inflammation and markers of

inflammation (both systemic and local), which, in turn, appear to play a central role in the development and progression of atherosclerosis.[10] Indeed, many patients seen by health-care professionals are at increased risk for MI or stroke because of undiagnosed and asymptomatic atherosclerosis which may be accelerated by chronic periodontal infection.

In 2002, the Centers for Disease Control and Prevention and the American Heart Association held a conference to examine (among other things) the selection and use of inflammatory markers to predict CVD risk. Recommendations made at the conference which have specific relevance to the present discussion follow:[42]

1) Of all the inflammatory markers identified, hsCRP, as an independent marker of risk, may be used at the discretion of the physician as part of an office-based global risk assessment (i.e., the Framingham Heart Study) in adults without known CVD. HsCRP may identify those patients for further intervention or therapy in the primary prevention of CVD.[42]

Dental professionals also are well-positioned to assist patients in assessing their global risk for CVD through use of an assessment such as the Framingham instrument.

2) Testing for hsCRP provides an additive element to global risk assessment. As a result, patients without known CVD who were not previously considered to be at risk will be identified and targets for more aggressive risk reduction interventions. It was recommended that hsCRP be measured in patients who are at intermediate risk of CHD per 10 years (as indicated in global risk assessment) to direct further evaluation and therapy in the primary prevention of CVD.[42]

A good example of this would be a patient who has been identified by a dental professional as being at intermediate risk of CVD via global risk assessment such as the Framingham risk assessment. For example, if a person's cardiovascular risk score - judged by global risk assessment - is low (the possibility of developing CVD is <10% in 10 years), hsCRP testing is not immediately warranted.[39] If the risk score is in the intermediate range (10% to 20% in 10 years), such a test can help predict a cardiovascular and stroke event and help direct further evaluation and therapy.[39] However, the benefits of such therapy based on this strategy remain uncertain.[39] If a dental professional intercepts a person with a high risk score (>20% in 10 years) or established heart disease or stroke, this is an individual who should receive intensive medical care regardless of hsCRP levels[38] and should be triaged to the care of a cardiologist as soon as possible.

3) It was recommended that patients with persistently unexplained marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for noncardiovascular causes, such as infection and inflammation.[42]

These are the types of patients cardiologists should refer to periodontists to be examined for periodontal disease.

4) It was suggested that detection of an elevated hsCRP might serve to motivate patients to adhere to better preventive therapies.[42]

This might be the case for a prediabetic patient whose hsCRP is tested by a dental hygienist chairside and discovered to be edging toward "high normal" (2 mg/L to 10 mg/L), which is predictive of heart disease. In this situation, a dental hygienist has a valuable role to play in motivating that patient to adhere to proper diet, physical fitness programs, compliance to medication regimens, or, possibly, smoking cessation counseling.

Testing for hsCRP in Dental Practices

Is it time for dental professionals to screen patients for risk of future cardiovascular events by performing chairside testing for hsCRP? Yes, and those technologies are now entering the health-care market.

The cardiologist who co-authored this article frequently asks new patients who have heart disease or who are at high risk for heart disease when they last saw their dentists, and whether they were examined for periodontal disease. He also visually examines the gingival tissue and general conditions of the teeth. An example of collaborative care involves a young, non-obese female patient with an elevated hsCRP, but normal serum lipids and blood pressure, who presented with severe gingival inflammation. The cardiologist referred this patient to a periodontist. Four months later, following periodontal therapy, her hsCRP was normal.

The cardioprotective benefits of periodontal treatment may represent an efficacious modification to contemporary therapies for vascular diseases. Several pilot studies have shown that periodontal therapy consisting of scaling and root planing and application of antimicrobial agents were effective in reducing levels of serum inflammatory markers, specifically hsCRP, IL-6, and TNF-α.[43,44] However, larger scale, randomized interventional clinical trials are needed to investigate the potential cardiovascular benefits of periodontal therapy.[7] If future research provides evidence that treatment of periodontitis reduces hsCRP and/or decreases the incidence of CVD, this would provide a strong rationale for a change in health-care policy that would position periodontal care as medically necessary for the prevention and management of CVD.[7] In the meantime, it is time for physicians and other nondental health-care providers to begin to identify those patients who are at greater risk for periodontal disease because of their individual risk profiles. Specifically, patients who smoke are at 3 to 7 times greater risk and patients with diabetes are at 2 to 5 times greater risk for developing periodontal disease.[45] Patients who report that a sibling or parent lost their teeth at an early age may be genetically predisposed to periodontal disease with an odds ratio that confers 3 to 5 times greater risk for developing periodontal disease.[45] Those patients who both smoke and who are genotype positive have an 8 to 10 times greater risk for periodontal disease.[45] These scenarios represent excellent opportunities for the medical community to screen for periodontal disease and triage patients to dental professionals for evaluation and treatment of periodontal disease.

Discussion of the significance of periodontal infection in cardiology would be incomplete without mentioning the potential role subantimicrobial doses of doxycycline may play in inhibiting MMPs. MMPs participate in degradation of the fibrous cap of an atherosclerotic lesion (the vulnerable plaque), which ultimately leads to rupture, in-situ thrombosis, and subsequent vascular events.[46] Although larger studies are needed to investigate its potential to reduce the risk of rupture of atherosclerotic plaque, it appears that subantimicrobial doses of doxycycline, approved by the U.S. Food and Drug Administration for suppression of collagen-destroying enzymes in the treatment of periodontal disease, may also have cardioprotective benefits.[46]

Conclusion

Despite the fact that the formation of the atherosclerotic lesion and its impending threat to cardiovascular health has a very complex etiology, dental screening to identify patients at risk for CVD and those patients with diagnosed CVD who are at greater risk for recurrent cardiovascular events offers an undeniable intervention opportunity. Likewise, physicians have an enormous part to play by screening patients for periodontal disease.

For patients at intermediate risk (10% to 20% risk of CHD per 10 years) as defined by the Framingham risk score, testing for hsCRP may help direct further evaluation and therapy in primary prevention for CVD.[47] For patients with stable coronary disease and acute coronary syndromes, in-office testing in dental practices for hsCRP may prove to be invaluable in identifying those patients who require significantly more aggressive therapies provided by cardiologists.

Although the cardioprotective benefits of periodontal treatment remain speculative at present, awareness of the relationship between the increased burden of infectious agents and systemic inflammation may have a significant effect on the prevention and treatment of chronic inflammatory diseases and conditions. Transition toward interdisciplinary health-care management must increase to better target those at high risk and to devise a multidisciplinary integrated care pathway for CVD. Those physicians and dentists who collaborate on this integrated care pathway will be ahead of the curve.

It is not unusual to hear from physicians that they have seen patients with hyperparathyroidism, diabetes, osteoporosis, and various other diseases that were first diagnosed in the dental office. Indeed, astute dentists and dental hygienists are often the first to note an undesirable side effect of calcium channel blockers (i.e. drug-induced gingival overgrowth). Many within the medical profession also recognize the significant contributions of many dental professionals in monitoring patients' blood pressure. It is important to realize that we are now in an unprecedented era of explosion of research related to periodontal medicine. For the well-being of our patients, the time has come for physicians, dentists, nurses, and dental hygienists to work together to identify those at risk, both for atherosclerosis and periodontal disease. Indeed, we are all treating "a patient," not just one part or one organ.

It is interesting that the oldest medical school in the world, the University of Bologna in Bologna, Italy (founded in 1088), still requires all medical students to take a one-year course in oral medicine and dentistry. Nine hundred seventeen years later, all physicians and dentists must realize that we treat an organism. The mouth is attached to the body and each may have an effect on the health of the other. We must remember the ankle bone is connected to the leg bone and, indeed, the oral cavity is connected to the body.

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These risk factors are defined as major risk factors by the American Heart Association

§ Body weights are currently defined according to BMI as follows: normal weight 18.5 kg/m^2 to 24.9 kg/m^2; overweight 25 kg/$m^2$to 29 kg/m^2; obesity >30.0 kg/m^2; (obesity class I 30.0 kg/$m^2$to 34.9 kg/m^2; class II 35.9 kg/$m^2$to 39.9 kg/m^2, class III ≥50 kg/m^2). Abdominal obesity is defined according to waist circumference: men >102 cm (>40") and women >88 cm (>35").

Figure 2 - Endothelial dysfunction in atheroslerosis.
The earliest changes preceding the formation of atherosclerotic lesions involve the endothelial lining of the vessel lumen. The changes include increased endothelial permeability that leads to acculumation of lipoproteins and development of the fatty streak; up-regulation of endothelial adhesion molecules that facilitate the aggregation of monocytes, T-lymphocytes, and blood platelets; and endothelial/platelet interactions resulting in the release of growth factors that, in turn, promote progressive development of the lesion.

Figure 3 - Fatty-streak formation in atherosclerosis.
Fatty streaks initially consist of lipid-laden monocytes and macrophages (foam cells) together with T-lymphocytes. Later, they are joined by increasing numbers of smooth muscle cells, some of which may also contain varying amounts of lipid. The increasing population of smooth muscle cells is promoted by various growth factors, such as Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and Transforming Growth Factor-ß (TGF-ß).

Figure 4 - Formation of an advanced, complicated lesion of atherosclerosis.
Intermediate and advanced atherosclerotic lesions are characterized by a fatty streak covered by a fibrous connective tissue cap. The cap represents a healing response to injury and forms a barrier between the underlying lesion and the vessel lumen. The fibrous connective tissue layer is infiltrated by lipid-filled macrophages and smooth muscle cells, all of which cover a mixture of leukocytes, extracellular lipids, and debris that, in turn, may form a necrotic core.

Figure 5 - Unstable fibrous plaques in atherosclerosis.
Rupture or ulceration of the fibrous cap can lead to hemorrhage and thrombosis and usually occurs at sites where the connective tissue layer is thin. Thinning of the fibrous cap is apparently because of the continuing influx and activation of macrophages, which release metalloproteinases and other proteolytic enzymes. The enzymes degrade collagen and noncollagenous matrix proteins, which then leads to hemorrhage, thrombus formation, and occlusion of the vessel. In some cases, an embolus of clotted blood may be released and occlude a downstream vessel.

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STRATEGIES FOR DENTAL HYGIENIST AND NURSE COLLABORATION IN TARGETING PERIODONTAL AND CARDIOVASCULAR DISEASES

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With more than 2,600 Americans dying of CVD each day,[1] at a rate of one death every 34 seconds,[1] medical practitioners and policymakers are currently facing statistics on CVD that are daunting. This comes at a time when both public and private sectors are calling for health care promotion and primary prevention strategies that will preempt the incidence and severity of chronic diseases and conditions. Indeed, wellness instead of health repair has become the battle cry in public health arenas and at the center of consumer demands. However, instead of primary prevention to preempt the beginning of disease, the best option we currently have is secondary prevention aimed at minimizing the loss or disability resulting from chronic diseases. The widespread adoption of progressive disease management strategies that incorporate health wellness models and primary prevention still seems far away.

Our capacity to provide even secondary preventive care is challenged beyond the capacity of our current health-care delivery system. Unfortunately, the outlook for the future may be even more dismal. As a group, the massive population of baby boomers are living longer, but living with multifactorial diseases like hypertension and diabetes which already tax the health-care system. In addition, the explosive increase in the prevalence of obesity and type 2 diabetes and their related complications, such as hypertension, hyperlipidemia, and atherosclerosis, and an alarming increase in unattended risk factors in younger populations will fuel the CVD epidemic for many years to come.[1] Given the projections of the incidence of CVD expected during the next 20 years,[1] the present way of delivering health care may soon be incapable of treating patients with already diagnosed CVD, and primary prevention aimed at intercepting patients at risk for CVD, our nation's number one killer, is a real long shot. The development of effective and efficient intervention strategies that address the multifactorial risk associated with chronic diseases and conditions like CVD is overdue. It is time to think beyond traditional models of care. At the heart of this health-care campaign may very well be one of the most powerful models of care ever mobilized - bilateral point-of-care screening, which relies on collaboration between dental hygienists and nurses in identifying and triaging patients at risk for systemic inflammation and chronic diseases, such as periodontitis and CVD.

CVD Statistics Going the Wrong Way

More than 70 million Americans have CVD,[1] which translates into one in four people with some form of CVD, including 7 million people with coronary heart disease (CHD) (myocardial infarction, angina pectoris), and more than 5 million people with stroke.[1] Table 1 chronicles a series of alarming statistics related to the prevalence, incidence, and mortality of CHD and stroke.[1] Even more frightening are the statistics related to the failure to assess CVD risk and to diagnose CVD. As an example, research indicates that for 50% of men and 64% of women who died suddenly of CHD, there was no previous recognition of the disease.[4] Furthermore, it was found that a significant proportion of the population with identified risk factors for CVD were not diagnosed with CVD and include individuals who are not being treated for CVD adequately.[4] Other studies have found that among insured people, 29% of adults with hypertension and 51% of adults with high cholesterol had undiagnosed CVD.[4] For the uninsured, projections of CVD prevalence were even more pronounced, with 41% of uninsured people having undiagnosed hypertension and 71% having undiagnosed hypercholesterolemia,[4] both highly recognized major risk factors for CVD.

There is a new twist to the etiology of CVD - about half of the patients presenting with myocardial infarctions (MI) do not have classic risk factors for CVD.[5] And contrary to the long-held belief that CVD is primarily induced by hypercholesterolemia, high cholesterol is relevant in only 50% of patients with coronary artery disease (CAD).[6] As a result, researchers are aggressively pursuing other biological mechanisms that may implicate less obvious, more novel risk factors for CVD.

In Search of Novel Risk Factors for CVD

One of the biological mechanisms under investigation is the role periodontal infection may play in increasing the risk for CVD. During the last 20 years, many case-control and cross-sectional studies have shown have association between periodontal disease severity and CVD.[7] It has been known for some time that there is a biological gradient between periodontal infection and the incidence of CHD and a dose relationship between various levels of bone loss and the cumulative incidence of angina and MI.[8]

Although many research findings point to intriguing evidence of a relationship between periodontal disease and CVD, a cause-and-effect relationship has yet to be proven. Experts at the 2003 American Academy of Periodontology (AAP) Workshop on Contemporary Science in Clinical Periodontics concluded that although there was a moderate level of evidence to suggest that periodontal disease is associated with CVD, additional large-scale longitudinal epidemiological and intervention studies are necessary to validate the association.[9] What still remains a mystery is whether the association is causative or because of etiological factors common to both disease processes.[9] The consensus opinion of the 2003 workshop stated there was insufficient evidence to support advising patients that periodontal treatment could prevent the onset or progression of atherosclerosis-induced diseases like CVD and stroke.[9]

Since the consensus findings of the 2003 AAP workshop, mounting evidence reported in dental and medical journals seems to strengthen the supposition that periodontal bacterial pathogens and the resulting host immune response are directly implicated in the development of atherosclerosis and in the increased risk for cardio- and cerebrovascular events.[10-15] The Oral Infections and Vascular Disease Epidemiology Studies (INVEST) published within the last few years have provided more substantial evidence that periodontal disease may actually accelerate the development of atherosclerosis-related diseases (i.e. CVD and stroke).[16] The INVEST studies also reported that patients with significant periodontal bacterial burden had increased carotid intima-media thickness (IMT),[16] which is an indicator of subclinical (undetected) atherosclerosis and a precursor to CVD.

One of the most reliable markers of systemic inflammation is high sensitivity C-reactive protein (hsCRP), which is one of the acute phase proteins that is produced by the liver in response to ischemia, trauma, burns, infections, and other inflammatory conditions.[7] C-reactive protein (CRP) is an independent risk factor for CVD.[17] The growing consensus is that testing CRP levels in the blood with high sensitivity assay (hsCRP), which is now widely available, can consistently predict new coronary events in patients with unstable angina and acute MI.[18] It has also been suggested that increased hsCRP will elevate an individual at intermediate risk for CVD within 10 years to a higher risk category.[18] Recent research indicates that there may be a gradient effect between the extent and severity of periodontal disease and elevated levels of hsCRP[19] and that the presence of CVD seems to be highest in those individuals in whom periodontal disease co-exists with elevated hsCRP.[20] Patients with periodontitis have increased systemic levels of hsCRP and fibrinogen, both of which affect coagulation, platelet activation, and aggregation contributing to atheroma formation, thereby increasing the risk for CVD.[21,22]

It is true that randomized controlled clinical trials to demonstrate the potential cardiovascular benefits of periodontal treatment are needed before sweeping changes in health-care policy can be established. Some of this research, in fact, may be on the way. The National Institute of Dental and Craniofacial Research (NIDCR) has just completed but not yet reported the findings of a study of 400 participants called PACE (Periodontitis and Cardiovascular Events) to determine if treating periodontal infections will lead to fewer MIs, cardiac revascularization, fatal coronary disease, unstable angina and hospitalized ischemic stroke.[23] This pilot clinical trial, involving investigations at five university treatment facilities, will provide supporting data for the development of a larger randomized clinical trial that will include about 4,000 participants from 15 academic centers across the United States.[23]

Another study that is especially intriguing is being conducted at Boston University. Also sponsored by NIDCR, this study is designed to determine whether effective treatment of periodontal disease improves endothelial function and reduces inflammation.[24] The term being used to describe this kind of approach to therapy is reversible atherosclerosis (S. Amar, oral communication, Nov 2005). The investigators are halfway into clinical trials, with results expected in 2009.

The overwhelming statistics related to the prevalence, incidence, and mortality of CVD, in combination with the emerging body of evidence implicating periodontal infection as a potential risk correlate for CVD, provides an unprecedented opportunity for dental and medical collaboration. This includes prevention, early identification and progressive treatment of CVD, and recognition of novel risk factors related to systemic inflammation arising from chronic infections like periodontitis. Dental hygienists and nurses have a major role to play in bringing about this level of action. Although well-supported recommendations for preventing heart disease and stroke have been available for more than 50 years, these guidelines have not been well implemented by physicians and patient compliance is poor.[25] For example, the American Heart Association (AHA) recommends that adults 40 years of age or older with no history of CVD be assessed for their risk for CHD every five years.[4] Unfortunately, research among primary care physicians found that such an assessment has not been widely implemented.[4] Mobilizing point-of-care providers such as dental hygienists and nurses to perform risk assessment for periodontal disease and CVD may net the greatest gains in progressive prevention and detection of these diseases.

Perhaps one of the most compelling statistics to support ramping up dental hygienist and nurse collaboration in integrating risk assessment protocols is that 250,000 sudden deaths from CHD occur each year without hospitalization or in the absence of any previous history of CHD.[26] For these victims, there was no opportunity for treatment because no one identified their risk for CVD. In effect, death became the first sign of CVD. Collectively, the CVD statistics and emerging evidence of a relationship between periodontal disease and CVD provides a strong justification for using dental hygienists and nurses to provide progressive point-of-care intervention strategies.

Robust Reduction of Risk for CVD

It has been said that, “No matter what advances there are in high-technology medicine, the fundamental message is that any major reduction in deaths and disability from CVD will come from prevention and not cure. This must involve robust reduction of risk factors.”[27] Because atherosclerosis is associated with the majority of cases of CVD, robust reduction of risk factors for CVD necessarily begins with reducing the risk for atherosclerosis.

The development of an atherosclerotic lesion, which is implicated in the majority of CVD cases,[9] is thought to be a multifactorial and complex process.[6] Atherosclerosis is an inflammatory sequela, arising from injury, leading to dysfunction of the endothelial cells lining the lumen of an

artery.[6] The degree of endothelial dysfunction depends on the cumulative burden and severity of cardiovascular risk factors, including the cumulative burden of infections[6] like periodontitis. Several causes of endothelial dysfunction that lead to atherosclerosis and, therefore, increased risk for CVD include, but are not limited to, elevated low-density lipoprotein, cigarette smoking, diabetes mellitus, and hypertension.[6] Beck and Offenbacher recently wrote that, "The problem regarding CVD management is that since it requires decades to initiate and propagate, it also requires sustained intervention to prevent or treat."[3] So true, yet without developing and sustaining primary prevention and health promotion intervention strategies that address all risk factors including those implicated in systemic inflammation, we will continue to see increasing numbers of people with CVD risk factors, increasing numbers of first and recurrent heart attack and stroke victims, and increasing numbers of people who die from CVD.[28]

When Healthy People 2010 was published in 2000, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) shared joint responsibility for moving the nation toward achieving the goals set forth in the report and periodically reporting the progress over the course of the decade.[28] The Healthy People 2010 Heart and Stroke Partnership set into place four goals based on different intervention approaches for prevention, detection, and treatment of risk factors related to CVD:[25]

- Prevention of risk factors
- Detection and treatment of risk factors
- Early identification and treatment of heart attacks and strokes
- Prevention of recurrent cardiovascular disease

Recommendations in the form of clinical practice guidelines for detecting and treating risk factors and preventing heart disease and stroke have been published by the AHA/American Stroke Association (ASA), the American College of Cardiology (ACC), and the National Heart, Lung, and Blood Institute (NHLBI).[25] These recommendations embody three points of intervention of CVD (see Figure 1):

- Primordial prevention of CVD, Point A, includes the promotion of a combination of favorable health habits and conditions that protect against the development of CVD.[25] Cardiovascular health promotion targets individuals at any age who have not yet developed risk factors because the intervention occurred before the risk factors began to incite changes in the vasculature that lead to CVD.[25] Such interventions should start in childhood - some would argue even during gestation - and continue throughout adulthood to prevent risk factors from ever developing.[25]
- Primary prevention, Point B, is intended to prevent a first heart attack or stroke by detecting and treating risk factors of individuals with CVD risk factors but no clinical manifestations of CVD.[25]
- Secondary prevention, Point C, aims to reduce the risk for recurrent heart attacks or strokes by treating CVD and the risk factors of individuals with established CVD, including survivors of CVD events.[25]

The probability of achieving the risk prevention, reduction, and treatment goals contained in Healthy People 2010 and implementing the clinical practice guidelines set forth by the AHA/ASA, the ACC, and the NHLBI may be significantly increased with a collaborative model of care that aligns dental hygienists and nurses in the integration of clinical protocols and bilateral screening for CVD and periodontitis.

Mobilizing Dental Hygienists in Collaboration with Nurses

In fiscal year 2005, Congress appropriated $45 million for the Heart Disease and Stroke Prevention Program.[29] The CDC, which has advocated for the adoption of a long-term national health-care policy that includes primary prevention of premature atherosclerosis,[29] currently funds risk reduction programs in 32 states and the District of Columbia.[29] The priorities of these programs include control of high blood pressure and high cholesterol.[29] What seems to be missing in these funding priorities are strategies for reducing systemic inflammation, which is becoming increasingly recognized as a serious threat to cardiovascular wellness. Although the CDC acknowledges that collaboration in bringing about cardiovascular health is key, there is no reference to dental-medical collaboration or dental hygienist-nurse collaboration. This may represent a departure from the Surgeon General's recommendations for interdisciplinary care among dental and nondental care providers embodied in the Oral Health in America report published in 2000.[30] Bypassing this collaborative model of care may forfeit the potential of a valuable alliance in providing primary prevention in daily patient care.

Health-care usage patterns indicate that individuals tend to seek routine and preventive oral health care on a more frequent and regular basis than routine and preventive medical care.[4] Glick and Greenberg[4] recently reported a national probability sample that estimated that among people aged 40 to 85, about 25% reported having no history of CHD, heart attack, stroke, or angina, and no previous diagnosis of hypertension or high cholesterol levels. A number of these people with unidentified risk factors had not seen a physician within the previous 12-month period; however, they had seen a dentist within that same time period.[4] When the researchers applied the Framingham-based risk calculation to this sample group, 18.3% of men were found to be at increased risk for a first CVD event.[4] The findings from this study substantiate that dental-care providers are uniquely positioned to intercept CVD in patients who are unaware of their increased risk. Unfortunately for many people with undiagnosed CVD, it is hospitalization for an acute coronary event that provides the "teachable moment" for secondary prevention of a recurrence. The dental practice setting could provide the "teachable moment" for interception of those individuals with unidentified risk factors for CVD, a primary prevention strategy that is easily integrated into daily patient care.

Assessing the Risk of Periodontal Disease as an Exposure for Systemic Injury

Unfortunately, many practitioners still hold the view that periodontal disease is the clinical outcome of interest rather than a potential contributor to a greater disease process within the human body. This philosophy of practice may prevent clinicians from taking responsibility

and becoming accountable for periodontal-systemic outcomes.

If the strength of evidence from epidemiological studies and intervention trials net the results that many researchers have speculated, it seems inevitable that the classification of inflammatory periodontal disease will have to be modified to reflect the level of risk it may pose for a potential exposure event for atherosclerosis-related systemic diseases such as CVD. Along those lines, various researchers have already developed concepts that attempt to quantify the risk of systemic consequences of periodontal infection. One of the most notable is the Periodontal Index for Risk of Infectiousness (PIRI).[31,32]

The PIRI computes the amount of ulcerated subgingival space exposed to the infection burden and the potential systemic threat that the bacterial challenge poses to patients with periodontal disease.[32] Using the PIRI to determine a patient's level of risk for periodontal-systemic consequences, individual patients are assigned penalty points. By taking into account the probing depths of the deepest periodontal lesions and their number per patient, this methodology gives a quick, gross estimation of the surface area of the interface between the subgingival biofilm and the epithelial walls of the periodontal niches.[32] This provides a relative value for the level of individuals' risk for the release of proinflammatory mediators from the periodontium.[31,32] When researchers used the PIRI to quantify the level of risk that periodontal infection posed to cardiovascular health, they found a significant dose response relationship between increasing PIRI scores and the presence of CAD; specifically that subjects who had the highest PIRI scores had a 13.8 times greater risk of having CAD than patients with the lowest scores.[32]

The theory that periodontal infections predispose certain individuals to accelerated progression of carotid atherosclerosis (and therefore increased risk for stroke), MI and CVD may no longer be a stretch. To that end, it seems entirely appropriate for nondental practitioners to begin to categorize infection from periodontal origin as a risk correlate for CVD. It also seems right that nondental care providers start to recognize novel risk factors like elevated hsCRP, which is implicated in both CVD and periodontitis. Elevated levels of hsCRP have been shown to predict future coronary events and may add predictive value to testing for cholesterol levels.[33] In the future, medical and dental practices may screen patients to quantify certain markers of systemic inflammation implicated in diseases like CVD and periodontitis. Analyzers designed to monitor hsCRP and HbA1c are now available to use in-office or chairside, which can provide the mechanism for onsite screening for markers of systemic injury of patients in dental and medical practices. These technologies place into the hands of medical and dental practitioners tools for both primary and secondary prevention of cardiovascular events, which are easily incorporated into patient care.

Should future events dictate that periodontal treatment is medically necessary to decrease the risk for systemic complications, such as CVD and ischemic stroke, it seems likely that the demand for periodontal services will increase. This, in turn, will prompt significant changes in insurance and reimbursement mechanisms. Assessing risk properly and triaging patients to appropriate health-care providers is pivotal in bringing about elimination and reduction of patients' risk for both periodontal and cardiovascular diseases and will require highly integrated dental-medical care. The actual implementation of periodontal medicine most appropriately falls to dental hygienists and nurses who are uniquely well positioned to play a key protective role by preventing the initiation, escalation, and/or acceleration of systemic events via bilateral point-of-care screening.

Building the Case for Dental Hygienist and Nurse Bilateral Point-of-Care Screening

Screening for individuals at risk for CVD and integrating the research findings associated with the theorized link between periodontal disease and CVD exceeds the capacity of any one profession. Indeed, it will take practitioners from both the medical and dental side, at all levels, to implement scientifically justified prevention strategies. It will also require targeted interventions that are multidisciplined for a sustained period of time to change the risk profile of an individual who has identified risk factors for CVD and more extensive and sustained interventions for those who have already suffered a coronary event. Accordingly, there needs to be a purposeful shift from prevention and treatment of two distinct diseases (i.e., dental practitioners' sole focus on periodontal disease and medical practitioners' exclusive focus on CVD) to a transdisciplinary model of care. These overlapping boundaries of care are centered around prevention and treatment of a cluster of interrelated clinical signs and symptoms of chronic inflammation, with CVD, ischemic stroke, and periodontal disease being part of this cluster. Hypertension and diabetes (or insulin resistance), when present, may also be part of this cluster of interrelated signs and symptoms of chronic inflammation. New research may actually add validity to the assertion that health-care providers may need to start thinking of CVD and periodontal disease as part of a cluster of interrelated variables.[3]

Beck and Offenbacher[3] recently published a study that was designed to determine which CVD outcomes are affected by oral diseases and under what related circumstances individuals may be at greater risk for CVD.[3] Using a statistical technique called principal component analysis, the researchers explored the relationship and the strength of correlation between traditional risk factors for CVD (i.e., smoking, hypertension, obesity, and age), periodontal pathogen exposure levels (low to high), antibody levels to those pathogens (low to high) and cardiovascular outcomes. The authors noted four distinct biofilm microorganism-host response patterns and speculated that there is a clustering of variables (i.e., traditional risk factors for CVD, levels of periodontal pathogens and antibody levels) within those biofilm patterns that correspond to CVD outcomes.[3] In evaluating an individual's CVD health in comparison with the level of periodontal microorganisms and their antibody levels, the researchers found that IMT is more closely associated with antibody levels, and that stroke and CHD are more influenced by the level of periodontal microorganisms, especially when antibody levels are high.[3] Of particular interest was the finding that individuals with early periodontitis, low levels of periodontal microorganisms and high antibodies are more likely to have CHD and stroke than individuals with severe periodontitis, high levels of organisms, and high antibodies.[3] Elevated antibodies appeared to be associated with periodontal disease and chronic systemic conditions (i.e., CHD and diabetes). In conclusion, the researchers noted the importance of understanding the underlying relationships between oral infection and CVD and the implication of this in enabling better diagnosis, treatment, and management of CVD.[3] This research presents a unique perspective and an intriguing concept that should be considered by both medical and dental professionals in moving toward transdisciplinary prevention and management of CVD. The clustering of interrelated variables also represents a domain of periodontal medicine that must be shared and equally understood by point-of-care providers like nurses and dental hygienists. Both medical and dental professionals are responsible for implementing this information into clinical practice.

Ideas for Implementing Bilateral Point-of-Care Screening by Dental Hygienists and Nurses

Recognizing the points at which clinicians have an opportunity to alter the course of disease is the key to the implementation of successful intervention strategies. Figure 1 illustrates various points of intervention and valuable therapeutic opportunities for dental hygienists and nurses.

Intervention Point A represents primordial preventive measures, including health promotion (therapeutic seeding) directed toward lifestyle changes that emphasize exercise, weight loss or control, and knowledge of risk factors in healthy patients. Examples of therapeutic seeding include novel patient education strategies aimed at preventing obesity, smoking, sedentary behavior, and chemical addictions. In addition, education of certain ethnic populations known to be at greater risk for chronic diseases and patients with suspected genetic predisposition to periodontal disease is vital. Primordial prevention also includes proactive educational campaigns targeting such things as healthy nutrition and physical activity. Calibration of these messages between the nursing and dental hygiene professions would reinforce the same important patient information.

Intervention Point B corresponds to primary prevention and includes screening for the presence of an undiagnosed disease like diabetes and risk for CVD and ischemic stroke. Screening tools such as the Framingham global risk assessment, in-office hsCRP and HbA1c testing, the use of body mass index (BMI) tracking, and diabetic profiling, fall into this prevention category. This level of care has the potential to significantly impact chronic disease trends, but only if integrated screening can be incorporated into dental and medical practices. This transdisciplinary model of care adds significant value to the positions of both dental hygienists and nurses as preventive specialists.

Intervention Point C is secondary prevention and includes the treatment of chronic conditions in an attempt to minimize disability and/or the loss of function in individuals with already diagnosed diseases. Among other things, secondary prevention includes treatment of periodontal disease, metabolic control of diabetes, and management of hyperlipidemia and hypercholesterolemia with the goal of reducing disability or increasing compromised function.

With consumer demand for wellness and newly emerging philosophies of care that embrace the wellness model over the repair model, we can expect to see a push toward developing primary and secondary prevention strategies that pre-empt the incidence and severity of chronic disease. The implementation of bilateral point-of-care screening by dental hygienists and nurses provides a potential clinical pathway that may have a profound effect on disease prevention or, possibly, disease reversal. Ideas relative to implementation of bilateral point of care screening by dental hygienists and nurses are as follows:

- It has been observed that the risk for CVD is highest in individuals with periodontitis, elevated hsCRP concentrations, and serum antibody levels to periodontal pathogens.[20] This observation suggests that periodontitis increases CVD risk, primarily in those individuals who react to periodontal infections with a profound systemic inflammatory and immune response.[20] Interestingly, it has also been suggested that patients exhibiting both periodontitis and elevated hsCRP levels are not necessarily those with the most severe periodontal disease.[20] Regardless, researchers have reported that treating periodontitis in patients with elevated hsCRP results in decreased levels and may, therefore, translate into decreased risk for CHD.[34]

This information, in addition to other evidence concerning the relationship between hsCRP and periodontal disease, provides a compelling rationale for hsCRP testing by dental hygienists. These rationales include:

1. The use of hsCRP testing in dental offices may detect those individuals who present with less severe periodontal disease but react to periodontal infection with more profound systemic inflammation and immune response.
2. The use of hsCRP testing in dental offices may increase the detection of individuals at high risk for CVD and ischemic stroke beyond that of lipid testing (cholesterol) alone.[33]
3. The use of hsCRP testing in dental offices may allow improved identification of individuals who would benefit from statin therapy (cholesterol-lowering drugs).[33]
4. The use of hsCRP testing in dental offices may increase the rate of identification of those cardiac patients who are at greater risk for an acute coronary syndrome.[33]

- Extensive periodontal disease and BMI were found to be commonly associated with increased hsCRP levels in otherwise healthy middle-aged adults, suggesting the need for both medical and dental diagnoses when looking for the sources of acute phase response in some patients.[35]

Nurses screening otherwise healthy middle-aged adults for elevated hsCRP and obesity as determined by BMI may identify those patients at high risk for periodontal disease. Conversely, dental hygienists screening for those periodontal patients who are obese may identify patients at risk for increased hsCRP levels. Both of these strategies represent secondary prevention.

- Obesity is associated with multiple-risk factor syndromes, such as hypertension, hyperlipidemia, type 2 diabetes, periodontal disease, and atherosclerosis.[36] Among adults aged 18 and older, the prevalence of two or more risk factors increased from 23.6% in 1991 to 27.9% in 1999.[1] It is important to note that multiple risk factor syndromes increased for both men and women and across all race, ethnic, age, and education groups.[1] Among those with two risk factors in 1999, the most common combination was hypertension and high cholesterol (23.9%).[1] Among those with three risk factors, the most common combination was hypertension, high cholesterol, and obesity (32.5%).[1]

Recognition by both nurses and dental hygienists of the interrelationships of the multiple-risk factor syndromes stated above allows for

significantly greater bilateral interception of at-risk individuals, and the opportunity to triage, in both directions, those cases that require more aggressive care. Less than 12% of people say that a health-care provider has talked to them about the need for weight loss over the past year.[37] To that end, those practitioners who are reluctant to start dialogues with patients about weight control need to overcome their discomfort and begin to educate patients about the risks imposed by obesity.

- Researchers found that, on average, adults who have experienced a coronary event had been small at birth and thin at 2 years of age, but then rapidly gained weight thereafter - a pattern of growth associated with insulin resistance in later life.[38] The researchers concluded the risk for coronary events is more strongly associated with the rate of childhood gain of BMI than to BMI attained in adulthood.[38]

Dental hygienists and nurses who incorporate aggressive therapeutic seeding related to prevention of childhood obesity into pedodontics and pediatrics may have the most significant influence on risk for future adult coronary events. Nurses also need to recognize that the incidence of periodontal disease starting in youth is projected to increase parallel to childhood obesity trends.[39] The current epidemiologic trend indicates that this younger population subset may also become predisposed to chronic inflammatory diseases at a much younger age than their older cohorts,[39] which is significant for dental hygienists to consider when designing health promotion programs, including screening protocols.

- With increasing severity of periodontitis, there is a progressive increase in left ventricular mass (a known independent predictor of CVD) in patients with essential hypertension. Researchers concluded that periodontal evaluation might contribute to refining cardiovascular risk assessment in patients with high blood pressure.[40]

A valuable addition to the assessment of individual patients would be a nurse's recognition that hypertensive patients with increases in left ventricular mass might also be at increased risk for periodontal disease. Triage of such at-risk patients to dental care providers constitutes an excellent opportunity for collaboration with the dental profession. On the other hand, a dental practitioner's measurement of blood pressure can identify the presence of hypertension and/or level of the patient's hypertension control,[41] both of which represent cases that should be triaged to a medical practitioner.

- Patients with diabetes are 2 to 5 times more likely, smokers are 3 to 7 times more likely, patients who report that parents or siblings lost their teeth at a young age may be 3 to 5 times more likely, and those with suspected genetic predisposition and who also smoke are 8 to 10 times more likely to develop periodontal disease.[42]

These are the very individuals who are at significantly higher risk for periodontal disease and when seen by medical practitioners should be triaged to dental practitioners. It is fairly simple to include known risk factors (i.e., smoking, diabetes, and genetic predisposition) for periodontal disease that do not require intraoral examination as part of nurses' assessment of their patients.

- Some investigators have found gingival inflammation may be considered a more significant risk factor for CVD than clinical attachment loss.[43]

If nurses used a screening tool as simple as a wooden toothpick to check for gingival inflammation and bleeding of gingival margins or interproximal papillae, it seems reasonable that cases of gingivitis could be identified in medical settings. Treatment intervention at this point may decrease patients' risk for CVD and ischemic stroke. Conversely, it should be noted that dental hygienists' recognition that periodontal disease and gingivitis may increase a patient's risk for CVD or ischemic stroke is important if patient wellness is the outcome of interest.

- Porphyromonas gingivalis has been implicated in several steps in the development of the atherosclerotic lesion.[44,45] In addition, hsCRP levels are highest in patients who are infected with periodontal pathogens.[46]

Another opportunity, albeit rather unconventional, for intervention would be the incorporation of DNA probe and sensitivity testing to screen for P. gingivalis and other periodontal pathogens in medical practices. Taking a sample of subgingival plaque is performed by placing a paper point subgingivally and although this is an intraoral procedure, taking the sample is relatively noninvasive and may be easily taught to nondental care providers.

- Recent research has found that radiographic evidence of severe periodontal bone loss was independently associated with nearly a four-fold increase in risk for the presence of carotid artery plaque.[47]

This has considerable significance for the dental community. Patients with radiographical evidence of periodontal bone loss may be excellent candidates for referral to the medical side; the addition of hsCRP testing might add further validity to the need for referral. Conversely, patients with diagnosed atherosclerosis represent those who medical care providers should triage for periodontal evaluation and treatment.

Conclusion

Central to all these point-of-care intervention strategies is the assumption that dental hygienists and nurses have a keen awareness of the systemic affects of cumulative infection and the systemic inflammatory burden implicated in atherosclerosis formation. Bilateral point-of-care screening for periodontal disease and cardiovascular risk also supposes that health-care providers on both sides understand the contribution of periodontal infection to systemic inflammation and that prevention or treatment of periodontal disease will reduce the cumulative pathogen and inflammatory burden. As a result, these types of intervention strategies may decrease the morbidity associated with chronic diseases. These strategies also assume that dental hygienists and nurses are intensely aware of how chronic disease states jeopardize patients' oral

health status.

No doubt screening and diagnostic technologies will some day soon make targeting those at risk a much more concrete science.Currently in development is a self-contained saliva test that would allow detection of periodontal and cardiovascular disease in dental offices, estimated to take no longer than 15 minutes to perform.[48] Until these types of non-invasive, efficient, and affordable tests of biological markers of chronic disease states are developed and commercialized, we must rely on traditional risk assessment of periodontal disease and CVD.

There is a significant body of evidence to support the concept of a cluster of interrelated signs and symptoms of chronic inflammation that includes periodontal disease and atherosclerosis-related diseases. To address this cluster of maladies, nurses and dental hygienists are uniquely positioned to deploy progressive disease intervention strategies within a collaborative framework that includes wellness promotion and primary prevention. Neither of these points of intervention are currently practiced in mainstream health care. Moving to a transdisciplinary model of care will no doubt be challenging. Proactive initiatives of the nursing and dental hygiene professions to achieve this goal should be a major focus of contemporary dental hygiene and nursing practice. Until there is reform of dental hygiene and nursing education that includes a strong oral-systemic component in the curriculum, the forerunners of this transdisciplinary model of care will most likely be individual dental hygienists and nurses who independently forge alliances to foster collaboration. These alliances will be comprised of practitioners who are committed to pursuing a wellness model of care, who are willing to abandon traditional professional boundaries, and who are willing to risk doing something yet uncharted to provide extraordinary patient care. For millions of people who are destined to lose their lives on their first encounter with CVD, mobilizing dental hygienists in collaboration with nurses to perform bilateral point-of-care screenings may significantly reduce premature death.

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GRAND ROUNDS
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THE SIGNIFICANCE OF PERIODONTAL INFECTION IN CARDIOLOGY

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Most of us have heard the refrain from an old song, “The ankle bone is connected to the leg bone.” Can we now sing, “The gums are connected to the heart?” As unlikely as this may sound, researchers and clinicians may have ample evidence to support this claim. Pilot intervention studies are now underway, but should we wait for those final answers before we consider periodontal disease as a risk correlate for CVD? And, if we move ahead now, how do health-care providers implement the current evidence?

Cardiologists and dental professionals appear to have a common enemy - chronic inflammation and its potential to accelerate the process of atherosclerosis, a widely recognized prelude to cardiovascular diseases. Science is beginning to revealthat destructive inflammatory periodontal diseases release substances that are involved in arterial wall inflammation, development of atherosclerosis, and rupture of established atheromas which result in myocardial infarction (MI) and stroke.[1,2] It is the atherosclerotic lesion that amplifies the risk for CVD.

Is human atherosclerosis an inevitability of aging? The hypothesis that human atherosclerosis is not an absolute consequence of aging and can be reversed was put forth in the 1980s by Malinow’s pioneering work aimed at halting the progression of atherosclerosis and promoting its regression.[3,4] Mounting evidence appears to strengthen Malinow’s hypothesis that old age may not necessarily equate to atherosclerosis. A recent study of more than 1,000 participants with a mean age of 73 found that for older adults, periodontal disease, which is one of the infections implicated as a cause of endothelial injury leading to atherosclerosis, is a modifiable risk indicator for elevated levels of systemic inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and hsCRP.[5] All three of these markers are widely recognized as being associated with periodontal infection.[6-8]The question becomes, “Could treatment of periodontal disease in patients both at an earlier stage and age translate into greater longevity?”

Challenges in Decreasing the Incidence and Severity of CVD -

More than 20 years have passed since Malinow tackled CVD. With an array of therapeutic strategies at hand, many health-care providers hoped that CVD would be eliminated by the end of the 20th century. At the beginning of the 21st century, despite cardiologists’ recommendations to patients for therapeutic lifestyle changes targeting classic risk factors - a diet restricted in calories to reach a body mass index of <25 kg/m^2; a waist circumference <105 cm in men and <90 cm in women; physical exercise, smoking cessation, and blood pressure control; and the widespread use of statins in treating hypercholesterolemia - CVD still accounts for 38% of all deaths in North America.[2] Largely because of its rapidly increasing prevalence in Eastern Europe and developing countries, and the obesity trends and rising incidence of diabetes in the West, coronary heart disease (CHD) is expected to be the main cause of death globally.[9] However, about half of patients presenting with MI do not have classic risk factors for CVD.[10] CVD was once thought of as a disease primarily induced by accumulation of lipid-laden cells. What we now know is that high cholesterol is important in only 50% of patients with coronary artery disease (CAD).[1] “Even with intensive statin therapy, the best current evidence-based treatment available, many patients will still have recurrent cardiovascular events.”[11] Although statin therapies have been successful for a large segment of the population, it appears that the medical community may need to pursue approaches beyond statins to modify the course of vascular diseases.[11]

Hardly daunted by the most progressive disease-management strategies, the prediction, prevention, and treatment of CVD represents one of the greatest challenges facing all of us in the health-care arena. This dismal revelation begs an important question: “If we are to implement the recommendations made by the Surgeon General in the Oral Health in America report,[12] already five years old, and achieve the target goals set by the Centers for Disease Control and Prevention,[13] should we include in risk assessments for CVD those factors associated but that, at present, are not proven to be causative, independent, or quantitative?

The answer may be “yes,” but this level of comprehensive care will require medical and dental professionals who are willing to champion this message and initiate models of collaborative care. The intervention trials necessary to prove a cause-and-effect relationship between periodontal disease and CVD are currently underway or about to be funded. Accumulation of that evidence will take years. In the meantime, do we not have enough evidence to support periodontal disease at least as a risk correlate for CVD?

The prevalence of both periodontitis and atherosclerosis is rampant. Periodontal disease is a “preventable [and treatable] contributor to the burden of cardiovascular disease,”[14] and as such, is a modifiable risk factor - a fact that may be escaping the attention of both medical and dental professionals. If only a marginal association between these two diseases is found, prevention and treatment of periodontal disease may have an impact on the prevalence of CVD. It is not premature to include periodontal disease as a risk correlate for CVD, and failure to do so may forfeit an important therapeutic opportunity to reduce or eliminate a modifiable risk factor for CVD.

Quantifying Risk for CVD -

Table 1 on page 26 classifies various risk factors according to their quantitative association with CVD as elucidated by the Framingham Heart Study, which estimates risk for people without clinical manifestations of CVD. Scores derived from the Framingham risk assessment only apply to the primary prevention of CVD.[15] Once coronary atherosclerosis is clinically manifested, the risk for future coronary events is much higher than that for patients without CVD, regardless of other risk factors.[15]Therefore, the Framingham scores no longer apply.[15]

When considering the various risk factors for CHD (Table 1), it is important to understand that major risk factors are additive in predictive power in that total risk can be estimated by the summation of the individual risks related to each factor.[15]However, the major risk factors for CVD as identified in Table 1 do not account for all the variations in the incidence and severity of CVD. Accordingly, it is important to point out that other, less well documented risk factors for CVD may play a significant role.[16]

A strong argument may be made that periodontal disease should be considered both a predisposing and a conditional risk factor for CVD. Predisposing risk factors are agents that worsen independent risk factors.[15]The bidirectional relationship between periodontal disease and diabetes would seem to qualify periodontal disease as a predisposing risk factor for diabetic complications.[17-21] Conditional risk factors are associated with an increased risk for CVD, although their causative contributions to CVD have not been well documented.[15]Such is the case for the correlation between periodontal disease and increased risk for atherosclerosis. The presence of predisposing and conditional risk factors in the assessment of risk for CVD may confer greater risk than revealed from the summation of the major risk factors.[15]Although their contribution has not been quantified, this does not mean that they do not make an independent contribution to risk when they are present.[15]Accordingly, what may be left off this list of risk factors in Table 1 is the contribution of periodontal infection in accelerating atherosclerosis eventuating in CVD.

During the last 20 years there has been significant progress in understanding the link between periodontal infections and risk for CVD such as heart disease[22], stroke, and peripheral vasculature disease, all of which share atherosclerosis as a common feature.[16,23] Recent research found bacterial levels were elevated in only those patients with a history of myocardial infarction, suggesting that increased loads of subgingival bacteria present a danger for systemic health.[24]

The growing research to support the contribution of periodontal infection to the inflammatory burden is theorized to be through both a direct action on blood vessel walls, and by indirectly inducing the liver to produce acute phase proteins (e.g., CRP) (Figure 1).[25] Until recently, DNA footprints comprised the bulk of evidence suggesting that periodontal bacteria were directly involved in atherosclerosis. However, research at the University of Florida has demonstrated that Porphyromonas gingivalis (P. gingivalis) and Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans) are capable of adapting to the vasculature to live in human atherosclerotic lesions.[26] On the medical side, a study recently reported in the American Heart Journal found that periodontal disease is common in patients with MI and associated with elevated hsCRP levels typical of an enhanced systemic inflammatory response.[27] These associations were found to be independent of other contributing factors.[27] Other studies indicate an association between periodontal disease and elevated hsCRP and IL-6, and, conversely, that periodontal treatment lowered hsCRP and IL-6 with a simultaneous improvement in endothelial function.[28] As compelling as this research may be, the truth is that the evidence only supports, but does not prove, a causal association between periodontal disease and atherosclerosis-related diseases. Until this etiological mystery is decoded, we are faced with the dilemma of how to implement treatment strategies that are supported by the existing body of evidence.

Although a combination of risk factors may contribute to the progression of an atherosclerotic lesion, researchers now consider infection to be a significant inflammatory stimulus.[28] Inflammation is directly implicated in destabilization of atherosclerotic plaque in the carotid artery[1] and may lead to aneurism and embolism.[1] Seeding of live periodontal bacteria from the oral cavity to vessel walls,[26] a hyperinflammatory response to those periodontal pathogens,[29] and activation of proinflammatory mediators are three biological mechanisms implicated in the induction of a systemic inflammatory response.[26] This chain of events may describe the link between periodontal disease and CVD.

To fully understand the significance of periodontal disease in the cascade of events implicated in the formation of an atherosclerotic lesion, it is important that dental practitioners understand that infection is a well-established risk factor for atheroma formation and thromboembolic events.[16] To that end, discussion and illustration of the role of infection in the developing atherosclerotic lesion may help readers gain a more comprehensive understanding of this cascade of pathological events.

The Contribution of Infection in the Developing Atherosclerotic Lesion -

It is known that atherosclerosis is the main cause of CVD.[1,2] Possible causes of the endothelial dysfunction that lead to atherosclerosis include elevated and modified low density lipoprotein (LDL); free radicals caused by cigarette smoking; hypertension and diabetes; genetic alterations; and elevated plasma homocysteine concentrations.[1] Most germane are the studies that have also linked infection to atherosclerotic-induced diseases. What has become apparent is that several types of microbial pathogens may contribute to atherosclerosis, making it highly unlikely

that a single microbe causes atherosclerosis.[2]It is now thought that the cumulative burden of infection at various sites is what affects the progression of atherosclerosis and its clinical manifestations of CVD.[2]

There are many studies to support the specific correlation of periodontal infection and atherosclerosis, and a few more recent pieces of evidence merit mention. Various studies have implicated P. gingivalis, a virulent periodontal pathogen, as part of a transient bacteremia that can lead to the direct invasion of blood vessels.[30] In addition, P. gingivalis is implicated in several steps involved in the formation of the atherosclerotic lesion.[31,32] In 2003, it was reported that subjects with advanced periodontal disease exhibited endothelial dysfunction and evidence of systemic inflammation (elevated serum CRP levels), placing them at increased risk for CVD.[33] More recently, there is serological evidence that an infection caused by P. gingivalis increases the risk for MI; high P. gingivalis antibody levels have been shown to predict MI independently of classical cardiovascular risk factors,[34] and infection caused by major periodontal pathogens may be associated with future stroke.[35] Periodontal disease was found to be a treatable, independent risk factor for cerebral ischemia in male subjects (<60 years of age). Those with severe periodontitis had a 4.3 times greater risk of cerebral ischemia than subjects with mild periodontitis or healthy subjects.[36] Gingivitis and severe radiological bone loss were also independently associated with the risk of cerebral ischemia while tooth decay was not.[36]

A recent investigation demonstrated a direct relationship between microorganisms from periodontal infection and subclinical (undetected) atherosclerosis.[37] This relationship was found to be independent of hsCRP.[37]The same research found that bacteria causally related to periodontitis are related to increased carotid intima-media thickness (IMT),[37] an important marker of early atherosclerosis. This was true even after adjusting for conventional risk factors (i.e., age, race/ethnicity, body mass index (BMI), smoking, diabetes, systolic blood pressure, LDL, and high-density lipoprotein [HDL] cholesterol),[37] providing even more evidence of a direct role of certain infections in the pathogenesis of atherosclerosis. The same study found that white blood cell values tend to rise with both increasing levels of periodontopathic bacteria and increased carotid IMT.[37] Similar research findings continue to accumulate, strengthening the evidence that inflammation, either direct or from a distance (as in periodontal disease) is a primary etiology for affecting alterations in endothelial function which, left untreated, eventually develops into an atherosclerotic lesion.

An atheroma forms in the arterial wall as a result of inflammation.[1] The atheroma is made up of smooth muscle proliferation in the media of the arterial wall.[1] Other inflammatory changes in the media are seen distorting the anatomy of the arterial wall.[1] This is covered by a fibrous cap on the luminal surface narrowing the lumen to a greater or lesser extent, depending on the circumstances.[38] Some feel that distortion is more dangerous than luminal stenosis.[38] Over time, the fibrous cap thins and ruptures with matrix metalloproteinases (MMPs) playing a role in the degradation of the collagen within the fibrous cap.[38] This presents a rough surface to flowing blood in the lumen.[38] Platelets adhere to this surface under the influence of adhesion factor activity, causing a coagulation cascade leading to an occluding clot, cutting off all blood flow.[38] This results in stroke or MI, depending on the location.[38]

Ross wrote a 1999 review article in the New England Journal of Medicine titled “Atherosclerosis - An Inflammatory Disease,” which is used in teaching institutions to provide a step-by-step description of the development of the atherosclerotic lesion.[1] In this review, Ross detailed the atherosclerotic process beginning with endothelial dysfunction, the formation of the fatty streak, and then the formation of the advanced complicated atherosclerotic lesion, ending with how unstable fibrous plaque can rapidly lead to thrombosis. Illustrations and accompanying explanations of the contribution of infection in the atherosclerotic process are provided in Figures 2 to 5 on page 29 to help readers better understand the pathobiological cascade of events implicated in the formation of an atherosclerotic lesion.

Making the Case for hsCRP Testing in Dental Practices -

It is becoming increasingly clear that the variety of cardiovascular events cannot be explained by a single pathobiological pathway. The relationship between novel biological markers of inflammation and traditional risk factors, such as high blood pressure, smoking, obesity, diabetes, low levels of physical activity, and use of hormone-replacement therapy, may be of variable importance for individual patients.[39]This has spawned a search for other factors that may be implicated and, when present, help to identify patients at greater risk for MI and other cardiovascular events.[10] Certain markers of inflammation (systemic and local) appear to play a central role in the development and progression of atherosclerosis.[10] HsCRP, one of the acute-phase proteins produced by the liver in response to infection, is a specific systemic marker of vascular inflammation that appears to have a strong association with adverse vascular events.[39]

Both hsCRP and LDL cholesterol levels are elevated in people at risk for cardiovascular events. However, hsCRP and LDL cholesterol measurements tend to identify different high-risk groups.[39] Researchers have found that independent effects were observed for hsCRP in analyses adjusted for all components of the Framingham risk score[39] (i.e., traditional risk factors for CVD). Specifically, hsCRP and LDL cholesterol levels are minimally correlated and hsCRP has been found to be a stronger predictor of future cardiovascular events than LDL cholesterol.[39] This advantage persisted after adjusting for all traditional cardiovascular risk factors and included the effect of hormone-replacement therapy at baseline.[39] The researchers further concluded that the combined evaluation of both hsCRP and LDL cholesterol proved to be a superior method of detecting risk for cardiovascular events than measurement of either biological marker alone.[39]

What is the normal range of hsCRP level? [40]

- If hsCRP level is lower than 1.0 mg/L, a person has a low risk of developing cardiovascular disease.
- If hsCRP is between 1.0 mg/L and 3.0 mg/L, a person has an average risk.
- If hsCRP is higher than 3.0 mg/L, a person is at high risk.

Low-grade chronic inflammation as measured by hsCRP predicts future risk of acute coronary syndromes independent of traditional cardiovascular risk factors.[41] Because periodontal infection appears to be a source of low-grade chronic infection, the use of hsCRP testing in dental practices provides an excellent opportunity for identifying patients at risk for acute coronary syndromes.

The Role of Dental Professionals in Screening Patients for CVD Risk -

Along with monitoring blood pressure, which has long been routine in practice, the addition of chairside hsCRP testing in dental practices has the potential to become a significant tool for identification of patients at risk for CVD. This may be especially valuable in primary prevention of CVD. Current research considers subclinical (undetected) inflammation to be an accelerant of vascular inflammation and markers of inflammation (both systemic and local), which, in turn, appear to play a central role in the development and progression of atherosclerosis.[10] Indeed, many patients seen by health-care professionals are at increased risk for MI or stroke because of undiagnosed and asymptomatic atherosclerosis which may be accelerated by chronic periodontal infection.

In 2002, the Centers for Disease Control and Prevention and the American Heart Association held a conference to examine (among other things) the selection and use of inflammatory markers to predict CVD risk. Recommendations made at the conference which have specific relevance to the present discussion follow:[42]

1) Of all the inflammatory markers identified, hsCRP, as an independent marker of risk, may be used at the discretion of the physician as part of an office-based global risk assessment (i.e., the Framingham Heart Study) in adults without known CVD. HsCRP may identify those patients for further intervention or therapy in the primary prevention of CVD.[42]

Dental professionals also are well-positioned to assist patients in assessing their global risk for CVD through use of an assessment such as the Framingham instrument.

2) Testing for hsCRP provides an additive element to global risk assessment. As a result, patients without known CVD who were not previously considered to be at risk will be identified and targets for more aggressive risk reduction interventions. It was recommended that hsCRP be measured in patients who are at intermediate risk of CHD per 10 years (as indicated in global risk assessment) to direct further evaluation and therapy in the primary prevention of CVD.[42]

A good example of this would be a patient who has been identified by a dental professional as being at intermediate risk of CVD via global risk assessment such as the Framingham risk assessment. For example, if a person's cardiovascular risk score - judged by global risk assessment - is low (the possibility of developing CVD is <10% in 10 years), hsCRP testing is not immediately warranted.[39] If the risk score is in the intermediate range (10% to 20% in 10 years), such a test can help predict a cardiovascular and stroke event and help direct further evaluation and therapy.[39] However, the benefits of such therapy based on this strategy remain uncertain.[39] If a dental professional intercepts a person with a high risk score (>20% in 10 years) or established heart disease or stroke, this is an individual who should receive intensive medical care regardless of hsCRP levels[38] and should be triaged to the care of a cardiologist as soon as possible.

3) It was recommended that patients with persistently unexplained marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for noncardiovascular causes, such as infection and inflammation.[42]

These are the types of patients cardiologists should refer to periodontists to be examined for periodontal disease.

4) It was suggested that detection of an elevated hsCRP might serve to motivate patients to adhere to better preventive therapies.[42]

This might be the case for a prediabetic patient whose hsCRP is tested by a dental hygienist chairside and discovered to be edging toward "high normal" (2 mg/L to 10 mg/L), which is predictive of heart disease. In this situation, a dental hygienist has a valuable role to play in motivating that patient to adhere to proper diet, physical fitness programs, compliance to medication regimens, or, possibly, smoking cessation counseling.

Testing for hsCRP in Dental Practices

Is it time for dental professionals to screen patients for risk of future cardiovascular events by performing chairside testing for hsCRP? Yes, and those technologies are now entering the health-care market.

The cardiologist who co-authored this article frequently asks new patients who have heart disease or who are at high risk for heart disease when they last saw their dentists, and whether they were examined for periodontal disease. He also visually examines the gingival tissue and general conditions of the teeth. An example of collaborative care involves a young, non-obese female patient with an elevated hsCRP, but normal serum lipids and blood pressure, who presented with severe gingival inflammation. The cardiologist referred this patient to a periodontist. Four months later, following periodontal therapy, her hsCRP was normal.

The cardioprotective benefits of periodontal treatment may represent an efficacious modification to contemporary therapies for vascular diseases. Several pilot studies have shown that periodontal therapy consisting of scaling and root planing and application of antimicrobial agents were effective in reducing levels of serum inflammatory markers, specifically hsCRP, IL-6, and TNF-α.[43,44] However, larger scale, randomized interventional clinical trials are needed to investigate the potential cardiovascular benefits of periodontal therapy.[7] If future

research provides evidence that treatment of periodontitis reduces hsCRP and/or decreases the incidence of CVD, this would provide a strong rationale for a change in health-care policy that would position periodontal care as medically necessary for the prevention and management of CVD.[7] In the meantime, it is time for physicians and other nondental health-care providers to begin to identify those patients who are at greater risk for periodontal disease because of their individual risk profiles. Specifically, patients who smoke are at 3 to 7 times greater risk and patients with diabetes are at 2 to 5 times greater risk for developing periodontal disease.[45] Patients who report that a sibling or parent lost their teeth at an early age may be genetically predisposed to periodontal disease with an odds ratio that confers 3 to 5 times greater risk for developing periodontal disease.[45] Those patients who both smoke and who are genotype positive have an 8 to 10 times greater risk for periodontal disease.[45] These scenarios represent excellent opportunities for the medical community to screen for periodontal disease and triage patients to dental professionals for evaluation and treatment of periodontal disease.

Discussion of the significance of periodontal infection in cardiology would be incomplete without mentioning the potential role subantimicrobial doses of doxycycline may play in inhibiting MMPs. MMPs participate in degradation of the fibrous cap of an atherosclerotic lesion (the vulnerable plaque), which ultimately leads to rupture, in-situ thrombosis, and subsequent vascular events.[46] Although larger studies are needed to investigate its potential to reduce the risk of rupture of atherosclerotic plaque, it appears that subantimicrobial doses of doxycycline, approved by the U.S. Food and Drug Administration for suppression of collagen-destroying enzymes in the treatment of periodontal disease, may also have cardioprotective benefits.[46]

Conclusion

Despite the fact that the formation of the atherosclerotic lesion and its impending threat to cardiovascular health has a very complex etiology, dental screening to identify patients at risk for CVD and those patients with diagnosed CVD who are at greater risk for recurrent cardiovascular events offers an undeniable intervention opportunity. Likewise, physicians have an enormous part to play by screening patients for periodontal disease.

For patients at intermediate risk (10% to 20% risk of CHD per 10 years) as defined by the Framingham risk score, testing for hsCRP may help direct further evaluation and therapy in primary prevention for CVD.[47] For patients with stable coronary disease and acute coronary syndromes, in-office testing in dental practices for hsCRP may prove to be invaluable in identifying those patients who require significantly more aggressive therapies provided by cardiologists.

Although the cardioprotective benefits of periodontal treatment remain speculative at present, awareness of the relationship between the increased burden of infectious agents and systemic inflammation may have a significant effect on the prevention and treatment of chronic inflammatory diseases and conditions. Transition toward interdisciplinary health-care management must increase to better target those at high risk and to devise a multidisciplinary integrated care pathway for CVD. Those physicians and dentists who collaborate on this integrated care pathway will be ahead of the curve.

It is not unusual to hear from physicians that they have seen patients with hyperparathyroidism, diabetes, osteoporosis, and various other diseases that were first diagnosed in the dental office. Indeed, astute dentists and dental hygienists are often the first to note an undesirable side effect of calcium channel blockers (i.e. drug-induced gingival overgrowth). Many within the medical profession also recognize the significant contributions of many dental professionals in monitoring patients' blood pressure. It is important to realize that we are now in an unprecedented era of explosion of research related to periodontal medicine. For the well-being of our patients, the time has come for physicians, dentists, nurses, and dental hygienists to work together to identify those at risk, both for atherosclerosis and periodontal disease. Indeed, we are all treating "a patient," not just one part or one organ.

It is interesting that the oldest medical school in the world, the University of Bologna in Bologna, Italy (founded in 1088), still requires all medical students to take a one-year course in oral medicine and dentistry. Nine hundred seventeen years later, all physicians and dentists must realize that we treat an organism. The mouth is attached to the body and each may have an effect on the health of the other. We must remember the ankle bone is connected to the leg bone and, indeed, the oral cavity is connected to the body.

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GRAND ROUNDS
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CHRONIC INFLAMMATORY PERIODONTAL DISEASE

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A Risk Factor For Cardiovascular Disease and Ischemic Stroke?

Ricardo Gapski, DDS, MS,† and Charles M. Cobb, DDS, PhD‡

Hujoel and colleagues[1] have calculated that among individuals with chronic periodontitis, the surface area of the dentogingival epithelium exposed to potential bacterial invasion and/or infiltration of antigenic microbial components ranges between 8 cm^2 and 20 cm^2. Thus, it is not surprising that a breach of this epithelial barrier is a common occurrence in chronic and aggressive periodontitis, and is likely to result in systemic dissemination of microbes, antigens, and mediators of inflammation.

Locally, bacteria and their byproducts of metabolism stimulate a cellular immune response represented by a dense infiltration of neutrophils, macrophages, and various lymphoid cells. These cells and the host connective tissue cells associated with the inflammatory lesion are stimulated to synthesize and release proinflammatory cytokines and prostanoids - interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), prostaglandin E_2 (PGE_2), and various matrix metalloproteinases (MMPs) - which play a role in the destruction of alveolar bone and connective tissues that furnish support to the teeth.[2] In addition to being a major cause of adult tooth loss, recent studies suggest that chronic and aggressive periodontitis may constitute an independent risk factor for cardiovascular disease and ischemic stroke.[3-14] However, other investigators have suggested that periodontitis may not be an independent risk factor but does represent a comorbid condition (i.e., a disease that coexists with other diseases because of a common causal factor). In some studies, smoking is shown as the common causal factor in periodontitis, cardiovascular disease, and ischemic stroke[15,16] In spite of the apparent differences in theory, periodontitis may add to the cumulative systemic insult derived from repeated exposures to other chronic inflammatory diseases during an individual's lifetime.[17-22]

Inflammatory markers

A variety of inflammation markers have been correlated to increasing severity of periodontitis, atherosclerosis, and ischemic stroke. For example, inflammation is characterized by the production of cell-derived mediators of inflammation, such as IL-6, TNF-α, and PGE_2. In turn, their systemic distribution via the vascular circulatory system induces the production of liver-derived markers of a systemic inflammatory reaction, such as c-reactive protein (CRP), serum amyloid A, fibrinogen, and haptoglobin. CRP is a particularly sensitive systemic marker of systemic inflammation. A serum CRP concentration of >10 mg/L is generally indicative of significant inflammatory disease. Compared with healthy controls, individuals with severe periodontitis are consistent in their expression of elevated serum CRP levels.[23-27] Other markers of inflammation elevated in cases of periodontitis, either in serum or gingival crevicular fluid, includehaptoglobin,[23] fibrinogen,[27] serum amyloid A, IL-1, IL-6, IL-8, PGE_2, TNF-α, and various MMPs.[2]

Noack and colleagues[24] reported that the degree of increases in CRP levels in patients with periodontitis, when adjusted for confounding modifying factors, is dependent on the severity of the disease. The authors also demonstrated a strong relationship between elevated CRP levels and the presence of several periodontal pathogenic microbes, i.e., Porphyromonas gingivalis (P. gingivalis), Prevotella intermedia (P. intermedia), Campylobacter rectus (C. rectus), and Tannerella forsythia (T. forsythia), thereby establishing an association between periodontal infections and elevated CRP levels. Serum levels of CRP, IL-6, fibrinogen, and IL-8 are also elevated in patients with unstable angina, myocardial infarction,[22] and ischemic stroke,[28] with higher levels being correlated toincreasingly poor prognoses.[22]

Periodontal pathogenic microbes and vascular disease

Animal studies - Following reports in medical literature that relate Chlamydia pneumoniae and cytomegalovirus infections to the etiology of atherosclerosis, Hzaraszthy and colleagues[29] reported that 40 of 50 (80 percent) endarterectomy specimens taken from patients with carotid stenosis were positive for periodontal pathogens, such as T. forsythia, P. gingivalis, P. intermedia, or Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans). In addition, almost 60 percent of the specimens were positive for two or more of the target microbes. Thus, their

hypothesis that oral microbes associated with severe chronic periodontitis may gain access to the systemic circulatory system and, thereby, play a role in development of atherosclerosis was supported.

Additional support for this hypothesis soon followed in a series of animal studies. Using a mouse experimental model, Kesavalu and colleagues[30] were able to induce pro-inflammatory cytokine expression (IL-1β, IL-6, and TNF-α) following subcutaneous injection of P. gingivalis and A. actinomycetemcomitans. Li and colleagues[31] demonstrated that repeated systemic inoculation of P. gingivalis resulted in significant macrophage-rich atherosclerotic plaque formation in the proximal aorta and aortic-tree vessels in a mouse model. Jain and colleagues[32] induced aortic lipid deposition in rabbits through a high fat-content diet while simultaneously inducing periodontitis in the mandibular molars in oneexperimental group. When compared with control animals in the second group without periodontitis, those animals with periodontal disease exhibited significantly greater accumulations of lipid (atheroma formation) in the aorta. Indeed, there was a positive correlation between the severity of periodontal disease and the extent of aortic lipid deposition.

Additionally, it has been demonstrated that whole cells of P. gingivalis and endotoxin derived from P. gingivalis are both capable of inducing, in vitro, foam-cell formation of mouse-derived macrophages when cultured in the presence of human low-density lipoprotein (LDL).[33] In another study, P. gingivalis and its endotoxin-laden vesicles promoted LDL binding to macrophages and promoted macrophage modification of native LDL, which plays an important role in foam-cell formation and the pathogenesis of atherosclerosis.[34] Further, Lalla and colleagues[35] demonstrated that mice, when infected with P. gingivalis, exhibited severe periodontitis, presence of P. gingivalis DNA in 22 percent of aortic biopsy specimens, and elevated serum IL-6 levels. Lastly, Gibson and colleagues[36] have shown that mice, when challenged with P. gingivalis, exhibited increased atherosclerotic plaque formation, which could be prevented by immunization against P. gingivalis.

Human studies - Because of the purported roles of P. gingivalis and A. actinomycetemcomitans in severe chronic periodontitis, Pussinen and colleagues[37, 38] chose to analyze the association of coronary heart disease and ischemic stroke to antibody levels specific for these two microbes. They found that coronary disease was more prevalent among edentulous than dentate subjects (19.8 percent vs. 12.1 percent, respectively). Further, coronary disease was more common among patients with positive antibody levels (seropositive) for P. gingivalis as compared with those who were antibody-negative (seronegative) - 14 percent vs. 9.7 percent, respectively. Seropositive individuals had a risk ratio of 1.6 for an ischemic stroke event. In addition, subjects with a history of stroke or coronary heart disease were more often seropositive for P. gingivalis and had an risk ratio of 2.6 for a secondary stroke event. These results suggest that periodontal infections, or response of the host against such infections, may play a role in the pathogenesis of coronary heart disease and ischemic stroke.

Kuramitsu and colleagues[39, 40] studied the interaction of P. gingivalis with human umbilical vein endothelial cells and were able to show that P. gingivalis was capable of inducing increased expression of a cytokine - monocyte chemoattractant protein-1 - that recruits monocytes. In addition, P. gingivalis increases the expression of a protein that facilitates attachment of monocytes to endothelial cells, called intercellular adhesion molecule-1 (ICAM-1). Lastly, P. gingivalis increases the cellular production of elastase/gelatinase (MMP-9), which has been implicated in atheroma plaque rupture.[40] The authors hypothesize that P. gingivalis-endothelial cell interactions may lead to recruitment and attachment of monocytes to the endothelial lining of blood vessels, thereby initiating vascular atheroma formation.

Research on the relationship of inflammation to cardiovascular disease has begun to focus on heat shock protein 60 (HSP60), which is strongly immunogenic. Further, HSP60 appears to be a signaling molecule that can mediate and influence a range of inflammatory responses. For example, both bacterial and host HSP60 activate human vascular endothelial cell expression of intercellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1). In addition, both types of HSP60 activate monocytes and/or macrophages to secrete IL-6 and TNF-α. Because of a high degree of sequence homology (molecular similarity) between bacterial and human HSP60, it has been suggested that HSP60 may be involved in human autoimmune disease mechanisms (i.e., the host immune system primed by HSP60 of bacterial origin can interact with its human host counterpart in gingival connective tissue or arterial walls).[41]

Yamazaki and colleagues[42] have examined the link between chronic periodontitis, atherosclerosis, and HSP60. Using both human and P. gingivalis HSP60 as the antigen, they compared humoral immune responses in atherosclerotic patients with responses in patients with chronic periodontitis and in healthy patients. Results showed antibody levels to both human and P. gingivalis HSP60 were highest in atherosclerosis patients, followed by periodontitis patients, and lowest in healthy patients. Similar results have also been reported by Chung and colleagues.[43]

Desvarieux and colleagues[44] reported a direct relationship, independent of CRP levels, between thickness of the tunica intima and tunica media of the carotid artery (indicating atherosclerotic plaque formation) and the presence of five periodontal microbial pathogens, P. gingivalis, A. actinomycetemcomitans, T. forsythia, Treponema denticola (T. denticola), and Micromonas micros. Shortly thereafter, Kozarov and colleagues[45] reported the presence of viable invasive A. actinomycetemcomitans and P. gingivalis in cells from human carotid artery atherosclerotic plaque. Marques da Silva and colleagues[46] used DNA probe techniques to examine 56 samples from aortic aneurysms taken from 51 patients for the presence of four periodontal microbial pathogens (A. actinomycetemcomitans, P. gingivalis, T. denticola, and T. forsythia). They detected bacterial DNA in 89.2 percent of the specimens. However, A. actinomycetemcomitans was detected in only four specimens (7.1 percent), and all specimens were negative for the other three microbes. An explanation for this seeming paradox is found in a previous study by Marques da Silva and colleagues[47] in which anaerobic culture and electron microscopy techniques were used to demonstrate the presence of several common oral microbes, such as Streptococcus mitis, Actinomyces naeslundii, and Actinomyces viscosus.

Recently, Fiehn and colleagues[48] identified DNA from periodontal pathogenic microbes in atherosclerotic plaques that were removed from carotid and femoral arteries. DNA of P. intermedia was consistently detected, but P. gingivalis DNA was noted only sporadically. Interestingly, when cultured under anaerobic conditions, none of the tissue specimens yielded growth of oral bacteria. Additionally, Dögan and colleagues[49] compared the total bacterial number in subgingival plaque samples from periodontitis patients with and without a history of recent myocardial infarction. The authors reported that bacterial levels were elevated in only those patients with a history of myocardial infarction, leading the

authors to suggest that increased loads of subgingival bacteria may present a risk for systemic health.

Current data does not indicate a direct involvement of the bacteria in development of aortic aneurysms. However, a dominant feature in the pathogenesis of aortic aneurysms is the proteolytic degradation of the aortic wall by MMPs. The expression of collagenase (MMP-1 and MMP-13) and elastase/gelatinase (MMP-2, MMP-9, and MMP-12) is increased in aortic aneurysm tissues. Theoretically, the presence of bacteria in a vascular wall lesion induces a localized inflammation with the inherent induction of various cytokines, primary mediators of inflammation that, in turn, stimulate MMP expression by host cells, eventually leading to an aortic aneurysm.

Clinical studies

Two studies in 1989 reported statistically significant relationships between oral health and myocardial and cerebral infarction.[50, 51] Since that time, several studies have reported epidemiological associations between chronic periodontitis and cardiovascular and cerebrovascular disease.[4-8, 52-56] It is now obvious that periodontal disease and atherosclerotic plaque-related diseases have several risk factors in common, such as smoking, diabetes, elevated levels of serum CRP, etc. Because of overlapping risk factors, it remains difficult to demonstrate a direct causal relationship between chronic periodontitis and cardiovascular and cerebrovascular disease. However, this does not minimize the role of chronic periodontitis as an inflammatory risk factor in atherosclerosis and its sequelae.[10]

Many studies have examined the role of chronic periodontitis as an independent risk factor and an “infectious burden” in general; taken collectively, they indicate a significant association with atheroma formation (Figure 1) and ischemic stroke.[11,14,19,26,28,57-62] It has been suggested that periodontal inflammation may contribute to a prothrombotic state via recurrent bacteremias, platelet activation, and elevated clotting factors, thereby increasing the risk of embolism formation and ischemic stroke.[14]

Other studies suggest that it is highly unlikely that a single infectious agent or inflammatory disease plays a unique role in atheroma development. It is more likely thatthe risk of developing atherosclerosis is related to the number of inflammatory disease events to which an individual has been exposed.[61-63] One can argue that periodontitis represents a chronic inflammatory infection that may exist for years, thereby exposing the patient to a continuous microbial insult and all of the inherent metabolic events associated with inflammation. Given such a scenario, moderate and severe chronic periodontitis represent an important risk factor for the development of atherosclerosis leading to cardiovascular and cerebrovascular disease. Thus, it is clinically relevant that three recent studies have reported that periodontal therapy consisting of scaling and root planing and subgingival delivery of antimicrobial agents is effective in reducing levels of serum inflammatory markers, specifically CRP, IL-6, and TNF-α.[64-66]

Conclusion

Inflammation in the vessel wall plays an essential role in the initiation and progression of atherosclerosis, the erosion or disruption of vascular atheromas, and eventual rupture of such plaques.[22] The collective body of literature suggests that immune activation in cases of severe chronic periodontitis results in the concomitant systemic dissemination of gram-negative microbes, antigens and endotoxins, and mediators of inflammation. The dissemination of these factors, in turn, appears to promote inflammation of the arteries involving the cardiovascular and cerebrovascular systems, leading to atherosclerosis, and ultimately initiating an acute coronary event or ischemic stroke, with circulating levels of the inflammatory markers reflecting the clinical course of the condition.

The general hypothesis that chronic infections, such as periodontitis, can contribute to the development of atherosclerosis and, thereby, cardiovascular disease and ischemic stroke, is based on the following observations:

- Infectious agents can directly interact with the cellular components of the tunica intima and tunica media of vessels.
- There is systemic dissemination of cytokines and mediators of inflammation because of chronic inflammatory disease, such as periodontitis.
- There is an increased expression of cytokines, mediators of inflammation, and cellular adhesion molecules resulting in local endothelial dysfunction.

Although the studies cited in this review point to a role for periodontal disease in the development of cardiovascular and cerebrovascular disease, it remains to be shown that treatment of periodontal disease will prevent atherosclerotic events. Currently, there is insufficient data to differentiate between the role of a direct infection of the vascular wall and stimulation of a proinflammatory state by periodontitis. In spite of these shortcomings, it is critical to test the hypothesis that intensive treatment of inflammatory periodontal disease and long-term maintenance will have a positive impact on the clinical course of atherosclerotic-related diseases.

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GRAND ROUNDS
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AHEAD OF THE CURVE

Casey Hein

Frank Formica, DDS; Bowie, MD

Patients in his community near Baltimore and Annapolis consider Dr. Frank Formica the authority in technical dentistry, including temporomandibular joint disturbances. Formica is also respected for providing excellent restorative dentistry and periodontal treatment. Much has changed during his 40-year career, but Formica acknowledges that implementing periodontal medicine is not new; he has been applying credible research findings related to the systemic effects of periodontal disease into his clinical protocols for many years.

Formica believes dentistry is a specialized field of medicine, and that dentists must be aware of new findings in medicine as these findings may directly relate to treatment. He cites articles published during the past 10 years in both dental and medical journals as being pivotal in convincing him to start talking with periodontal patients about their increased risk for cardiovascular diseases (CVD). Formica discusses this research with patients - specifically that heart attacks may be caused from infections such as periodontal disease.

“As a dentist with the knowledge that one of the most common infections of mankind is periodontal disease, I started to order a high sensitivity c-reactive protein (hsCRP) test on patients with the disease,” Formica said. HsCRP is a blood test used to identify candidates who are at greater risk for an acute coronary event. Concerned about the role of chronic periodontal infection in increasing patients’ risk for CVD, Formica has ordered hsCRP testing on many of his patients during the past five years. He shares the results with physicians, who have been helpful and willing to consult on the medical aspects of treatment.

“A patient related to me that after having had a heart attack, he asked his physician why the attack occurred,” Formica said. “The physician was unable to provide a clear explanation to this patient because he had no classic risk factors for cardiovascular disease. When the patient presented to my practice, we diagnosed him with chronic periodontitis. His physician was elated that a risk factor for CVD had been identified and treated.”

“In another case, a long-term patient with periodontal disease who refused treatment despite repeated warning of dangers of untreated periodontal disease, suffered a heart attack. The progress notes recorded over the years document the diagnosis of periodontal disease and subsequent recommendations for treatment. The last entry was, ‘This patient will have a heart attack,’ and six months later he suffered his first episode of myocardial infarction.”

Formica was asked what he thinks is the most needed change in educating dentists and physicians. The most important change he would make in achieving interdisciplinary education would be to add a course in internal medicine for dental students and a course in oral medicine for medical students so physicians would have the diagnostic knowledge necessary to refer to dentists those patients at risk for oral diseases and conditions.

When asked what he thought researchers will have discovered about the relationship between the oral cavity and the whole body in 20 years, Formica said, “The mouth mirrors what is happening in the body, and it can be an entry point for infections. The treatment of periodontal disease must be both local and systemic” (F. Formica, written communication, Nov 2005).

Jonathan Richter, DDS
Lauren Kilmeade, RDH
Great Neck, NY

Dr. Jonathan Richter and Lauren Kilmeade share a vision for building a practice totally dedicated to comprehensive periodontal medicine. Their dedication was jump started in part by the death of Kilmeade’s 59-year-old father, who died from heart disease and diabetes in 2001.

At the heart of their comprehensive wellness model is Kilmeade teaching patients how oral health affects overall systemic health. They credit dental assistants - one of whom is a licensed practical nurse - and members of the business staff for their knowledge of oral-systemic medicine and their ability to reinforce patient education.

Clinical protocols in Richter’s office include monitoring blood pressure at all recare appointments, using glucometers to monitor diabetic patients’ blood sugar before procedures, and using chairside HbA1c analyzers to screen patients for undiagnosed diabetes and to determine whether periodontal treatment was effective in reducing patients’ glycosylated hemoglobin.

Richter communicates with patients' physicians (endocrinologists, cardiologists, rheumatologists, obstetricians, and internists) to discuss specific cases and growing evidence to support periodontal systemic links. In addition, Richter is diligent about monitoring clinical endpoints that give him the information to more accurately refer to medical specialists those patients who do not respond favorably to periodontal treatment.

Richter and Kilmeade promote smoking cessation by providing relevant literature and recommending specific smoking cessation counselors. They have identified many patients who were at risk for diabetes and who later were confirmed diabetics upon evaluation by their physicians. Some patients credit early intervention of their diabetes to Richter and Kilmeade.

Richter and Kilmeade have organized round table discussions with members of the medical community. The intent is to share ideas on mutual patient care and foster collaborative relationships.

When asked how members of the medical community have reacted to their progressive diagnostic and treatment philosophies, Richter said, "Initially the medical community thought we were using the HbA1C to diagnose. When they realized how we were utilizing the data to manage and treat our patients comprehensively and to refer them to the proper physicians, they seemed to embrace the concept" (J. Richter, written communication, Nov 2005).

Kilmeade and Richter cite the lack of support from organized dentistry and medicine as a hurdle to the implementation of oral-systemic medicine, but that doesn't seem to have slowed them down.

When asked what patients say about this kind of comprehensive care, Kilmeade said, "Our patients choose us for their dental care because they are confident they are receiving comprehensive quality care that is customized to their individual needs. They indeed participate in helping us help them. Once the oral/systemic concept is presented and applied to their personal health, they are converted into true believers, taking their oral health to heart as much as we do" (L. Kilmeade, written communication, Nov 2005).

This column is dedicated to clinicians, educators, and researchers at the forefront of oral-systemic medicine. To call them early adopters is an understatement. Professionals who are ahead of the curve read the research and look for appropriate, innovative opportunities to transfer the research to private practices or academic settings. Pursuits for excellence fuel their purposes, plans, and searches for better ways to take care of patients and motivate students. To those ahead of the curve, PennWell says, "Well done."

Stories welcome: To contribute stories about other clinicians, educators, and researchers at the forefront of oral-systemic medicine, please e-mail Casey Hein, Chief Editor, at caseyh@pennwell.com.

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