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THE SIGNIFICANCE OF PERIODONTAL INFECTION IN CARDIOLOGY

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Abstract
Molecular and cellular biology and the physiologic mechanisms of disease constitute the basis of treatment in both cardiology and periodontics. Recognizing inflammation as the common denominator in the pathobiology of cardiovascular and periodontal disease provides an excellent opportunity for dental and medical professionals to collaborate on decreasing patients' risk for cardiovascular disease (CVD), or its progression. This article focuses on empowering dental and medical professionals to incorporate the latest evidence on the relationship of periodontal and cardiovascular disease by presenting an in-depth view of the inflammatory process involved with atherosclerosis. Further, this article will discuss the significance of infections such as periodontal disease in increasing the systemic inflammatory burden and risk for atherosclerosis and, thereby, increasing the risk for CVD. In addition, a rationale for why periodontal disease should be considered a risk correlate of CVD is presented. Also discussed is the use of the Framingham CVD risk assessment instrument and high-sensitivity C-reactive protein (hsCRP) testing in dental practices and screening for periodontal disease in medical practices. This article concludes by challenging readers to realize the undeniable therapeutic opportunity of medical-dental collaboration in reversing the rather somber trends in CVD.

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Key words: Periodontitis, cardiovascular disease, bacteria, inflammation, risk factors

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 reveal that 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

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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

Table 1
Factors Associated With Increased Risk for CVD.[15] *(Correlated to the Framingham Heart Study.)*
Should periodontal disease be added to this list?

Major Independent Risk Factors
- Advancing age
- Cigarette smoking
- Diabetes
- Elevated blood pressure
- Elevated serum total (and LDL) cholesterol
- Low serum HDL cholesterol

Predisposing Risk Factors
- Abdominal obesity§
- Ethnic characteristics
- Family history of premature coronary heart disease
- Obesity†§
- Physical inactivity†
- Psychosocial risk factors

Periodontal disease?

Conditional risk factors
- Elevated serum homocysteine
- Elevated serum lipoprotein (a)
- Elevated serum triglycerides
- Inflammatory markers (e.g. C-reactive protein)
- Prothrombotic factors (e.g. fibrinogen)
- Small LDL particles

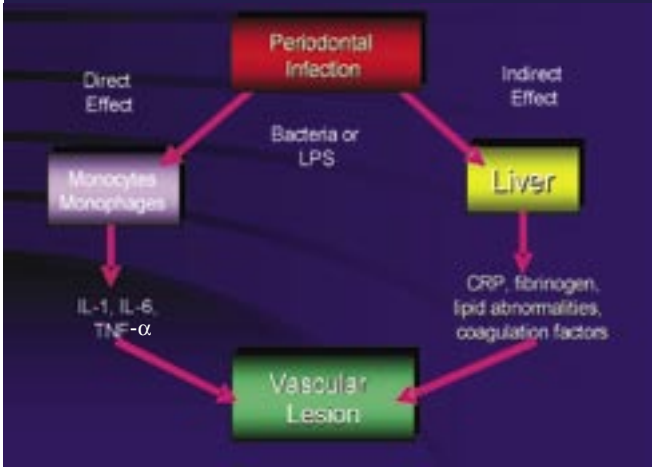
† These risk factors are defined as major risk factors by the American Heart Association
§ Body weights are currently defined according to BMI as follows: normal weight 18.5 kg/m² to 24.9 kg/m²; overweight 25 kg/m²to 29 kg/m²; obesity >30.0 kg/m²; (obesity class I 30.0 kg/m²to 34.9 kg/m²; class II 35.9 kg/m²to 39.9 kg/m², class III ≥50 kg/m²). Abdominal obesity is defined according to waist circumference: men >102 cm (>40") and women >88 cm (>35").

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

Figure 1¥ — Model for systemic spread of periodontal infection and effects on the vasculature



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

¥ Reprinted from *Periodontics: Medicine, Surgery, and Implants*, Rose LF, Mealey BL, Genco RJ, Cohen DW, pg 848, Copyright 2004, with permission from Elsevier.

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

Figures 2 — 5: Evolution of the atherosclerotic lesion

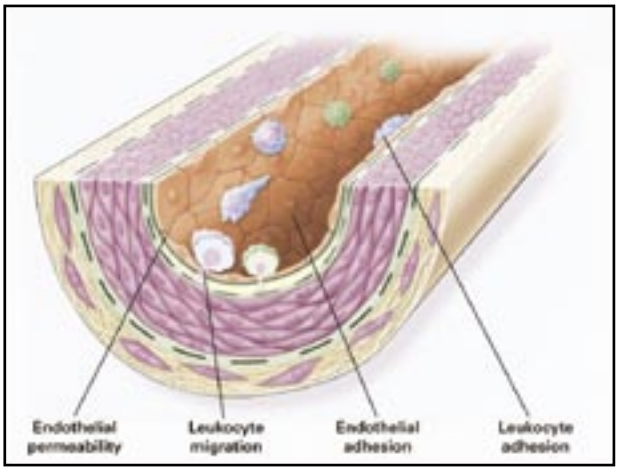


Figure 2 — Endothelial dysfunction in atheroslerosis.[1]
The earliest changes preceding the formation of atherosclerotic lesions involve the endothelial lining of the vessel lumen. The changes include increased endothelial permeability that leads to acculumation of lipoproteins and development of the 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.

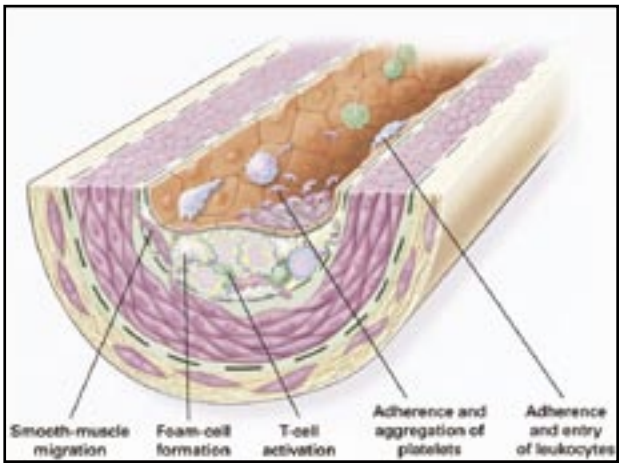


Figure 3 — Fatty-streak formation in atherosclerosis.[1]
Fatty streaks initially consist of lipid-laden monocytes and macrophages (foam cells) together with T-lymphocytes. Later, they are joined by increasing numbers of smooth muscle cells, some of which may also contain varying amounts of lipid. The 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).

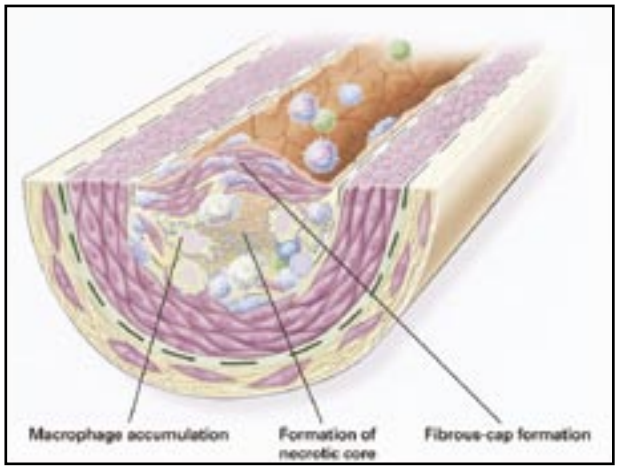


Figure 4 — Formation of an advanced, complicated lesion of atherosclerosis.[1]
Intermediate and advanced atherosclerotic lesions are characterized by a fatty streak covered by a fibrous connective tissue cap. The cap represents a healing response to injury and forms a barrier between the underlying lesion 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.

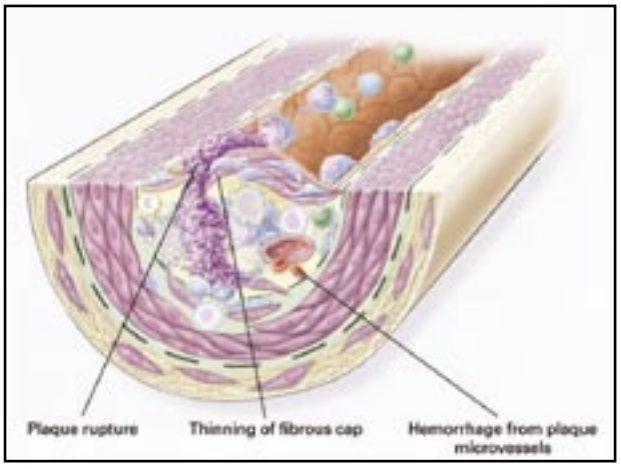


Figure 5 — Unstable fibrous plaques in atherosclerosis.[1]
Rupture or ulceration of the fibrous cap can lead to hemorrhage and thrombosis and usually occurs at sites where the connective tissue layer is thin. Thinning of the fibrous cap is apparently because of the continuing influx and activation of 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.

Medical illustrations used with permission from the *New England Journal of Medicine*

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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