



Destructive Periodontal Diseases, Systemic Inflammation, and Atherosclerotic Complications: The Emerging Role of the Dental Profession

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ABSTRACT An emerging body of evidence has associated moderate to severe periodontitis with atherosclerotic complications. The contribution of periodontitis to systemic inflammation may account for this association in view of the pivotal role inflammation plays in atherosclerotic complications. Periodontal therapy has been shown to decrease systemic inflammation and to improve early atherosclerotic events; however, to date, periodontal therapy has not been shown to decrease subsequent atherosclerotic complications although aggressive treatment in at-risk populations appears warranted.

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Over the past two decades, an ever-increasing number of studies have reported an association between destructive periodontal diseases and atherosclerotic complications, including myocardial infarction and stroke.¹ In addition, destructive periodontal diseases have also been found associated, to varying degrees, with other chronic systemic diseases or conditions including type 2 diabetes mellitus, pre-term low birth weight infants, chronic kidney disease, rheumatoid arthritis, and possibly Alzheimer's disease.²⁻⁹

These seemingly disparate chronic diseases are united by the discovery that increased systemic inflammatory burden is an underlying risk factor for all of these diseases. Of interest, destructive periodontal diseases, along with several other chronic infections and/or inflammatory conditions, have been shown to contribute to systemic inflammation and destructive periodontal diseases, although apparently decreasing in prevalence over the past decade mainly due to the decreased prevalence of smoking in the United States, are still relatively common in the adult population.¹⁰⁻¹³

These findings, therefore, raise the question of what is the role, if any, for the dental profession in the prevention or management of these commonly encountered systemic chronic diseases?

To address this question, the intent of this paper is to provide an overview for the dental health care professional of the contribution of destructive periodontal diseases to systemic inflammation. Using reports primarily published within the last five years, emphasis will be placed on the role destructive periodontal diseases may play in atherosclerotic complications since the greatest body of evidence has been assembled for this oral-systemic disease association.

Specific questions to be addressed in this overview are:

- What is the strength of the association between destructive periodontal diseases and atherosclerotic complications?
- What biologically plausible explanations have been forwarded to account for this association?
- How may destructive periodontal diseases contribute to systemic inflammation?
- Can the treatment or eradication of periodontal diseases reduce the risk of subsequent atherosclerotic complications?

The significance to the dental profession, if destructive periodontal diseases are indeed shown to contribute to atherosclerotic complications, is that periodontal therapy may become a medically necessary component of care in the prevention and management of atherosclerotic complications in the future.

Destructive Periodontal Diseases Are Associated With Myocardial Infarction and Stroke — Strength of the Association

Despite recent advances in health care and prevention, atherosclerotic complications, including myocardial infarction,

stroke, and thromboembolic events, continue to be a major cause of mortality in the United States. From 1995 to 2005, the national death rate due to cardiovascular diseases decreased by 26.4 percent. However, in 2005, the latest year complete data are available, the overall death rate from cardiovascular diseases was 278.9 deaths per 100,000 individuals, still a very prevalent rate of death. Preliminary data from 2006 also reports that cardiovascular diseases accounted for 34.2 percent of all deaths or for one of every 2.9 deaths in the United States.

PERIODONTAL THERAPY may become a medically necessary component of care in the prevention and management of atherosclerotic complications in the future.

Stroke accounted for one out of every 18 deaths.¹⁴ These data highlight that although considerable progress has been made in prevention and management in the last 10 years, death from atherosclerotic complications continues to be a major public health concern in the United States. Therefore, the search continues for additional means to decrease mortality from atherosclerotic complications.

In addition to conventional risk factors for atherosclerotic complications that include age, gender, lipid profiles, hypertension, smoking, diabetes mellitus, exercise, body mass index, and family history, non-conventional risk factors such as periodontal diseases have been increasingly associated with atherosclerotic complications.¹ The initial reports of an association between periodontitis and atherosclerotic compli-

cations came from Scandinavia in 1989. Mattila and co-workers reported that oral infections including caries, periodontitis, periapical lesions, and pericoronitis were more frequent in subjects with recent myocardial infarctions than in healthy populations.¹⁵

Syrajani and co-workers reported poor oral health was more frequently found in subjects with recent strokes than in stroke-free controls.¹⁶ Since 1989, an ever-growing body of evidence has linked periodontitis and atherosclerotic complications. Perhaps the most conclusive study to date is a comprehensive meta-analysis of prospective cohort studies, case-control studies, and prevalence studies.¹⁷ In this report, a meta-analysis of five cross-sectional studies that included 17,724 subjects found the prevalence of cardiovascular disease to be 1.59 times greater (confidence interval of 1.33-1.91) in subjects with periodontitis than in those subjects without periodontitis.¹⁷ This meta-analysis, encompassing several cross-sectional studies, suggests periodontitis is significantly, although moderately, associated with atherosclerotic complications. The clinical significance of these findings is that, since destructive periodontal diseases are treatable, they may comprise a reversible risk factor for atherosclerotic complications.

However, both adult periodontitis and atherosclerotic complications share several common risk factors including age, gender, BMI, smoking, diabetes mellitus, and socioeconomic status. Therefore, the possibility exists that the association between the two diseases may merely be due to common risk factors, also termed confounding factors. But this hypothesis fails to be supported by the results of prospective studies that suggest periodontitis may precede, and therefore, may contribute to atherosclerotic complications. A meta-analysis of five prospective cohort studies that together included 86,092 subjects reported subjects with periodontal disease, defined using a range of criteria,

were 1.14 times (confidence interval of 1.07-1.23) more likely to experience a subsequent cardiovascular disease event.¹⁷ Five prospective case control studies from the same meta-analysis comprising 1,423 subjects reported a 2.22 times greater risk (confidence interval of 1.59-3.12) of a subject with periodontitis experiencing a subsequent atherosclerotic complication.¹⁷ Therefore, results of prospective as well as cross-sectional studies support a positive, although modest, association between adult periodontitis and atherosclerotic complications.

It should be noted that a variety of factors can contribute to the variance observed in the results from the above cited studies, including the criteria used to define an atherosclerotic event and, perhaps more importantly, the criteria used to define periodontitis exposure. It has been suggested that periodontal indices such as pocket depth more strongly associate with acute serum markers, such as C-reactive protein and fibrinogen (discussed below), and that indices that record past periodontitis activity such as clinical attachment level and tooth loss more strongly associate with chronic markers, such as early signs of atherosclerosis such as arterial media thickness.¹⁸

In addition to atherosclerotic complications, periodontitis has also been reported to precede two additional chronic diseases: chronic renal disease and type 2 diabetes mellitus. A cross-sectional study of 5,537 subjects that participated in the Atherosclerosis Risk in Communities study, ARIC, found subjects with severe periodontitis to be twice as likely to have early renal insufficiency when compared to periodontally healthy controls.¹⁹ An analysis of the third National Health and Nutrition Survey, NHANES III, found a positive association between the presence of periodontitis and edentulism with decreased renal glomerular filtration rate, a precursor of chronic renal disease.²⁰ A longitudinal study of

Pima Indians found periodontitis to be predictive of death from both ischemic heart disease and diabetic nephropathy, and also to be predictive of overt nephropathy and end-stage renal disease in subjects with type 2 diabetes mellitus.^{2,3}

In addition to chronic renal disease and type 2 diabetes mellitus, maternal exposure to periodontitis has also been associated with preterm, low birth weight infants.^{5,6} Therefore, the question arises, what is the biologic mechanism responsible for the association between periodontitis and these chronic systemic diseases?

A LONGITUDINAL STUDY of Pima Indians found periodontitis to be predictive of death from both ischemic heart disease and diabetic nephropathy.

Elevated Systemic Inflammation Predicts Atherosclerotic Complications

Although several mechanisms have been forwarded to account for the association between periodontal disease and atherosclerotic complications, the contribution of moderate to severe periodontitis to systemic inflammatory burden is particularly attractive. Nearly half of the patients diagnosed with myocardial infarction and stroke do not present with the characteristic altered serum lipid profiles reported in the Framingham risk for cardiovascular disease studies. These lipid profiles include increased total cholesterol, low-density lipoprotein (LDL) and triglycerides, and decreased high-density lipoproteins (HDL). Therefore, clinical studies conducted in the past decade have expanded to examine other atherosclerotic risk factors such as

increased systemic inflammation.²¹ In sites of acute or chronic infection/inflammation, proinflammatory cytokines such as tumor necrosis- α (TNF- α), interleukin-1 (IL-1) and IL-6 are locally synthesized and released. If the local inflammatory response is particularly severe, the serum level of these proinflammatory cytokines also increases.

In response to infection/inflammation, the elevated level of proinflammatory cytokines, in turn, regulate the hepatic synthesis of a set of serum proteins, termed acute phase proteins. Acute phase proteins are thought to be a primitive host response to infection and trauma but have also been identified as risk factors for atherosclerotic complications. In particular, C-reactive protein (CRP), an acute phase protein and systemic marker of inflammation, has been identified as a major risk factor for atherosclerotic complications and supplements traditional serum lipoprotein profiles in the prediction of myocardial infarction and stroke.²²⁻²⁵ Most importantly, statin therapy that decreased levels of CRP below 2 mg/l resulted in a decreased incidence of cardiovascular events and mortality in the 3,745-subject "Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction" study.²⁶ The results of this study suggest inflammatory processes play an active role in atherosclerotic complications.

Destructive Periodontal Diseases Contribute to Systemic Inflammation

Although systemic inflammation can arise from many sources, moderate to severe periodontitis has been shown to be associated with elevated serum CRP levels and an acute phase response. The initial observation of a positive association between serum CRP levels and the severity of periodontitis was reported in 2000 from an analysis of the NHANES III data.²⁷ Since 2000, a series of studies have focused on periodontitis and acute phase proteins,

especially CRP. A recent meta-analysis of 18 reports, culled from more than 448 reports in the literature, found a consistent positive association between elevated CRP and periodontitis.²⁸ Severe periodontitis, in addition to elevated CRP levels, has also been associated with hyperglycemia and altered serum lipid profiles consistent with an acute phase response.²⁹ Increased systemic markers of inflammation including CRP, IL-6, fibrinogen and TNF- α were found in patients with acute coronary syndrome and periodontitis, while the severity of coronary artery disease, as determined by the number of occluded coronary vessels at angiography, correlated with the number of missing teeth, clinical attachment loss, and total bacterial burden of *Porphyromonas gingivalis*.³⁰

Periodontitis has also been found associated with early atherosclerotic events, such as atherosclerotic plaque progression. A study of 657 subjects without a history of myocardial infarction or stroke had levels of 11 periodontal pathogens measured by DNA hybridization. In addition, carotid intima-media thickness, IMT, an additional marker of atherosclerotic plaque progression, was measured by high-resolution ultrasound. The overall bacterial burden was found to correlate with cardiovascular IMT but no relationship was found for CRP.³¹ It is therefore plausible that increased systemic inflammatory burden, contributed perhaps in part by destructive periodontal diseases, may increase the risk of subsequent atherosclerotic complications.

Effect of Periodontal Therapy on Systemic Inflammation and the Incidence of Atherosclerotic Complications

If destructive periodontal diseases in fact contribute to systemic inflammation and therefore increase the risk for atherosclerotic complications, effective periodontal therapy and the eradication of periodontal infections should decrease levels of

systemic inflammation and the incidence of subsequent atherosclerotic complications. Recent reports have shown that effective periodontal therapy can decrease several markers of systemic inflammation and may also improve early pathologic events associated with atherosclerotic disease progression. Full-mouth extraction in patients with severe periodontitis has been shown to decrease levels of CRP, plasminogen activator inhibitor-1, fibrinogen, and total white cell counts, all systemic markers of infection/inflammation that have also been associated with atherosclerotic complications.³²

RECENT REPORTS have shown that effective periodontal therapy can decrease several markers of systemic inflammation.

Aggressive, nonsurgical periodontal therapy, including the use of locally applied subgingival antibiotics, has been reported to decrease serum CRP levels in those subjects responsive to treatment.^{33,34} Aggressive, nonsurgical periodontal therapy has also been reported to improve serum lipid profiles and to decrease systolic blood pressure.³⁵

However, not all intervention studies have observed a decrease in CRP with periodontal therapy.^{36,37} It should be noted that elevated systemic inflammation may arise from many sources including chronic diseases, such as rheumatoid arthritis, and commonly encountered conditions, such as obesity. Studies reporting a decrease in CRP after periodontal therapy have generally enrolled subjects that had severe periodontitis and elevated (>3.0 mg/L) CRP levels without other overt sources of

systemic inflammation, such as elevated BMI. Studies that have shown a decrease in inflammatory markers with periodontal therapy have also followed rigorous maintenance and recall protocols.

Several periodontal intervention studies have also reported improvement in early pathologic events associated with atherosclerosis. Aggressive, nonsurgical periodontal therapy has been shown to decrease endothelial dysfunction, a systemic vascular disorder characterized by decreased local expression of vasodilators, particularly nitric oxide, and an overexpression of vasoconstrictors by endothelial cells.^{38,39} Endothelial dysfunction has been identified as an early marker for atherosclerotic complications and is thought to reflect overall systemic inflammatory burden.⁴⁰

As compelling as the results of the above studies appear, no studies to date have demonstrated that effective periodontal therapy can decrease the incidence of atherosclerotic complications. Several explanations may account for this. Periodontal intervention trials for atherosclerotic complications, such as myocardial infarction, are difficult and expensive to conduct. The low rate of incidence for atherosclerotic complications in the general population implies a large study population would need to be recruited and followed for extended periods of time to capture a significant number of cardiovascular events. In addition, an intervention study would need to focus on and recruit subjects with severe periodontitis who would also comply with aggressive periodontal therapy and maintenance and recall regimens. In addition, subjects recruited into the study would need to be free from other sources of inflammation such as rheumatoid arthritis and high BMI. Also, multiple risk factors have been identified for atherosclerotic complications of which periodontitis may be only a single factor. Since the strength of

the association between atherosclerotic complications and destructive periodontal diseases is modest, large subject numbers would need to be recruited in the face of the large number of confounding factors.

Conclusions

At present, evidence from a large number of clinical studies supports an association between destructive periodontal diseases and atherosclerotic complications. The association is greatest for moderate to severe periodontitis, but, overall, the strength of the association is modest. Several mechanisms have been forwarded to account for the association but the contribution of periodontitis to systemic inflammation is particularly attractive in view of the role inflammation plays in atherosclerotic complications in addition to several other chronic systemic diseases that are also associated with periodontitis.

Intensive periodontal therapy has been shown in several studies to decrease systemic markers of inflammation, such as CRP, as well as to improve early events associated with atherosclerosis such as endothelial dysfunction. However, to date, periodontal therapy has not been shown to decrease the risk of subsequent atherosclerotic complications in at-risk populations. Nonetheless, since destructive periodontal diseases are readily amenable to treatment, it appears prudent to remove this reversible risk factor from the array of risk factors for atherosclerotic complications that include myocardial infarction and stroke. ■■■■

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