Editorial

Periodontal Disease and Atherosclerosis
From Dental to Arterial Plaque
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The conventional risk factors for atherosclerosis are well understood, but they can account for only about 50% to 70% of atherosclerotic events in the general population. Many other putative risk factors for atherosclerosis have been proposed, including traits related to obesity, inflammation, and infection. Periodontal disease is a candidate risk factor that shares many of these related traits. The periodontal diseases reflect a spectrum of oral pathology from gingivitis (gum inflammation) to severe periodontitis (progressive loss of gum attachment) with alveolar bone and tooth loss.

The pathogenesis of periodontal disease is thought to be due to accumulation of dental plaque (bacteria in subgingival biofilms) with consequent mucosal infection and inflammation. Abnormal host responses, with upregulation of matrix metalloproteinases, contribute to a more rapid disease progression in some patients. Periodontal disease is more common with cigarette smoking, obesity, and diabetes, and it affects about 75% of the adult population in the United States, with about 20% to 30% of adults having severe forms. Increasing evidence over the past decade suggests a link with about 20% to 30% of adults having severe periodontal disease.

Multiple cross-sectional studies have demonstrated a higher incidence of atherosclerotic complications in patients with periodontal disease. In the NHANES III cohort, severe periodontal disease was associated with an almost 4-fold higher incidence of myocardial infarction than found in patients without periodontal disease. In cross-sectional studies, the cardiovascular risk associated with periodontal disease appears dependent on severity of the disease, and it is independent of conventional risk factors (including smoking, poverty, diabetes, and body mass index). One problem with cross-sectional and case-control studies is that they do not tell us whether a disease is a cause or a consequence of another condition. For example, it is possible that atherosclerosis might exacerbate periodontal disease, by causing a systemic inflammatory response or even through subclinical ischemia.

Longitudinal cohort studies permit this possibility to be tested.

As is often the case with novel risk factors, the results of longitudinal studies have not been as uniformly or strongly positive as cross-sectional ones. However, several prospective studies have suggested a 1.5- to 2.5-fold increased risk of developing complications of atherosclerosis among patients with periodontal disease at baseline. Two large prospective studies failed to find an association between periodontal disease and atherosclerosis after adjusting for other risk factors. These inconsistent prospective studies may relate to lack of discrimination between mild and severe periodontal disease; the development of periodontal disease in patients free of it at baseline or confounding genetic variables, such interleukin genotype. These factors would tend to reduce the strength of any association. At the very least, the prospective studies demonstrate that periodontal disease precedes atherosclerosis. Overall, the observational studies support a strong link with atherosclerosis, but cannot prove causation.

There are several possible explanations for the association between periodontal disease and complications of atherosclerosis. First, it may merely reflect confounding by common risk factors that cause both periodontal disease and atherosclerosis, such as smoking, obesity, and diabetes. All of the observational studies have adjusted statistically for these risk factors, though such adjustments can be problematic when large differences in risk factor burden exist between groups. Additionally, there may be as yet unknown shared risk factors that cannot be taken into account.

Second, the association may reflect an individual propensity to develop an exuberant inflammatory response to intrinsic (age, sex, genes) or extrinsic stimuli (diet, smoking, etc) that then predisposes to both periodontal disease and atherosclerosis.

Third, the presence of an inflammatory focus in the oral cavity may potentiate the atherosclerotic process by stimulation of humoral and cell-mediated inflammatory pathways. The degree of inflammation in periodontal disease is clearly sufficient to cause a systemic inflammatory response, as evidenced by increases in C-reactive protein. Cross-reactivity of antibodies to periodontal pathogens with antigens present in platelets or endothelial cells might be an additional pro-inflammatory mechanism.

Fourth, the presence of periodontal infection may lead to brief episodes of bacteremia with inoculation of atherosclerotic plaques by periodontal pathogens such as Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, and Bacteroides forsythus. Subsequent growth of these bacteria could cause inflammation and plaque instability. Indeed,
there is evidence using immunostaining and polymerase chain reaction for bacterial rDNA that these pathogens are present in 18% to 30% of carotid atheromas. Identifying the true nature of the relationship between periodontal disease and atherosclerosis will be crucial so that appropriate screening and treatment recommendations can be made. Three new articles the July issue and in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology shed new light on the role of periodontal disease in atherosclerosis.19–21

Pussinen and colleagues21 report that antibodies to select periodontal pathogens are associated with coronary heart disease. These investigators developed multisertype ELISAs for detection of IgG antibodies to 3 strains of P. gingivalis and 6 strains of A. actinomycetemcomitans. These antibody tests have sensitivity of 70% and specificity of 90% for clinically and radiologically diagnosed periodontitis. In a sample of 1163 middle-aged men, combined antibody titers were associated with coronary heart disease (CHD).21 Because edentulous status was strongly associated with coronary disease, the investigators analyzed dentate and edentulous subjects separately. Though edentulous subjects tended to have lower antibody titers than dentate ones, high antibody titers (more than 3 standard deviations above the mean for periodontally healthy subjects) were associated with a 2- to 3-fold higher incidence of coronary heart disease. Similar findings were observed in dentate subjects, with high antibody titers associated with an odds ratio for CHD of 1.5, even after adjustment for conventional risk factors. Importantly, only antibodies to P. gingivalis were associated with CHD. This interesting study has several implications. First it confirms that edentulous status is a marker for atherosclerotic coronary disease. Caries was not associated with CHD, suggesting that it is periodontal disease that causes loss of teeth in these patients. However, because loss or removal of teeth appears to attenuate periodontal infection/inflammation (as evidenced by lower antibody titers), edentulous patients should be excluded or analyzed separately in these studies. Second, this study, using different methodology (serology) and in a larger sample, confirms previous work22 that periodontal infection is associated with coronary disease. Third, the apparent specificity of antibodies to P. gingivalis for incident CHD would support the hypothesis that infection with, or the host response to, this particular bacteria is particularly deleterious in terms of atherosclerotic complications. This possibility is supported by another of the studies published in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology.20 Fourth, the availability of this multisertype ELISA offers the future possibility of widespread and rapid screening for cardiovascularly significant periodontal disease, even outside dental practices. One limitation—because of the observational nature of this study, its results may still have been confounded by unrecognized associations with other risk factors for atherosclerosis.

Proof that periodontal disease can directly cause atherosclerosis requires experimental intervention either to stimulate periodontal disease or reverse it. Intravenous administration of P. gingivalis has been shown to potentiate atherosclerosis in a murine model, but this route of administration does not reflect the normal pathophysiology of periodontal disease.23 In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Lalla and colleagues20 describe an elegant model of periodontal disease that uses repeated oral inoculations with P. gingivalis to produce severe periodontitis with alveolar bone loss in apoE-null mice. Importantly, experimental induction of periodontitis exacerbated early atherosclerotic lesions (fatty streaks) within 4 months. In addition, serum II-6, aortic VCAM-1, and tissue factor antigen levels were increased in mice with P. gingivalis infection. Body weight, lipids, glucose, and renal function were unaffected by periodontal disease. Intriguingly, two infected mice (of 9) had evidence of DNA for P. gingivalis within aortic tissue. These studies provide experimental proof that periodontal disease can induce atherosclerosis, and they suggest that interventional randomized clinical trials to test the effect of periodontal treatment on atherosclerotic events are warranted.

The vascular mechanism(s) by which periodontal infection could predispose to atherosclerosis remains unclear. However, there is evidence that P. gingivalis can adhere to and infect cultures of coronary endothelial cells,24 with subsequent activation and expression of cell adhesion molecules.25 Endothelial involvement is supported by the report last month from Amar et al19 in Arteriosclerosis, Thrombosis, and Vascular Biology that relatively young patients with severe periodontal disease exhibit perturbed flow-mediated dilatation of the brachial artery compared with carefully matched controls. This appeared to be due to endothelial dysfunction, because nitroglycerin-mediated dilatation was normal. In line with epidemiological data, only severe periodontal disease was associated with endothelial dysfunction, and C-reactive protein was also increased in these patients. The authors made strenuous efforts to control for other risk factors for atherosclerosis, excluding patients with existing atherosclerosis, cigarette smokers, and those who have diabetes mellitus, hyperlipidemia, hypertension, and other systemic illnesses. One risk factor for both periodontal disease and atherosclerosis that they do not report is obesity; it would be interesting to know the body mass index of patients with periodontal disease and controls. Given that endothelial dysfunction appears to be an early event in the development of atherosclerosis,26 and also predicts plaque instability,27 these findings strengthen the link between periodontal disease and atherosclerosis.

These important studies shed new light on the role of periodontal disease in causation of atherosclerotic events. They do not prove that treatment of periodontal disease will prevent atherosclerotic events. This is not a minor issue. For example, though it is clear that menopause substantially increases risk of atherosclerotic events in women, hormone replacement therapy (as currently used) does not appear to reduce cardiovascular events. Thus, it is now critical to test the hypothesis that reversal of periodontal disease prevents atherosclerotic events and explore different therapeutic approaches to achieve this aim. Indeed, current studies do not provide sufficient information to differentiate between the possibilities of direct infection of the vascular wall versus stimulation of a pro-inflammatory state by periodontitis.
This distinction is crucial because some treatment strategies for periodontal disease, such as scaling/root planning, may promote hematogenous seeding of bacteria. 28 There is evidence that brief periods of systemic or local antibiotic coverage can improve periodontal disease in conjunction with mechanical approaches. 29 Other strategies, such as vaccination against P. gingivalis, may lead to a more robust immune response against shared antigens, which could have harmful vascular effects. However, there are promising data that interference with host inflammatory responses can improve periodontal disease, for example using sub-antibiotic doses of doxycycline (20 mg twice a day) to inhibit matrix metalloproteinase. 30–32 These issues are particularly topical given the welcome news that the National Institutes of Health has agreed to support a randomized clinical trial of periodontal treatment in several thousand patients with both atherosclerotic and periodontal disease (PAVE trial; http://www.cscu.unc.edu/pave). Antibiotic and anti-inflammatory strategies could be incorporated in this trial, perhaps using a factorial design. The results from the PAVE trial could provide important support for the concept that infection predisposes to atherosclerosis and initiate a new clinical approach to prevention of cardiovascular events.

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