

# Periodontal infections and cardiovascular disease

## The heart of the matter

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**A**fter two decades of research, it has been firmly established that an association exists between periodontal disease and cardiovascular disease (CVD). The pertinent question, however, is about the nature and relevance of this association. Specifically, does the infectious and inflammatory periodontal disease process contribute causally to heart attacks and strokes, or are these two conditions coincidentally associated?

Although the evidence of a potentially contributory role of periodontal infections in the natural history of CVD continues to mount, there are well-founded reasons for skepticism. With this in mind, we provide a state-of-the-science article regarding the association between periodontal disease and CVD.

### TRADITIONAL STUDIES OF PERIODONTAL DISEASE AND CARDIOVASCULAR DISEASE

In 1989, two Scandinavian reports revived a century-old hypothesis relating chronic infections with vascular disease that originally was proposed by French and German scientists.<sup>1</sup> Mattila and colleagues<sup>2</sup> found higher combined levels of caries, periodontitis, periapical lesions and pericoronitis (all serving as surrogate markers of oral infections) more frequently in patients with recent myocardial

## ABSTRACT

**Background.** Oral infection models have emerged as useful tools to study the hypothesis that infection is a cardiovascular disease (CVD) risk factor. Periodontal infections are a leading culprit, with studies reporting associations between periodontal disease and CVD. The results, however, have varied, and it often is unclear what conclusions can be drawn from these data.

**Summary.** An association exists between periodontal disease and CVD. It is unknown, however, whether this relationship is causal or coincidental. Early studies predominantly used nonspecific clinical and radiographic definitions of periodontal disease as surrogates for infectious exposure. While most studies demonstrated positive associations between periodontal disease and CVD, not all studies were positive, and substantial variations in results were evident. More recent studies have enhanced the specificity of infectious exposure definitions by measuring systemic antibodies to selected periodontal pathogens or by directly measuring and quantifying oral microbiota from subgingival dental plaque. Results from these studies have shown positive associations between periodontal disease and CVD.

**Conclusions.** Evidence continues to support an association among periodontal infections, atherosclerosis and vascular disease. Ongoing observational and focused pilot intervention studies may inform the design of large-scale clinical intervention studies. Recommending periodontal treatment for the prevention of atherosclerotic CVD is not warranted based on scientific evidence. Periodontal treatment must be recommended on the basis of the value of its benefits for the oral health of patients, recognizing that patients are not healthy without good oral health. However, the emergence of periodontal infections as a potential risk factor for CVD is leading to a convergence in oral and medical care that can only benefit the patients and public health.

**Key Words.** Cardiovascular; infection; periodontitis; epidemiology.  
*JADA 2006;137(10 supplement):14S-20S.*



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infarction than in healthy control patients from the same population. Syrjanen and colleagues<sup>3</sup> observed relatively poor oral health among patients who had experienced a recent stroke compared with control patients who had not experienced stroke.

These authors drew careful conclusions, primarily because of the substantial overlap noted between risk factors for both periodontal disease and CVD—being older, being male, cigarette smoking, diabetes and low socioeconomic status. If periodontal disease and CVD simply share common risk factors, a correlation between the two would be expected even if a causal link did not exist. This epidemiologic phenomenon is referred to as “confounding.”<sup>4</sup>

These studies enrolled patients when they came to a hospital with a heart attack or stroke, which meant that measures of oral health were taken after the cardiovascular event had occurred, raising the possibility that the cardiovascular event might have influenced oral health negatively. The geographical homogeneity and small number of participants enrolled in these studies precluded any reliable generalizations beyond the specific study population.

Subsequently, studies addressing many of these limitations have made substantial contributions to our understanding of periodontal disease and CVD associations.<sup>5,6</sup> These studies collectively included more than 100,000 adult men and women from diverse populations, which has enhanced the consistency and generalizability of the proposed association between periodontal disease and CVD. Because many of these studies were prospective or retrospective,<sup>7-13</sup> the assessment of periodontal disease often was done before the occurrence of cardiovascular events, thus better establishing the temporality of the association.

Several authors also rigorously tested whether periodontal disease was associated with CVD independent of risk factors common to both conditions. Specifically, most studies reported positive associations after accounting for the effects of multiple risk factors such as age, sex, diabetes, cholesterol levels, blood pressure, obesity,

smoking status, dietary patterns, race/ethnicity, education and socioeconomic status.<sup>7-11,13</sup> These results have particular importance in the case of smoking, as some have postulated that the association between periodontal disease and CVD is due to smoking-related bias.<sup>14</sup> While smoking status was assessed in most studies, the level of adjustment varied, with some studies providing a more detailed smoking assessment. For example, Morrison and colleagues<sup>10</sup> observed that participants with periodontal disease had more risk of developing fatal coronary heart disease and experiencing stroke even after controlling for smoking status by classifying current smokers according to the number of cigarettes smoked per day. Others have controlled for smoking by restricting their analyses to never-smokers. Jshipura and colleagues<sup>13</sup> reported an 80 percent

elevation in stroke risk for people with zero to 24 teeth compared with those who had 25 or more teeth among never-smokers. Desvarieux and colleagues<sup>15</sup> reported similar findings between tooth loss and carotid atherosclerosis, unmodified by smoking status. Nevertheless, underlying the “confounding by smoking” argument is the possibility of a healthy bias effect, in which people who smoke are more likely to have unhealthy lifestyles, which can lead to both periodontal disease and CVD.

Grau and colleagues<sup>16</sup> provide important information concerning the specificity of the hypothesis to periodontal disease; they reported a 400 percent increase in stroke risk associated with periodontitis but found no relationship between

caries and stroke. The specificity of these findings to periodontal disease argues against a healthy lifestyle bias in which people with poor oral health practices, which can lead to both caries and periodontal disease, also would be less likely to engage in behaviors related to cardiovascular health.

Not all studies have found a positive relationship between periodontal disease and CVD. Reports from the Health Professionals Follow-Up Study<sup>17</sup> and the Physicians’ Health Study<sup>18</sup> observed no association between periodontal disease and either coronary heart disease or stroke

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among more than 66,000 male health professionals. The large sample sizes of these two studies provide a good reason for caution with regard to the overall hypothesis. However, a major limitation of these studies stems from the self-report nature of periodontal disease assessment in which participants were asked via questionnaire whether they had a history of periodontal disease as opposed to receiving an in-person clinical examination.<sup>17,18</sup>

Hujoel and colleagues<sup>19</sup> found no association between periodontal disease and coronary heart disease in the First National Health and Nutrition Examination Survey (NHANES I) cohort. Among younger participants (younger than 55 years), however, there was an approximately 50 to 80 percent increased risk of developing coronary heart disease associated with periodontitis.<sup>5,19</sup> Although subgroup results of this nature are susceptible to chance findings, these results are consistent with the findings of Janket and colleagues<sup>5</sup> and Mattila and colleagues,<sup>20</sup> which suggest that periodontal disease might pose a stronger risk for CVD among younger participants.

Interestingly, two of the studies reporting no association between periodontal disease and coronary disease are at odds with stroke findings from the same population. Wu and colleagues<sup>11</sup> found strong positive associations between periodontal disease and stroke in the same NHANES population in which Hujoel and colleagues<sup>21</sup> reported no relationship between periodontal disease and coronary disease. Joshipura and colleagues reported no association between periodontal disease and coronary disease,<sup>17</sup> but they did find a positive association for stroke<sup>13</sup> in the same cohort. These discrepancies are consistent with the literature, which indicates that periodontal disease might be a stronger risk factor for cerebrovascular disease than for coronary disease.<sup>5</sup>

In another report, Hujoel and colleagues<sup>21</sup> reported that edentulous participants did not have a lower coronary heart disease risk compared with dentate participants with periodontitis. While these data could be interpreted as arguing against an association between vascular disease and periodontal disease, other explanations should be considered. Indeed, while total tooth extraction prevents exposure to periodontal infection, it does not remove the history of exposure. For example, in populations in which tooth loss primarily is due to periodontal disease, this may lead to an apparent paradox in which cumu-

lative exposure to periodontal infections is not meaningfully different between edentulous patients and those with periodontitis.<sup>15</sup> Reports from the Oral Infections and Vascular Disease Epidemiology Study (INVEST) and the Study of Health in Pomerania (SHIP) demonstrated that in both U.S. and German cohorts, participants with more tooth loss had more clinical periodontal disease, suggesting that periodontal disease might have been an important reason for tooth loss.<sup>15,22</sup>

Furthermore, data from INVEST<sup>15,23</sup> and SHIP<sup>22</sup> suggest that edentulous people remain at an elevated or a potentially intermediate risk of developing subclinical CVD. Consequently, it is possible that the potential risk from periodontal infections might not be reversible after a certain threshold of subclinical CVD has developed.

Reports from the United States<sup>11</sup> and Germany<sup>16,23</sup> have provided evidence that the association between periodontal disease and CVD might be stronger among men than among women. The possibility that novel risk factors might partly explain some of the sex differential in CVD risk is intriguing.<sup>23</sup> For example, in SHIP, Desvarieux and colleagues<sup>22</sup> reported that men had more severe periodontal disease than did women, raising the possibility that women did not reach a threshold of inflammation necessary for systemic effects.

In summary, research supports a moderate relative association between CVD and periodontal disease assessed clinically and radiographically.<sup>5,6</sup> This relationship appears to be more pronounced in younger participants, possibly different in male and female subjects and consistently stronger for clinical stroke outcomes. Although the existence of some null publications provides reason for caution, these studies were based on self-reported periodontal disease status, contradicted by other analyses of the same dataset or potentially explained by threshold effects. Nevertheless, substantial variation in results among studies is apparent. A likely explanation for this variation is the nonspecificity of clinically or radiographically defined exposures used by traditional studies. New research designed to measure oral infection exposure more directly is needed.

#### **NOVEL RESEARCH APPROACHES TO REFINE AND TEST MORE SPECIFIC HYPOTHESES**

The study of periodontal disease and CVD associations has its roots in the broader hypothesis concerning infections and CVD. Therefore, recent

research has provided new insights by obtaining more precise measures of exposure to periodontal microbes, incorporating outcome measures of sub-clinical CVD or both.

**Systemic antibody titers.** Moving away from the earlier studies linking clinical and radiologic periodontal disease with vascular disease, Pussinen and colleagues<sup>24,25</sup> reported that elevated antibodies to selected periodontal pathogens were associated with an increased prevalence of coronary heart disease, increased atherosclerosis in the carotid artery and more risk of developing coronary events during 10 years of follow-up. In a separate cohort, they reported more risk of experiencing stroke associated with elevated antibody titers.<sup>26</sup> Both studies were conducted in European populations.

In a U.S. cohort, Beck and colleagues<sup>27,28</sup> reported that increased systemic antibody levels to periodontal microbes are related to an increased prevalence of coronary heart disease and subclinical atherosclerosis. Although these findings are not prospective, they are consistent with previous findings that demonstrated an association between clinical periodontal disease and atherosclerosis in the same population.<sup>29</sup> These findings also are of interest because they show a relationship between antibody titers and coronary heart disease even among never-smokers, providing further evidence that the observed relationship is not simply a result of smoking-induced bias.

**Direct measurement of oral microbiology.** An even more direct approach to assessing exposure to periodontal microbes is to measure bacteria quantitatively in periodontal plaque samples, a procedure that has not been undertaken frequently in large samples because of the substantial undertaking and costs. INVEST researchers analyzed nearly 5,000 subgingival plaque samples in 657 dentate participants for quantification of 11 known periodontal bacteria, including four (*Actinobacillus actinomycetem-comitans*, *Porphyromonas gingivalis*, *Tannerella forsythensis* and *Treponima denticola*) defined a priori as being related etiologically to periodontal disease<sup>30,31</sup> and seven other bacterial species acting as controls. Desvarieux and colleagues<sup>32</sup> reported that carotid atherosclerosis as measured by intima-media thickening increased with higher

levels of the periodontal bacteria, after adjustment for traditional risk factors. This relationship with atherosclerosis was specific for the four periodontal etiologic bacteria. No relationship was found between increased atherosclerosis and the group of control bacteria, diminishing the likelihood of an unhealthy lifestyle bias. These results constitute the most direct evidence to date of a possible contributory role of periodontal infections to atherosclerosis. However, while these findings are novel, they also are cross-sectional; thus, we must await prospective results to determine whether oral microorganisms are associated with atherosclerotic progression that will translate into clinical events in this cohort.

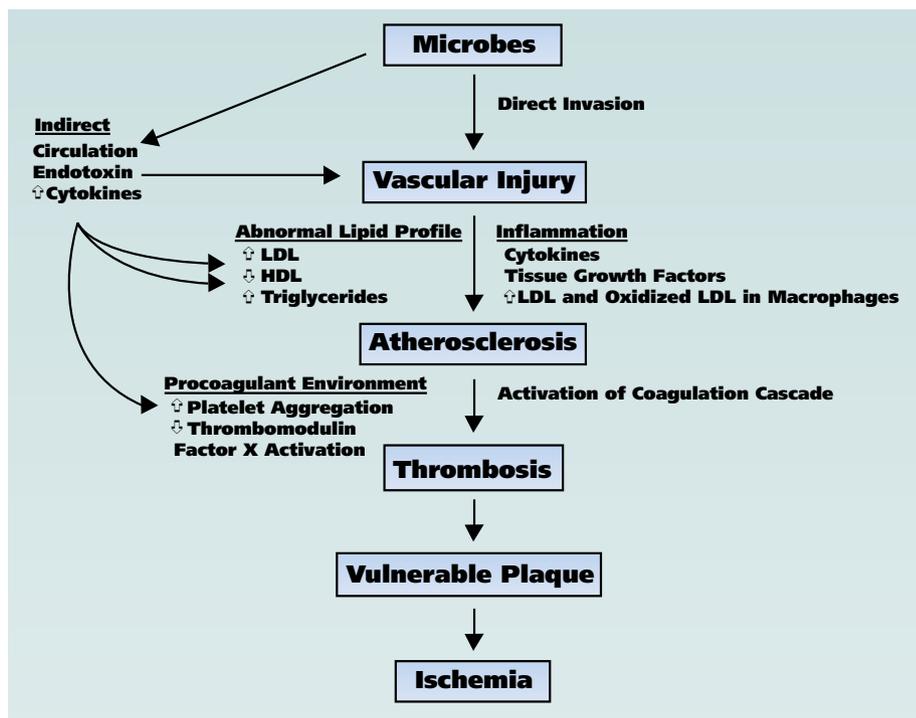
Recently, Spahr and colleagues<sup>33</sup> provided evidence that these subclinical effects might be translated into clinical coronary disease. They directly assessed the periodontal pathogen burden and found that an increased pathogen burden was related positively to the presence of clinical coronary heart disease.

**Subclinical intervention studies.** We are aware of three intervention studies that have assessed the impact of periodontal treatment on subclinical markers of CVD.<sup>34-36</sup> Each reported that periodontal treatment was associated with improved measures of systemic inflammation or subclinical CVD. While these findings are novel and support potential cardiovascular benefits from periodontal treatment, some important limitations should be noted. First, these interventions were not randomized, and they lacked an untreated control group of subjects with periodontal disease. Second, oral infection was not measured directly at baseline and follow-up to address the contributions of oral microbiology to these findings. Finally, these studies included small numbers of participants, and researchers were unable to determine if these subclinical findings translated into fewer clinical cardiovascular events.

#### **MECHANISMS BY WHICH PERIODONTITIS MAY RELATE TO CARDIOVASCULAR DISEASE**

A number of reviews have been published that outline potential biological mechanisms linking infections and periodontal disease to CVD (Figure).<sup>37-40</sup> We provide an overview of the

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**Carotid  
atherosclerosis as  
measured by  
intima-media  
thickening increased  
with higher levels  
of the periodontal  
bacteria.**  
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**Figure.** Example of a potential mechanism of infectious agents in atherosclerosis. LDL: Low-density lipoprotein. HDL: High-density lipoprotein. Source: Fong.<sup>37</sup>

leading biological hypotheses.

**Direct pathways.** Oral microbes and their byproducts can gain systemic access via the circulatory system. Geerts and colleagues<sup>41</sup> showed that gentle mastication can induce endotoxemia, and this risk was elevated according to an increased severity of periodontal disease. Kinane and colleagues,<sup>42</sup> Rajasuo and colleagues,<sup>43</sup> Roberts<sup>44</sup> and Forner and colleagues<sup>45</sup> have shown that dental procedures and toothbrushing can induce bacteremias. Recent research indicates that the magnitude of bacteremia after scaling was amplified among patients with periodontitis as opposed to patients with gingivitis or healthy control patients.<sup>45</sup> Studies of carotid endarterectomy samples have found common periodontal pathogens from arterial plaques.<sup>46,47</sup> In gaining systemic access, oral microbes have the potential to directly influence subclinical mediators of cardiovascular events such as hypercoagulability, atherosclerotic development or both.

A mice study demonstrated that intravenous inoculation with *P. gingivalis* accelerates atherosclerotic development.<sup>48</sup> Lalla and colleagues<sup>49</sup> induced periodontal infection via oral inoculation with *P. gingivalis* and were later able to recover *P. gingivalis* DNA from the aortic tissue of infected mice only and observe signs of acceler-

ated early atherosclerosis among infected mice. Giaccona and colleagues<sup>50</sup> found that certain strains of *P. gingivalis* are capable of infecting macrophages and enhancing foam cell formation in the vascular wall, adding further credence to *P. gingivalis*' ability to initiate or exacerbate the atherosclerotic process. Finally, in vitro studies demonstrated the ability of *Streptococcus sanguis* and *P. gingivalis* to induce platelet aggregation and hypercoagulability, increasing the likelihood of thrombus formation, which can lead to ischemic cardiovascular events.<sup>51-54</sup>

#### Indirect pathways.

Atherosclerosis has a strong inflammatory component,<sup>55,56</sup> and epidemiologic evidence suggests

that increased levels of systemic inflammation are predictive of cardiovascular events.<sup>57,58</sup>

People with periodontal disease have elevated levels of systemic inflammatory markers, such as C-reactive protein,<sup>59-63</sup> and treatment for periodontal disease has been reported to decrease systemic inflammation levels.<sup>64</sup> There are many potential triggers for this enhanced systemic inflammatory response, including transient bacteremias and the local release of bacterial by-products such as lipopolysaccharide.<sup>34,65</sup>

Another plausible mechanism connecting oral infection and CVD is molecular mimicry, in which antibodies targeted toward bacterial (including periodontal) species inadvertently cross-react with host cells. For example, heat shock protein 60 has been studied for its potential role in mediating infection-induced atherosclerosis, as human and bacterial heat shock proteins 60 are conserved highly.<sup>66</sup> These instances of mistaken identity could lead to vascular inflammation and atherosclerosis.

#### CONCLUSION

At a minimum, periodontal infections are epidemiologically associated with CVD; that is, periodontal infections seem to be found more fre-

quently in patients with CVD. However, the critical question of whether periodontal infections are a risk factor for or contribute causally to CVD and cerebrovascular disease remains unanswered. The possibility that periodontal disease and CVD share common risk factors or are manifestations of a similar underlying pathology remains, as several analyses were conducted post hoc and statistical adjustment for confounders can be imperfect. However, the mounting evidence points to an association of periodontal disease at the biological, clinical, radiographic and microbiological levels in relation to clinical and subclinical vascular disease. Because periodontal infections are so prevalent, the potential attributable risk of such an association would be substantial at the population level. There is, however, no direct peer-reviewed evidence to suggest that treating or preventing periodontal infections leads to fewer clinical cardiovascular events. Some insurance company studies, however, find fewer medical care needs in patients who maintain their periodontal health. If the relationship holds, one of the remaining issues will be to determine whether the possible contribution of periodontal disease to CVD risk can be addressed better via treatment of existing disease or through prevention before a threshold of irreversible subclinical CVD is reached.

It will be necessary to conduct large-scale randomized intervention trials designed specifically to test these questions. Before valid and powered—large and costly—clinical intervention trials can be organized, it is important to obtain the results of ongoing national and international observational research studies and new mechanistic or intermediate trials testing focused hypotheses. Results from these studies will help inform future intervention designs by answering questions regarding such topics as optimal exposure definitions, treatment targets and optimal windows of intervention, mechanisms of disease, appropriate biological markers and appropriate populations in which to conduct interventions.

Recommending periodontal treatment solely for the purpose of atherosclerotic CVD prevention is not warranted based on current scientific evidence. Periodontal treatment must be recommended on the basis of the value of its benefits for the oral health of patients, recognizing that patients are not healthy without good oral health and taking into account American Heart Association recommendations.<sup>67</sup> However, the emergence

of periodontal infections as a possible risk factor for CVD is leading to a convergence in oral and medical care. As dental, public health and medical researchers and practitioners reach across disciplines, a holistic approach to care can only benefit the patients and public health as a whole. ■

This work was supported by National Institute of Dental and Craniofacial Research grant R01 DE 13094 and Projct ANR R05115DD from the French Agency for Research.

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