



Periodontal disease and cardiovascular disease

Epidemiology and possible mechanisms

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Mild forms of periodontal disease affect 75 percent of adults in the United States, and more severe forms affect 20 to 30 percent of adults. Because periodontal disease is common in the population, it may account for a significant portion of the proposed infection-associated risk of cardiovascular disease.

The evidence suggests a moderate association—but not a causal relationship—between periodontal disease and heart disease.

We summarize the current findings regarding the association between periodontal disease and cardiovascular disease. Studies reviewed include epidemiologic studies, as well as animal and laboratory studies that focused on possible mechanisms underlying the associations.

EPIDEMIOLOGIC STUDIES OF THE ORAL AND SYSTEMIC DISEASE CONNECTION

Case-control and cross-sectional studies. Several epidemiologic studies have examined the association between dental health status and the risk of cardiovascular disease, or CVD, events. A series of case-control and cross-sectional studies¹⁻⁹ has shown a significant association between various indexes of poor dental health and coronary heart disease, or CHD.

For example, Arbes and colleagues⁷ evaluated the association between periodontal disease and CHD in the Third National Health and Nutrition Examination

Background. Many early epidemiologic studies reported an association between periodontal disease and cardiovascular disease. However, other studies found no association or nonsignificant trends. This report summarizes the evidence from epidemiologic studies and studies that focused on potential contributing mechanisms to provide a more complete picture of the association between periodontal and heart disease.

Types of Studies Reviewed. The authors summarize the longitudinal studies reported to date, because they represent the highest level of evidence available regarding the connection between periodontal disease and heart disease. The authors also review many of the case-control and cross-sectional studies published, as well as findings from clinical, animal and basic laboratory studies.

Results. The evidence suggests a moderate association—but not a causal relationship—between periodontal disease and heart disease. Results of some case-control studies indicate that subgingival periodontal pathogenic infection may be associated with myocardial infarction. Basic laboratory studies point to the biological plausibility of this association, since oral bacteria have been found in carotid atheromas and some oral bacteria may be associated with platelet aggregation, an event important for thrombosis. Animal studies have shown that atheroma formation can be enhanced by exposure to periodontal pathogens.

Conclusions. The accumulation of epidemiologic, in vitro, clinical and animal evidence suggests that periodontal infection may be a contributing risk factor for heart disease. However, legitimate concerns have arisen about the nature of this relationship. These are early investigations. Since even a moderate risk contributed by periodontal disease to heart disease could contribute to significant morbidity and mortality, it is imperative that further studies be conducted to evaluate this relationship. One particularly important study to be carried out is the investigation of a possible clinically meaningful reduction in heart disease resulting from the prevention or treatment of periodontal disease.

Survey, or NHANES III, and found that the odds of having a history of heart attack increased with the severity of periodontal disease. The highest severity of periodontal disease in the population was associated with an odds ratio, or OR, of 3.8 (95 percent confidence interval, or CI, 1.5 to 9.7) compared with no periodontal disease, after adjusting for age, sex, race, poverty, smoking, diabetes, high blood pressure, body mass index and serum cholesterol levels. Thus, this cross-sectional study confirmed the association seen in other cross-sectional studies, as well as in case-control studies, and also showed a direct relationship between heart disease and increasing levels of periodontal disease.

Genco and colleagues⁹ assessed the association between specific subgingival periodontal organisms and myocardial infarction, or MI. They compared 97 subjects with nonfatal MI with 233 control subjects. A panel of nine subgingival bacteria was evaluated, and subjects infected with one or more of these bacteria were compared with noninfected subjects. For MI, the adjusted OR (95 percent CI) was 2.99 (1.40 to 6.35) for the presence of *Bacteroides forsythus*, and 2.52 (1.35 to 4.70) for *Porphyromonas gingivalis*, two periodontopathic bacteria. These findings support the notion that specific pathogenic bacteria found in cases of periodontal disease also may be associated with MI.

Longitudinal studies. Since there have been no randomized clinical trials conducted to determine the effect of periodontal disease prevention or treatment on cardiovascular events, longitudinal studies are the highest form of evidence available. Therefore, we review each of the eight published studies below.

Six of the longitudinal studies¹⁰⁻¹⁵ suggested that indicators of poor periodontal health precede cardiovascular events (Table 1), while three studies^{12,16,17} found no such relationship (Table 2, page 17S). DeStefano and colleagues¹¹ analyzed data from NHANES I and its 15-year epidemiologic follow-up. They found that in 9,760 men and women, periodontal disease was a significant predictor of subsequent CHD disease. These associations were independent of age, sex, race, education, poverty index, marital status, blood pressure, serum cholesterol levels, diabetes status, body mass index and alcohol consumption.

Beck and colleagues¹³ assessed 921 men (aged 21 through 80 years) who were free of CVD at baseline for a follow-up period of about 18 years. They found that high levels of alveolar bone loss

at baseline (a measure of periodontal disease) were a significant predictor of total CHD incidence and stroke (OR = 1.5 for total CHD, OR = 1.9 for fatal CHD and OR = 2.8 for stroke). These findings were independent of other cardiovascular risk factors, including age, smoking, body mass index, serum cholesterol levels, blood pressure, diabetes status and education.

A study by Joshipura and colleagues¹² found that the association between self-reported history of periodontal disease and incidence of heart disease was no longer significant after adjusting for other risk factors (Table 2). Because these results were taken from a large, well-characterized, longitudinal study, these findings deserve additional comment. Most of the studies showing an association have found that the amount of periodontal disease (that is, the burden) was important. Since the subjects in the study by Joshipura and colleagues responded to a “yes or no” question about periodontal disease, it is not possible to quantify the extent of the periodontal disease present. In addition, misclassification from subjects’ self-reports of periodontal disease is likely.

However, the Joshipura and colleagues study does support other studies that had positive results (Table 1) in that the affirmative response to a question regarding a tooth lost to periodontal disease (an event often indicating serious periodontal disease, especially in older adults) remained significantly associated with incident CHD, even after adjustments were made.

Hujoel and colleagues¹⁶ conducted a longitudinal study that also failed to show an association between periodontal disease and subsequent CHD. These authors evaluated the NHANES I study and its 21-year follow-up findings. It is interesting to note that the study by DeStefano and colleagues¹¹ used the same database and did find a relationship between periodontal disease and subsequent heart disease in the NHANES I study at follow-up 15 years later.

The study by Hujoel and colleagues¹⁶ extensively adjusted for possible confounding factors and this may have accounted for the lack of a relationship after adjustment. It is possible that Hujoel and colleagues overadjusted for factors that may be strongly connected with infections such as periodontal disease. It also is possible that there was significant misclassification of the periodontal status of subjects over time, with those classified as having no periodontal disease at baseline actually developing it during the

TABLE 1

ASSOCIATIONS BETWEEN ORAL CONDITIONS AND CARDIOVASCULAR DISEASE IN SIX LONGITUDINAL STUDIES WITH POSITIVE FINDINGS.

SOURCE, YEAR	COUNTRY (FOLLOW-UP PERIOD)	EXPOSURE	OUTCOME	MEASURE OF ASSOCIATION	ADJUSTED FOR POTENTIAL CONFOUNDERS
DeStefano and colleagues,¹¹ 1993	United States (15 years)	Russell's Periodontal Index	Admitted to hospital/death from CHD* (men < age 50 years)	RR [†] = 1.2 [‡] RR = 1.7 [‡]	Smoking, hypertension, age, sex, triglycerides, SES [§] , diabetes, serum lipids, BMI [¶] , previous myocardial infarction
Mattila and colleagues,¹⁰ 1995	Finland (seven years)	Total Dental Index	New myocardial infarction or death from CHD	HR [#] = 1.2 [‡]	Age, sex, race, education, poverty, marital status, SBP ^{**} , BMI, cholesterol level, diabetes, physical activity, alcohol use, smoking
Joshi-pura and colleagues,¹² 1996	United States (six years)	Reported tooth loss due to periodontitis in men	Fatal and nonfatal myocardial infarction and sudden death	RR = 1.7 [‡]	Age, BMI, exercise, smoking, alcohol use, vitamin E, family history of myocardial infarction before age 60 years
Beck and colleagues,¹³ 1996	United States (18 years)	Whole-mouth bone level	New CHD Fatal CHD Stroke	OR ^{††} = 1.5 [‡] OR = 1.9 [‡] OR = 2.8 [‡]	Age, BMI, cholesterol level, smoking, diabetes, blood pressure, family history, education
Morrison and colleagues,¹⁴ 1999	Canada (23 years)	Mild, severe gingivitis, periodontitis	Fatal CHD and stroke	RR at age 35-69 years: mild gingivitis = 3.6 [‡] ; severe = 6.9 [‡] ; periodontitis = 3.4 [‡]	Age, sex, cholesterol level, smoking, diabetes, hypertension, province of residence
Wu and colleagues,¹⁵ 2000	United States (National Health and Nutrition Examination Survey I: 21 years)	Gingivitis and periodontitis (≥ 4-mil-limeter pockets); edentulous by Russell's Periodontal Index	Incident non-hemorrhagic stroke	RR: gingivitis = 1.2; periodontitis = 2.1 [‡]	Sex, age, race, education, poverty index, diabetes, hypertension, smoking status, average alcohol use, BMI, cholesterol level, sample design

* CHD: Coronary heart disease.
 † RR: Relative risk.
 ‡ Statistically significant adjusted measure of association.
 § SES: Socioeconomic status.
 ¶ BMI: Body mass index.
 # HR: Hazard ratio.
 ** SBP: Systolic blood pressure.
 †† OR: Odds ratio.

21-year study. Also, the authors may have misclassified subjects who had periodontal disease at baseline, as a result of treatments and extractions over time. This nondifferential misclassification, accentuated during the 21-year follow-up, would support the study's null hypothesis, leading to a conclusion of no relationship between periodontal disease and heart disease.

Howell and colleagues¹⁷ published the most recent longitudinal study, which was based on the

Physician's Health Study, a randomized, double-blind, placebo-controlled trial of aspirin and beta carotene in the prevention of cancer and cardiovascular disease among 22,071 U.S. male physicians. The periodontal disease exposure consisted of a questionnaire that asked, "Do you have a personal history of any of the following?", with one option in the list of possible responses being periodontal disease. Follow-up questionnaires asked, "Since you filled out the last questionnaire (about

TABLE 2

ASSOCIATIONS BETWEEN ORAL CONDITIONS AND CARDIOVASCULAR DISEASE IN THREE LONGITUDINAL STUDIES WITH NEGATIVE FINDINGS.					
SOURCE, YEAR	COUNTRY (FOLLOW-UP PERIOD)	EXPOSURE	OUTCOME	MEASURE OF ASSOCIATION	ADJUSTED FOR POTENTIAL CONFOUNDERS
Joshiyura and colleagues, ¹² 1996	United States (six years)	Reported history of periodontal disease in men	Fatal and nonfatal myocardial infarction and sudden death	RR* = 1.04	Age, BMI [†] , exercise, smoking, alcohol consumption, vitamin E use, family history of myocardial infarction before age 60 years
Hujoel and colleagues, ¹⁶ 2000	United States (National Health and Nutrition Examination Survey I: 21 years)	Gingivitis and periodontitis (≥ 1-millimeter pockets) by Russell's Periodontal Index	Death or hospitalization due to CHD [‡] or revascularization	Gingivitis HR [§] = NS [¶] ; periodontitis HR = 1.14	Age, age squared, sex, race, poverty index, marital status, education, marital status/sex [#] , log ^{**} smoking duration, log height and weight, log alcohol use per day, physical activity, nervous breakdown, sample design
Howell and colleagues, ¹⁷ 2001	United States (12.3 years)	Reported history of periodontal disease	Death due to CHD, nonfatal myocardial infarction or stroke	RR = 1.13 (confidence limits: 0.99, 1.28) adjusted for age and treatment; RR = 1.01 (confidence limits: 0.88, 1.15) fully adjusted	Age, aspirin and beta carotene treatment assignment, smoking, alcohol use, history of hypertension, BMI, history of diabetes, physical activity, parental history of myocardial infarction, history of angina

* RR: Relative risk.
 † BMI: Body mass index.
 ‡ CHD: Coronary heart disease.
 § HR: Hazard ratio.
 ¶ NS: Not significant.
 # Marital status/sex: Interaction between marital status and sex.
 ** log: Logarithm.

12 months ago), have you been newly diagnosed as having any of the following conditions?" Again, one possible response was periodontal disease.

The study outcomes were diagnoses of nonfatal MI and stroke and death due to CVD. The results included data collected up to October 1995, with a mean follow-up time of 12.3 years. Adjusting only for age and treatment assignment (that is, aspirin or beta carotene), the authors found a nonsignificant positive trend (relative risk, or RR, = 1.13; 95 percent CI, 0.99 to 1.28). Further adjustments for smoking, alcohol use, history of hypertension or diabetes, body mass, physical activity, history of angina and parental history of MI reduced the RR to 1.01 (95 percent CI, 0.88 to 1.15), which represented no association at all.

The bulk of evidence from a total of eight longitudinal studies and six case-control studies suggests an association between periodontal disease

and heart disease, although the associations appear to be moderate in nature. Not enough evidence exists for us to conclude that the associations are causal.

CONCERNS ABOUT THE CURRENT EVIDENCE

Strength of the associations. In any epidemiologic study, there is always concern that the reported associations could be confounded by other factors, especially when the adjusted associations are in the moderate range (that is, an OR of approximately 1.5). With moderate-level associations, there is concern that certain critical potential confounders may not have been controlled for in some studies (that is, lack of control of confounding), and that even though studies may have controlled for confounders, the studies may not have accounted for all of the potential effects of the confounders (that is, residual confounding).

Thus, some researchers and clinicians have called for longitudinal studies of periodontal disease,¹⁸ CHD and stroke that would be large enough to adequately investigate these moderate associations. However, people also are concerned that, since we do not understand fully the mechanisms involved in this association, we actually may be controlling for potential confounders that may be influenced by periodontal disease itself (that is, overcontrolling for confounders).

Inconsistent study findings. As we have noted in this report, some studies have found no association between periodontal disease and heart disease after adjusting for potential confounders. Inconsistent findings serve as a warning that we should be conservative in making conclusions about causality. Differences in the way studies were conducted can bias the findings, especially when associations are moderate in degree. New studies are needed that attempt to explain the inconsistent findings.

Some possible reasons for these inconsistent findings could include the differences in ages of the subjects in the studies (there are indications from several of these studies^{11,14} that the association between periodontal disease and heart disease is stronger in younger people); smoking status not adequately adjusted for; lack of control of confounding factors; residual confounding; overcontrol of confounders; the outcome measure being studied (for example, CHD vs. stroke); the way the outcomes are measured; and the manner in which the exposure (that is, periodontal disease) is measured.

Differences in outcomes. One basic problem in comparing results involves the outcomes that have been used in studies (Tables 1 and 2). Although many of the cardiovascular measures have been consistent across studies (most use new fatal and nonfatal MIs and hospitalization for cardiovascular procedures), some studies also include evidence of a “silent” or nonsymptomatic MI or a stroke. These different inclusion criteria for the outcome being studied may explain differences in findings.

Stroke deserves special mention since it is a different type of event and probably should be considered separately from other outcomes. In fact, the studies that focused on stroke appear to

demonstrate stronger relationships with periodontal disease than do studies that used CHD as an outcome. For example, Wu and colleagues¹⁵ found that periodontal disease was a significant risk factor for cerebrovascular disease—in particular, nonhemorrhagic stroke. This study was based on the NHANES I survey and included 9,962 adults (aged 25 through 74 years), with a 21-year follow-up. The results were adjusted for design features (for example, sampling), as well as baseline information about sex, race, age, education, poverty index, diabetes status, hypertension, smoking status, alcohol use, body mass index and serum cholesterol levels.

The RR was 2.11 (CI, 1.30 to 3.42) for incident nonhemorrhagic stroke and 2.90 (CI, 1.49 to 5.62) for fatal nonhemorrhagic stroke for subjects with periodontitis at baseline compared with subjects

with normal periodontal tissues at baseline. This association was consistent among subjects, who were composed of white men, white women, African-American men and African-American women. As with heart disease, the association between periodontal disease and cerebrovascular events does not prove a causal role. Further mechanism and intervention studies are needed to better understand the role of periodontal disease in stroke.

Measures of periodontal disease. A second basic problem

involves the variety of measures that have been used to describe the exposure (periodontal disease) (see Tables 1 and 2). One study¹⁰ used the Total Dental Index, which is a combination of probing measures, furcation involvement and dental caries infection. Three studies^{11,15,16} used Russell’s Periodontal Index, or RPI, which is a nonprobing index. The RPI once was the standard epidemiologic index for measuring periodontal disease, but it was abandoned about 10 years ago because it no longer represented current concepts of periodontal disease. Measurement of clinical attachment level more likely reflects periodontal disease.

The study by Morrison and colleagues¹⁴ did not specify the exposure measure used, but it appears to be the RPI. One study used bone loss¹³ and the other two studies^{12,17} used self-reported periodontal disease. The variability in exposure meas-

The studies that focused on stroke appear to demonstrate stronger relationships with periodontal disease than do studies that used coronary heart disease as an outcome.

ures used is unavoidable when conducting secondary analyses of data from available longitudinal studies. However, the measures used to assess periodontal disease do appear to be related to the strength and significance of the associations reported (see Box).

Nonclinical signs of periodontal disease. In addition to being concerned about how the clinical signs of periodontal disease are measured, some researchers believe that the non-clinical signs of periodontal disease also should be measured. In a review of associations between infections and heart disease, Danesh¹⁸ pointed out that studies of the association between periodontal disease and heart disease were the only studies that did not have some measure of the infection (either bacterial counts or antibody levels to oral pathogens).

Instead, these studies represented the exposure only by clinical measures of periodontal disease. Because the clinical signs of periodontal disease are a result of infection with microorganisms interacting with the host's immune and inflammatory response, it is likely that including measurement of this interaction between infection and host response would have been a more direct measure of the exposure that we think of as periodontal disease. This concern is especially relevant when we consider the findings from studies that focused on the mechanisms (for example, antibody level) that may underlie this association.

Biological plausibility. Danesh and colleagues¹⁹ recently conducted a meta-analysis of the data relative to the role of other infections associated with heart disease. The authors concluded that the data demonstrating an association between heart disease and *Helicobacter pylori* were weak. However, the data supporting an association between heart disease and *Chlamydia pneumoniae* and cytomegalovirus were more convincing. Evidence from epidemiologic studies supports, but does not prove, a causal association between *C. pneumoniae* and CHD. However, considerable in vitro and animal model evidence exists to support a plausible set of mechanisms by which *C. pneumoniae* may contribute to heart disease. This evidence has prompted several clinical trials to determine if treatment of *C. pneumoniae*

BOX

MEASUREMENTS OF PERIODONTAL DISEASE EXPOSURE IN LONGITUDINAL STUDIES.

- Two studies used clinical probing measures or bone loss^{10,13}; both found significant associations.
- Three studies used nonprobing clinical measures^{11,15,16}; two of these studies found significant associations, one found a nonsignificant trend.
- One study did not specify the measure used¹⁴ (appears to be nonprobing); a significant association was found.
- Two studies used self-reported periodontal disease^{12,17}; both had negative findings.

infection by antibiotics will result in decreased risk of heart disease.

DISEASE MECHANISMS

Herzberg and colleagues²⁰ and Herzberg and Meyer²¹ have proposed a direct effect of some of the bacteria found in dental plaque that enter the bloodstream during bacteremic episodes. The oral gram-positive bacteria *Streptococcus sanguis* and the gram-negative periodontal pathogen *P. gingivalis* have been shown to induce platelet activation and aggregation through the expression of collagenlike platelet aggregation-associated proteins. The aggregated platelets may then play a role in atheroma formation and thrombosis.

Periodontal pathogens. A recent study²² identified periodontal pathogens in human carotid atheromas. The authors analyzed 50 carotid atheromas obtained at endarterectomy for the presence of bacterial 16S rDNA via polymerase chain reaction, or PCR, using synthetic oligonucleotide probes specific for the periodontal pathogens *Actinobacillus actinomycetemcomitans*, *B. forsythus*, *P. gingivalis* and *Prevotella intermedia*. Fifteen (30 percent) of the specimens were positive for *B. forsythus*, 13 (26 percent) were positive for *P. gingivalis*, nine (18 percent) were positive for *A. actinomycetemcomitans* and seven (14 percent) were positive for *P. intermedia*. In addition, *C. pneumoniae* DNA was detected in nine (18 percent) of these atheromas.

These studies suggest that periodontal pathogens may be present in arteriosclerotic plaques where, like other infectious organisms such as *C. pneumoniae*, they may play a role in the development and progression of atherosclerosis. For example, the findings of a recent case-control study²³ indicate that high levels of peri-

odontal pathogens—specifically *B. forsythus*, *P. gingivalis*, *Fusobacterium nucleatum* and *Eikenella corrodens*—are independently associated with stroke after one adjusts for age, sex, tooth loss, smoking, alcohol consumption, hypertension, diabetes, education, history of cardiovascular disease and history of cerebrovascular disease. In addition, two studies^{24,25} found that *P. gingivalis* is capable of invading the coronary and carotid endothelium in cell culture.

Monocyte-derived cytokines such as tumor necrosis factor-alpha, or TNF- α , and interleukins (IL-1, IL-6 and IL-8) may be released in response to a series of stimuli secondary to periodontal infection. One of these potential stimuli, the endotoxin lipopolysaccharide, or LPS, is present in subgingival plaque associated with periodontal disease. LPS and other bacterial components can activate an impressive cascade of inflammatory cytokines that, in turn, can play a role in atherosclerotic heart disease, either through a direct action on the vessel wall or by inducing the liver to produce acute-phase proteins.^{26,27}

For example, acute-phase proteins, such as C-reactive protein, or CRP, and fibrinogen, affect coagulation, platelet activation and aggregation. The LPS and inflammatory cytokines that are present in periodontal disease may also increase the expression of leukocyte adhesion molecules such as intercellular adhesion molecules, or ICAM, or vascular cell adhesion molecules, or VCAM, by endothelial cells.^{13,28-36} ICAM and VCAM, in turn, are associated with atheroma formation.

CRP and fibrinogen levels. Recent studies by Wu and colleagues³⁷ and Slade and colleagues³⁸ provide evidence that periodontal disease is associated with cardiovascular risk factors, including acute-phase proteins, CRP and plasma fibrinogen. Using data from the NHANES III, both studies found that people with periodontitis have increased systemic levels of CRP and fibrinogen. Both CRP and fibrinogen contribute to atheroma formation via several possible mechanisms, including CRP-triggered complement activation and fibrinogen-clotting effects. These associations remained statistically significant after adjustments were made for dental calculus, ethnicity, years of schooling, sex, age, family size, poverty

index, body mass index, family history of MI, diabetes, and tobacco and alcohol use.

In case-control studies, Ebersole and colleagues,³⁹ Loos and colleagues⁴⁰ and Noack and colleagues⁴¹ demonstrated that CRP levels were elevated in patients with periodontal disease compared with levels in periodontally healthy people. Loos and colleagues⁴⁰ also showed that this elevation was not associated with seropositivity to *C. pneumoniae*, cytomegalovirus or *H. pylori* in subjects with periodontal disease. Noack and colleagues⁴¹ demonstrated that the CRP levels were highest in patients who were infected with periodontal pathogens. Furthermore, Ebersole and colleagues³⁹ have shown that treating patients who have periodontal disease with scaling, root planing and flurbiprofen is associated with a trend toward reduced CRP levels one year after therapy.

There is an extensive body of literature associating CRP and fibrinogen, among other inflammatory factors, with CHD. Meta-analyses of these studies¹⁹ are consistent, with statistically significant associations of the acute-phase proteins, fibrinogen and CRP, as well as elevated white blood cell counts, with a subsequent risk of cardiovascular disease.⁴²⁻⁴⁵ For example, CRP is an independent risk factor for CVD; however, detailed information is lacking about the mechanisms by

which CRP participates in the pathogenesis of atheromas. CRP localizes with complement in human hearts during MI, suggesting that CRP binds to diseased muscle tissue, fixes complement and, hence, triggers complement-mediated inflammation that contributes to atheroma formation.⁴⁶ Periodontal infections may be associated with an increased risk of atherosclerotic processes, such as coronary artery disease and strokes, in part via the association of periodontal infections with elevated levels of CRP.

Another potential linking mechanism includes immune responses that result in production of antibodies to periodontal bacteria, including antibodies to bacterial heat-shock proteins that cross-react with heat-shock proteins of the heart. These autoreactive antibodies to heat-shock proteins are found in patients with periodontal disease and may contribute to atheroma formation.^{47,48}

Animal studies. Animal model studies^{49,50}

Animal model studies suggest that infection with *Porphyromonas gingivalis* activates the acute-phase response, increases lipemia and enhances atheroma lesion formation.

suggest that infection with *P. gingivalis*, one of the important pathogens associated with human periodontal disease, activates the acute-phase response, increases lipemia and enhances atheroma lesion formation in ApoE(+/-) mice (that is, heterozygous genotype). ApoE(+/-) mice have increased susceptibility to atheroma formation and hence are sensitive to factors that contribute to atheroma formation. In addition, Chung and colleagues⁴⁹ found *P. gingivalis* using PCR analysis of hepatic homogenates up to three weeks after the bacterial challenge, indicating that *P. gingivalis* remains in the liver much longer than would be expected.

Using the same ApoE (+/-) mouse model, Geva and colleagues⁵⁰ showed that infection of mice with *P. gingivalis* leads to calcification of aortal atherosclerotic plaques, with the amount of calcification increasing with the length of exposure. In no instance was calcification found in mice that were not exposed to *P. gingivalis*. In addition, these authors found significantly greater amounts of bone morphogenic protein, or BMP-2, in the atheromas of the *P. gingivalis*-challenged mice. The presence of BMP-2 in the atheroma may help explain the tendency of atheromas to calcify, since BMP-2 is involved in the development of calcified tissues.

CONCLUSION

The accumulation of epidemiologic, in vitro and animal evidence presented to date suggests a potential role of periodontal infection as a risk factor for CVD. The findings from cross-sectional and longitudinal epidemiologic studies are supported by in vitro and animal studies describing plausible mechanisms linking periodontal infection to development of atherosclerotic diseases, to the triggering of clinical coronary events or to both.

The cumulative evidence presented in this report supports, but does not prove, a causal association between periodontal infection and atherosclerotic cardiovascular disease or its sequelae. A number of legitimate concerns have arisen about the nature of this relationship and, indeed, about the appropriate definitions for periodontal disease when it is thought to be an exposure for systemic diseases. We are mindful of the fact that research into this relationship is still in its early stages compared with research on more established risk factors for cardiovascular disease. Consequently, more focused studies are

needed to investigate the concerns mentioned above and to further elucidate the mechanisms involved.

However, the current evidence supporting an association raises an important question: "If periodontal infection is suppressed by anti-infective intervention, will this result in a decreased risk of heart disease?" Answers to this question would be clinically meaningful and may more directly implicate periodontal disease as a risk factor for cardiovascular disease, and possibly as one of its causes. ■

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