Dental Infection and Vascular Disease

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ABSTRACT

Periodontitis is a chronic inflammatory response to bacterial plaque in which the anchoring bone and soft tissues supporting teeth are destroyed, resulting in tooth mobility and loss. Dental caries involves the spread of infection from the dentine to the vascular dental pulp and periapical bony tissues, before involvement of adjacent soft tissues and spreading sepsis. Several case-controlled, cross-sectional, and cohort studies report correlation between periodontitis and increased cardiovascular, cerebrovascular, and peripheral artery disease, as determined by clinical disease, angiography, ultrasonography, and reduced flow-mediated dilation. Some studies report a similar relationship of atherosclerosis with periapical infection and potentially also with coronal caries, and this review identifies the need to investigate these associations further. Smoking and cadmium exposure are epidemiologically confounding environmental risk factors shared by atherosclerosis and periodontitis. Further complicating epidemiological studies are the risk factors for both atherosclerosis and periodontitis, with which periodontitis appears to have separate positive feedback relationships. These include diabetes, increased plasma lipid levels, hypertension, and white blood cell count. Animal and human intervention studies provide some direct support of a causal role for periodontitis in atherosclerosis, and possible mechanisms include bacterial invasion of arteries, specific atherogenic properties of oral bacteria, the acute phase response, and cytokine polymorphisms.

KEYWORDS: Atherosclerosis, periodontal disease, periapical infection, epidemiology, intervention studies

PERIODONTAL DISEASE, CARIES, AND PERIAPICAL INFECTION

The mouths of most vertebrates are armed with highly calcified teeth for the purposes of defense and masticating food. Although vital for these important physiological functions, by piercing the mucosal barrier from their bony anchorage, teeth also provide a unique opportunity for bacterial invasion (Fig. 1). Plaque bacteria accumulating at the gingival margin perpetually threaten invasion of the soft tissues and bone, and the epithelial attachment, gingiva, and periodontal ligament are evolved to protect from this. If plaque is permitted to irritate the gingivae for any prolonged period, a chronic inflammatory response develops, *gingivitis*, and is characterized by swelling, redness, and susceptibility to bleed. Gingivitis is a successful response to the bacterial onslaught, but on occasion it may progress to periodontal disease in which the soft tissues and bone are destroyed.[1] Most adults have some mild manifestations of periodontal disease, but in 5 to 20% of the population severe

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Coagulopathies and Thrombosis: Usual and Unusual Causes and Associations, Part IV; Guest Editors, Giuseppe Lippi, M.D., Emmanuel J. Favaloro, Ph.D., M.A.I.M.S., and Massimo Franchini, M.D.

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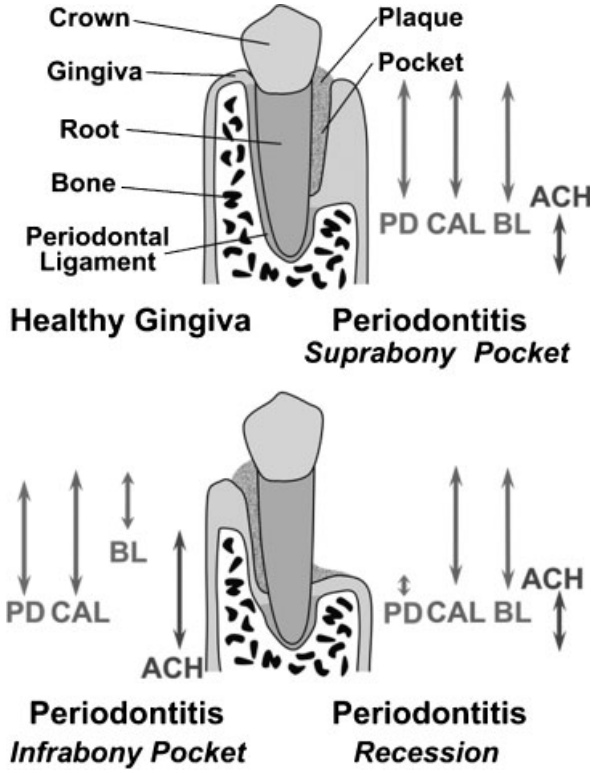

Figure 1 Diagram of anatomical variants of periodontal disease illustrating the numerical measures used to record severity of disease. In health, the gingiva attaches at the cemento-enamel junction where the crown and root meet. The root is anchored into the adjacent alveolar bone via a collagenous periodontal ligament, but this attachment is destroyed when bacterial plaque causes periodontal disease. Most often, suprabony periodontal pockets form in which the periodontal ligament is destroyed and the alveolar bone lost, but with retention of soft tissues to form a deep periodontal pocket colonized by plaque bacteria. Occasionally, however, infrabony pockets form when bone and soft tissues are not lost, despite destruction of the periodontal ligament. When both bone and soft tissues are resorbed together with destruction of the periodontal ligament, the tissues are described as having undergone recession. Not illustrated are vertical defects in which the vertical bony contour changes rapidly, and furcation lesions where periodontitis reaches the branch points of multirooted teeth. Graduated probes are used to measure probing depth (PD) and clinical attachment loss (CAL); radiographs are used to evaluate alveolar crest height (ACH) and bone loss (BL). Notably, the biological significance of these measures clearly depends on the precise anatomical form of periodontitis involved, which has relevance when interpreting published reports.

disease develops, during which teeth become loose and fall out (Fig. 1). Periodontal tissue destruction occurs in bursts independently across the mouth, seemingly due to the accumulation of vascular basement membrane and interstitial amyloid deposits that restrict neutrophil emigration.[2–5] Destruction of the periodontal ligament is the only constant anatomical feature of periodontal disease (Fig. 1) and may be due to direct bacterial invasion, bacterial or host enzyme activity, downgrowth of the epithelial attachment, or proliferation of epithelial embryonic root sheath remnants.[1,5,6] Depending on the pattern of soft and hard tissue resorption, periodontal pockets form and trap highly irritant gram-negative anaerobic bacterial plaque against the remnant tissues, establishing a chronic inflammatory state that may persist for decades (Fig. 1). Although hundreds of bacterial species combine to form the periodontal microbial flora, *Porphyromonas gingivalis* and *Aggegatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans)* appear particularly important in periodontal disease.[1] Irregular calcification of plaque often occurs and adds to the anatomical difficulty of removing the bacterial irritant that drives periodontal disease. Management of periodontitis involves improved oral hygiene, the removal of plaque and calcified deposits from teeth by careful debridement of periodontal pockets, and, where appropriate, surgical reconstruction to obliterate pocket spaces and restore attachment.

Dental caries is the most prevalent infectious disease in humans and is initiated by attack of the crown by bacterial acids followed by bacterial invasion of dentine and the vascular dental pulp (Fig. 2). The periapical foramen restricts vascular supply to the dental pulp, which limits the inflammatory response such that untreated caries often progresses to pulp necrosis and gangrene. Gangrenous material escaping through the periapical foramen infects the periapical tissues, resulting variously in acute or chronic abscesses, replacement of resorbed bone with chronic inflammatory granulation tissue, or epithelial cysts from stimulated remnants of the embryonic root sheath (Fig. 2). Although distinct pathological entities, these different periapical lesions may progress from one form to another, and spread of infection into the adjacent soft tissues with potentially life-threatening sepsis are the final stages in the natural history of dental caries (Fig. 2).[1] The surgical management of caries involves removal of infected hard tissues and restoration with fillings. In cases where the pulp is necrotic and there is periapical infection, the gangrenous pulp tissues must be removed either by extraction or root canal therapy. In root canal therapy, a series of delicate files is used to remove necrotic material before obliterating the pulp chamber with a root canal filling (Fig. 2).[1]

THE ASSOCIATION OF DENTAL INFECTION WITH VASCULAR DISEASE

Initial Reports That Dental Infection Correlates with Myocardial Infarction and Stroke

Widespread interest in the relationship between dental infection and atherosclerosis was initiated by two

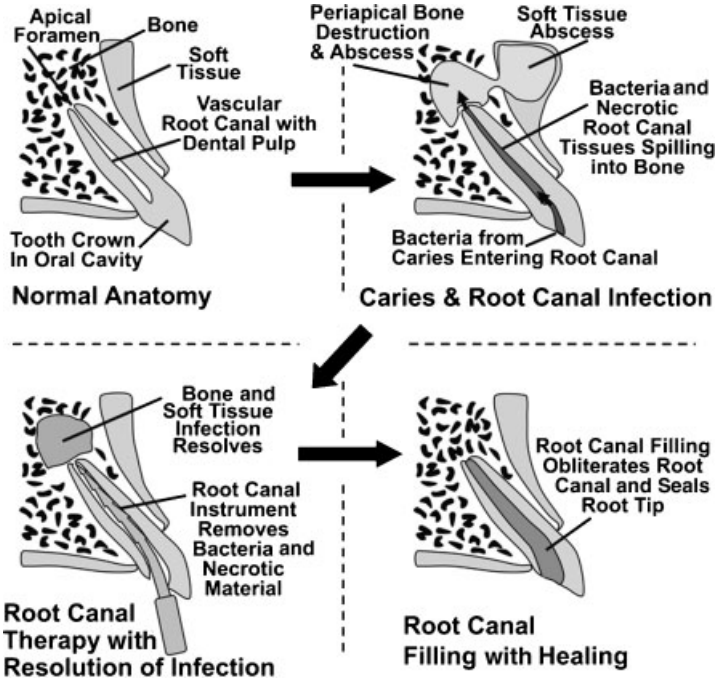

Figure 2 Diagram illustrating the natural history of dental caries and periapical lesions, as well as treatment of periapical lesions by root canal therapy. The tooth is anchored in alveolar bone, with only its crown penetrating into the oral cavity through the mucosal soft tissues. The root canal containing the vascular dental pulp receives its circulation via a delicate apical foramen at the root apex. Bacteria enter the tooth during dental caries and invade the root canal containing the dental pulp. The inability to mount an effective inflammatory response in the dental pulp results in necrosis and gangrene of the pulp, and this necrotic bacterial mix spills into the periapical bony tissue via the apical foramen to cause periapical infection. Periapical infection usually results in bone loss with replacement by chronic inflammatory granulation tissue, and these lesions may also form cysts (not shown) or develop into abscesses as illustrated. Spread of infection into the adjacent soft tissues is common and may progress to widespread sepsis. Treatment of periapical infection requires either extraction or root canal therapy using appropriately delicate files to remove the necrotic material. Once periapical infection has resolved during root canal therapy, the root canal is filled to seal the root tip and prevent recurrent infection.

separate publications in 1989, investigating first acute myocardial infarction[7] and then stroke.[8] Earlier work had indicated a correlation of atherosclerotic disease with a range of infections,[9–13] and this, together with a clinical impression that patients with myocardial infarcts had poor teeth, led to the question of a possible role for dental infection in vascular disease.[7]

An important challenge for these early studies was to develop a meaningful numerical measure for overall dental infection, and to this end a "total dental index" was established taking into account the number of carious lesions, periodontal pocket depth, visibly apparent pus in gingival pockets, the presence of vertical bone loss, the number of periapical lesions, and pericoronitis.[7,8] Total dental indexes were determined for patients with either acute myocardial infarction[7] or stroke[8] and compared with case-matched controls. The association of dental infection with vascular disease was found to be independent of known risk factors for atherosclerosis, establishing a need to consider dental infection itself as a possible independent risk factor.[7,8]

Periodontitis and Cardiovascular Disease

Since these initial important reports correlating a broad range of oral infective processes with vascular disease,[7,8] most further efforts have been directed toward the study of periodontitis. Several similar case-controlled studies have demonstrated a positive correlation between periodontitis and acute myocardial infarction,[14–17] clinically apparent coronary heart disease,[18,19] and both clinical and subclinical coronary artery disease detected by angiography.[20–22] Cross-sectional studies in which associations between variables are evaluated within single populations have similarly supported a relationship between periodontitis and cardiovascular disease.[22–28] Cohort studies in which individuals with and without potentially predisposing conditions are followed over time are generally considered to provide stronger evidence for associations than either case-controlled or cross-sectional analyses,[29] and several such longitudinal cohort studies also support an association between periodontitis and coronary heart disease.[30–35]

The specific criteria for periodontal disease used in these studies and found to correlate with coronary heart disease have varied greatly and include bleeding on

probing,[14,19–21,26] pocket depth,[14–17,19–22] clinical attachment loss,[17,19,21,25,27,28] bone loss or alveolar crest height,[15–19,24,26] the worst pocket depth,[23,24] the number or presence of periodontal pockets,[18,30,31,34,35] the number of vertical periodontal defects,[18] involvement of furcation areas between molar roots,[26] the extent of plaque or calculus deposits,[20,27,30] self-reported bleeding gums,[23] a total dental index,[32] and the sum of scores for missing teeth, apical lesions, caries, and marginal bone loss.[33]

There has been similar diversity among these studies in the specific criteria used for cardiovascular disease, which include acute myocardial infarction,[14–16,28] survival of earlier myocardial infarction,[17,35] clinically confirmed chronic coronary artery disease and/or angina,[14,18,19,24,25,27,28,32,35] angiographically confirmed coronary artery disease,[20–22] the extent of multiple vessel disease as determined by angiography,[27] self-reported cardiovascular disease,[23,26] admission to hospital for cardiovascular disease,[25,28,30] and finally death from cardiovascular disease.[24,28,30–35]

This diversity, expressed not only in the features of periodontal disease considered for analysis, but also in the criteria for cardiovascular disease, may account for some of the variability seen among studies in the strength of association between these two conditions. Nonetheless, a recent meta-analysis of a range of case-controlled and cross-sectional studies strongly supports the relationship between cardiovascular disease and periodontitis, with a pooled odds ratio [OR] of 2.35 (95% confidence interval [CI], 1.87 to 2.96).[36]

Throughout, investigators have made significant effort to control for potentially confounding variables including age and gender,[14–16,18–23,25–27,30–35] smoking,[14,16,18–20,22,23,25,26,28,30–32,34,35] alcohol consumption,[19,20,28,30,34,35] body mass index,[18,19,25,28,30,32,34,35] physical activity,[19,20,30] race or ethnicity,[25,30] educational level,[18–20,23,25,30,35] socioeconomic status,[19,20,23,30,32,35] marital status,[30,35] place of birth,[18] locality,[20] blood pressure and hypertension,[25,26,28,30–32,34,35] diabetes mellitus,[18,22,25,28,30–32,34,35] blood glucose,[25,34,35] total serum cholesterol,[14,19,22,25,30–32,34,35] serum triglyceride,[14,19,25,32,34,35] serum low-density lipoprotein (LDL),[25,32,34] and serum high-density lipoprotein (HDL).[14,22,25,32,34,35] Although not all studies considered all potential confounding factors, taken as a whole, these studies do suggest that the association of periodontitis with cardiovascular disease is independent of other commonly recognized risk factors.

The Relationship Between Periodontitis, Stroke, and Subclinical Atherosclerosis

Since the initial report in 1989,[8] several further case-controlled studies,[8,37–41] cross-sectional studies,[24,42,43] and cohort studies[44–47] have demonstrated positive and independent correlation between periodontitis and stroke. Consistent with this is a similar correlation between periodontitis and transient ischemic attack in case-controlled[38,48] and cross-sectional studies.[43] There is also an association between periodontitis and peripheral vascular disease.[49,50]

Although overt atherosclerotic disease is clinically important, it is scientifically interesting that subclinical atherosclerosis, as revealed by coronary angiography,[51] altered carotid intima-media thickness,[52,53] or ultrasonographically or radiographically revealed carotid atherosclerotic plaques,[54–56] also correlate with periodontitis in case-controlled[52] and cross-sectional studies,[51,53–56] independent of separate confounding risk factors.

Tooth Loss Correlates with Atherosclerotic Disease

Tooth loss is an important clinical outcome of dental disease, and it is also much easier to record data on missing teeth than on periodontitis. For these reasons, it has been valuable to consider coronary heart disease with regard to tooth loss,[21,23,25,27,46,57–59] edentulism,[18,34,35] or denture wearing,[18] independent of periodontitis in case-controlled,[18] cross-sectional,[26,60,61] and cohort studies.[46,57–59] Stroke[25,43,46] and transient ischemic attack[43] also correlate with tooth loss[46] and edentulism[25,43] in cross-sectional[25,43] and cohort studies.[46]

The association of tooth loss with atherosclerosis may be a statistical epiphenomenon reflecting dental infection sufficiently serious to result in extraction. However, the possibility remains that tooth loss itself influences propensity for vascular disease, independent of preceding dental infection. Possible mechanisms for such a direct effect of tooth loss include consumption of a proatherogenic diet with reduced chewing efficiency and chronic denture-associated candidal infection.

Periapical Infection and Atherosclerosis

It is important to recall that caries and consequent periapical infection is the main cause of tooth loss.[1,62,63] Recalling also that the earliest reports in this area evaluated overall dental infection including caries and periapical lesions,[7,8] it seems that investigators have neglected possible associations of atherosclerosis with caries and periapical infection relative to periodontitis. Nonetheless, some case-matched,[64] cross-sectional,[37,56] and cohort studies[32,33] have been performed supporting a similar independent relationship between periapical infection and coronary artery disease,[32,33,64] stroke,[37] and, to a lesser extent, subclinical carotid athoerosclerosis[56] to that seen in periodontitis.

Studies relating atherosclerosis to periapical infection suggest it is not any particular quality of periodontitis

driving the correlation with atherosclerosis, but rather it is the total infective load that may be important. Supporting this idea is a dose–response relationship between increasing myocardial infarction and an increasing number of periapical lesions,[64] as well as an inverse relationship between the number of completed root canal therapies and myocardial infarction.[64] In addition, a cross-sectional study in which periodontal disease and periapical lesions were considered separately demonstrated independent association of these two dental infections with stroke.[37]

Although it seems likely that periapical infection rather than coronal caries is the most important aspect of caries relating to atherosclerosis, this is an assumption unsupported by published data, and it is problematic that no reports have described the individual relationship with atherosclerosis of coronal caries, periapical infection, and periodontitis. Moreover, although there are several distinct pathological forms of periapical lesion (Fig. 2),[1] the effect of this diversity on the association with atherosclerosis has not been studied. There is both need and scope for significantly more research investigating the relationship of atherosclerosis with both coronal caries and periapical infection.

Factors Complicating Interpretation of the Relationship Between Vascular Disease and Dental Infection

Although all of the published studies investigating the relationship between atherosclerosis and dental infection describe attempts to control for the effect of known separate risk factors for vascular disease, the possibility remains that dental infection and atherosclerosis share as yet unidentified risk factors.

Smoking[65–69] and cadmium exposure[70] are known environmental risk factors shared by atherosclerosis and periodontitis, and they can in principle be readily controlled for in studies investigating the relationship between the two diseases.

Disease-associated risk factors shared by atherosclerosis and periodontitis are surprisingly difficult to disentangle because of apparent feedback relationships between periodontitis and the risk factors involved. For example, diabetes mellitus is a risk factor for both atherosclerosis and periodontitis,[71–73] but treatment of periodontal disease appears to improve diabetic control,[74,75] making it difficult to control for the effect of diabetes in studies examining periodontal and vascular disease. Similarly, hypertension,[76–78] high white blood cell count[76,79–82] elevated total plasma cholesterol,[82–86] raised plasma LDL levels,[82–84] elevated very low-density lipoprotein (VLDL),[86] raised fatty acid,[86] and increased plasma triglyceride levels,[83,85–88] as well as reduced plasma HDL levels,[82,89] are also well-established risk factors for both atherosclerosis and periodontitis but improve with periodontal therapy,[90–96] suggesting a feedback relationship between periodontitis and these risk factors. Although most studies seek to control for the overlap of such shared risk factors, there seems to be a need for any epidemiological data linking atherosclerosis with periodontal disease to be interpreted in a highly conservative manner.

A common observation made across many of the studies currently reviewed is that the association between periodontitis and atherosclerotic changes is stronger in younger people[19,35,40,47] and sometimes not seen in older subjects.[19,35] One reasonable explanation for this may be the cumulative nature of periodontal disease and tooth loss, such that as subjects age there are fewer teeth available for periodontitis to act on.[25]

The specific periodontal variable measured has a bearing on study outcomes, with one case-controlled study, for example, reporting different ORs for myocardial infarction dependent on whether pocket depth (OR: 2.19; 95% CI, 1.66 to 2.89), clinical attachment loss (OR: 1.46; 95% CI, 1.26 to 1.69), alveolar crest height (OR: 1.3; 95% CI, 1.14 to 1.49), or the number of missing teeth (OR: 1.04; 95% CI, 1.02 to 1.07) was used to perform the calculation.[17] Although at first confusing, this differential outcome might be explained in context of the active inflammation inherent to all deep pockets, which would be greatly reduced when there is recession (Fig. 1). Although such differential results indicate a need for clarification of the most biologically relevant periodontal measures for future studies,[17,97] they may also provide guidance as to possible pathological mechanisms.

The complicating factors just outlined may account for several case-controlled,[98,99] cross-sectional,[100] and cohort studies[101–105] in which no clear association between dental infection and atherosclerosis was seen. In light of the previously described complexities, it is difficult to achieve certainty from epidemiological observations alone of a causal relationship between dental infection and atherosclerosis. Fortunately, some data are available from both human intervention studies and animal experiments that can inform interpretation of epidemiological studies.

Animal Studies Supporting a Causal Relationship of Periodontitis for Atherosclerosis

A variety of animal model systems have been used to study the relationship between periodontal disease and atherosclerosis including New Zealand rabbits fed a high-fat diet,[97,106,107] transgenic ApoE-deficient mice,[108–114] and pigs.[115]

The ability of periodontopathic organisms to increase atherosclerosis is well demonstrated in experiments where intravenous infusion of *P. gingivalis*,[108,111,115] or *A. actinomycetemcomitans*,[113,114] in

ApoE-deficient mice[108,111,113,114] or pigs[115] increases the severity of atherosclerotic lesions. The potentially causal role of periodontitis is, however, more directly demonstrated in experiments where atherosclerosis is made more severe upon induction of periodontitis by oral infection with *P. gingivalis* in rabbits fed a high-fat diet[97,106] or in apolipoprotein E (ApoE)-deficient mice.[109,110]

P. gingivalis DNA has been detected in aortic mouse atherosclerotic lesions,[109,110] as well as in both aortae and coronary arteries of pigs,[115] supporting a role for direct bacterial invasion. The importance of bacterial cell attachment to the arterial wall is illustrated by reduced atherogenic activity for mice of a fimbrial-deficient strain of *P. gingivalis*.[110]

Immunization of apolipoprotein E–deficient mice against *P. gingivalis* is protective against atherosclerosis exacerbated by *P. gingivalis*,[110–112,116] further supporting a causative role for oral bacterial infection in vascular disease.

Human Intervention Studies for Atherosclerosis by Treating Periodontal Disease

The most convincing evidence of a causal role for periodontal disease in human atherosclerosis would be clinical intervention trials demonstrating protection against vascular disease by treating periodontitis.[29,117] Making this difficult, however, is that both periodontitis and atherosclerosis progress over many decades, and both diseases also have only limited potential for recovery. As a consequence, it is recognized that intervention trials may not readily detect an effect of periodontal treatment on atherosclerosis outcomes.[29,97]

A range of serum biomarkers correlate with increased atherosclerosis including increased C-reactive protein (CRP), fibrinogen, interleukin(IL)-6, total cholesterol, and LDL, as well as reduced HDL.[118–123] Reduction in response to treatment for periodontitis of circulating levels of CRP,[90,93–95,124–129] IL-6,[90,95,124,125,128–131] fibrinogen,[93,94,128] total cholesterol,[90] and LDL,[130] as well as increased HDL,[95] supports a role for periodontal disease in atherosclerosis. Also, treatment of periodontitis is reported to reduce circulating $CD4^+HLA\text{-}DR^+$, $CD4^+CD44^+$, and $CD4^+CD49d^+$ T cells suggested as contributing to atherogenesis.[94] Significant for the potential therapeutic value of periodontal interventions is that these changes in T cells as well as improvements in circulating levels of CRP and fibrinogen are largely lost by 12 months post-treatment, apparently reflecting recurrence of periodontal disease.[94] Periodontal treatment failed, however, to reduce fibrinogen levels in a recent study, although a surprising increase in hematocrit and hemoglobin was reported.[132]

Endothelial dysfunction as reflected by reduced flow-mediated dilation of the brachial artery is considered a reasonable indicator for early atherosclerotic disease,[133] and improved flow-mediated dilation following treatment for periodontitis,[126,131,134–137] without improvement in responsiveness to nitroglycerin,[126,131,134,135] is consistent with a causative role for this oral disease in atherosclerosis.

Anatomical demonstration of improved atherosclerosis following treatment of human periodontitis seems currently limited to a single report of reduced carotid intima-media thickness together with the previously mentioned changes in CRP, fibrinogen, and lymphocyte populations.[94]

A large multicenter randomized controlled Periodontitis and Vascular Events (PAVE) trial is currently underway, evaluating the effect on cardiovascular events of periodontal therapy as compared with "community dental care." Preliminary results thus far reported are equivocal, with no statistically significant improvement in serious adverse events between the two groups studied, although a modest trend toward improved vascular outcomes is seen.[138,139] The PAVE trial, however, is at a very early stage, and it may be too early for statistically meaningful data to have emerged.

MECHANISMS LINKING DENTAL INFECTION TO VASCULAR DISEASE

Direct Bacterial Infection of the Arterial Wall

In periodontitis, expanded blood vessels are in intimate contact with an atrophic pocket epithelium so that bacterial plaque may be separated from circulating blood by as few as two cells.[140] Bacteremia is consequently frequent in periodontitis and provides a pathway for periodontal pathogens to access the arterial wall. DNA of *A. actinomycetemcomitans*,[141–143] *P. gingivalis*,[115,141–145] and other periodontopathic organisms[141–143,145] has been demonstrated in carotid,[141,144] coronary,[115,142,145] and aortic[115,143] endarterectomy specimens. DNA from streptococci implicated with caries and not periodontitis has also been found in atherosclerotic plaques,[143] suggesting that caries should perhaps be investigated as a potential independent risk factor for atherosclerosis.

The Virulence of Oral Bacteria for Atherosclerosis

Circulating antibody levels against a range of periodontopathic bacteria correlate with intima-medial wall thickness, and the plaque microbial load for these species is also proportionate to cardiovascular disease,[29] supporting an atherogenic role for these organisms. *P. gingivalis* seems particularly important as a potential microbial link between human periodontitis and atherosclerosis,

as indicated by correlation between circulating specific antibody and risk for stroke[146] and cardiovascular disease,[61,147,148] and antibody levels against *A. actinomycetemcomitans* are also correlated with increased coronary heart disease[61,149] and stroke.[150] Adhesion of *P. gingivalis* is strongly affected by the fimbrial genotypes expressed, and it is interesting that there is overrepresentation of some fimbrial forms in atherosclerotic lesions.[151] Streptococci, normally associated with caries rather than periodontal disease, also have potential to contribute to arterial vascular disease via thrombogenic activity,[152] and potentially prothrombotic von Willebrand factor correlates with levels of circulating antibody against *A. actinomycetemcomitans*.[153]

Lipopolysaccharide shed by gram-negative organisms such as *P. gingivalis* associates preferentially with VLDL and intermediate-density lipoproteins, and it has been suggested that these lipoproteins deliver lipopolysaccharide from periodontal lesions to atherosclerotic plaques.[154] A range of separate potentially atherogenic activities has been demonstrated for *P. gingivalis* in cell culture experiments including increased human endothelial apoptosis,[155] increased endothelial expression of monocyte chemoattractant protein-1,[155,156] stimulation of U-937 monocyte adhesion to aortic endothelium,[157] increased tissue factor and reduced tissue factor pathway inhibitor expression in human aortic endothelium,[158] and platelet aggregation.[159] Of interest is that increased levels of CRP are associated with elevated levels of *P. gingivalis* and *A. actinomycetemcomitans* in dental plaque.[160] However, in light of the large number of other species contributing to the microbial plaque of periodontitis lesions, it seems likely that there are many other important but as yet uninvestigated microbial activities of relevance for atherosclerosis. This is supported by correlation between hypertension and discrete patterns of oral microbial ecology considered causative for periodontitis.[161]

The Acute Phase Response in Periodontitis and Atherosclerosis

In the acute phase response, IL-6 released from inflamed tissues accesses the liver via the circulation to stimulate greatly increased synthesis of a range of plasma proteins including CRP and fibrinogen.[162] Because serum IL-6[129,163] and CRP[79–81,127,129,163–165] are elevated in periodontitis, and periodontal therapy reduces circulating IL-6,[124,125,127–129,163] CRP,[94,124,125,128,129,163] and fibrinogen levels,[94,128] the acute phase response is suggested as important in mediating the link between periodontal disease and atherosclerosis.[5,166,167]

IL-6 synthesis is highly inducible in cultured endothelium,[168] and it is noteworthy that IL-6 mRNA and protein is expressed by endothelium in inflamed periodontal tissues.[169,170] Supporting periodontal endothelium as a likely source for IL-6 is that these cells have a unique opportunity to secrete IL-6 directly into the circulation, and ultrastructural features of high endothelial-like venules in periodontitis are consistent with high synthetic activity.[5,171] Plasminogen activator inhibitor (PAI)-1 is also a major product of endothelium,[172] and raised plasma levels of this antifibrinolytic protein in periodontitis suggests a role in atherogenesis.[81,173] Also, a case-matched study demonstrates reduced circulating levels of antithrombotic protein C with periodontitis.[165]

Cytokine Polymorphisms in Periodontitis and Atherosclerosis

Polymorphism among inflammatory cytokines may account for individual differences in host response. Notably, polymorphisms in IL-1,[174,175] IL-6,[174] and tumor necrosis factor α[174] are associated with enhanced systemic changes in periodontal disease, including elevated serum IL-6 and CRP levels,[174] as well as increased susceptibility to cardiovascular disease.[175]

CONCLUSION

Despite uncertainties inherent in considering individual studies, a balanced reading of the current literature strongly supports the suggestion that periodontal disease contributes to atherosclerosis, and several plausible mechanisms are supported by published data. Nonetheless, the distinct roles of coronal caries and periapical infection in atherosclerosis remain unclear, as do the precise atherogenic mechanisms involved. The outcome of long-term intervention studies determining the effect of dental treatment on atherosclerosis will be of interest not only with regard to improved understanding of the systemic effects of dental disease but also from the perspective of providing a further therapeutic avenue for vascular health.

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