Associations Between Periodontal Disease and Risk for Atherosclerosis, Cardiovascular Disease, and Stroke. A Systematic Review

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BACKGROUND

Etiology of Atherosclerosis, Cardiovascular Disease, and Stroke

The major contributing factor in the majority of cases of cardiovascular disease (CVD) and cerebrovascular disease (stroke) is atherosclerosis. One of the outcomes of this disease process is the narrowing of the arteries resulting from subendothelial deposition of cholesterol, cholesterol esters, and calcium within the vessel walls. These cholesterol-rich plaques also contain a variety of cell types, including fibroblasts and immune cells.1 Rupture of the atherosclerotic plaques yield thrombi that travel distally to occlude the artery, resulting in myocardial infarction or stroke.

Several factors increase the risk for atherosclerosis including a predisposition for elevated levels of cholesterol and triglyceride in the blood; high blood pressure; diabetes; and cigarette smoking.

Normal cells obtain most of the cholesterol they need for normal functioning by taking up cholesterol from the blood through receptor-mediated endocytosis. Cholesterol is transported in the blood bound to low-density lipoproteins, or LDLs. These LDLs bind to specific transmembrane receptor proteins for...
transport into the cell. Cholesterol uptake is blocked in some people (e.g., due to an apolipoprotein E defect), and excess cholesterol accumulates in the blood to eventually form atherosclerotic plaques. If these plaques occlude blood flow in brain arteries, the result can be stroke; if they occur in coronary arteries, it can lead to myocardial infarction.

Role of Inflammation in Atherosclerosis, Cardiovascular Disease, and Stroke
A recent and growing literature implicates infection, local and/or systemic inflammation, and possibly autoimmunity in the pathogenesis of atherosclerosis. Arterial inflammation may be locally increased by lipid imbalances, hemodynamic stress, and immune reactions directed against the vascular wall, eventually leading to the formation of complicated atherosclerotic lesions. This inflammation-mediated damage may initiate or contribute to the progression of the atherosclerotic plaque. A number of pathogens appear to be associated with atherosclerotic plaques, and alterations in the immune responsiveness may compromise clearance of the organism from these plaques. One of the best studied of these associations involves Chlamydia pneumoniae, a common intracellular bacterium that causes pneumonia and milder respiratory tract infections. Recently, C. pneumoniae DNA and proteins have been detected in arteries of patients with giant cell arteritis, and in endarterectomy samples. Elevated antibody levels against C. pneumoniae have been measured in patients with coronary heart disease compared to controls.

Serum inflammatory biomarkers such as C-reactive protein (CRP) appear to be elevated in subjects with atherosclerosis. Other suggested biomarkers include fibrinogen, cell adhesion molecules, and various inflammatory cytokines. In fact, models using CRP together with lipid profiles appear to predict risk for cardiovascular events better than the use of lipids alone.

RATIONAL
The first suggestion that periodontal inflammation may be related to atherosclerosis came in a paper published in 1988. These investigators compared the oral health (measured by the Community Periodontal Index of Treatment Needs) of 211 male patients in Yugoslavia who experienced an MI with 336 control patients. They noted that the MI group had worse periodontal health than did the control group. Subsequent case-control studies also showed a relationship of poor oral health to MI. In addition, risk indicators for cardiovascular disease have also been shown to be elevated in subjects with periodontitis. There has been an ever-increasing literature in response to this notion. Although the majority of publications have suggested an association between poor oral health and atherosclerosis, several epidemiologic studies have found no such relationship.

The goal of this systematic review was to identify all literature pertinent to this issue, to critically evaluate it and understand the current state of knowledge on this subject, and to point out directions for additional research.

FOCUSED QUESTION
We attempted to answer the following focused question, “Does periodontal disease influence the initiation/progression of atherosclerosis (and therefore CVD, stroke, and peripheral vascular disease)"

SEARCH PROTOCOL
Data Sources and Search Strategy
The search strategy was defined to include randomized controlled clinical trials (RCTS), longitudinal, cohort, and case-control studies.

Search terms: Searches were run by one of the reviewers (RB) using Ovid Search software of MEDLINE (1966-March 2002), MEDLINE Daily Update, and Cochrane Controlled Trials Register (CCTR) updated to first quarter of 2002. MEDLINE and MEDLINE Daily Update were searched using medical subject headings (MeSH terms). Reference lists of previously published review articles were also searched. All MeSH terms employed were exploded to expand retrieval to those records that were assigned the more narrow related MeSH term. The CCTR database and Pre-MEDLINE required use of keywords (we used both American and British spellings). All searches included the term “and human.”

MeSH terms: Cardiovascular diseases, or heart diseases, or arteriosclerosis, or cerebrovascular disorders, or carotid artery diseases, or peripheral vascular diseases, or cerebrovascular accident, or hypercholesterolemia.

Oral conditions: Periodontal diseases, tooth diseases, or dental plaque index.

Key words: Arteriosclerosis, or atherosclerosis, or carotid artery disease, or myocardial infarction, or coronary disease, or cardiovascular disease, or peripheral vascular disease, or hypercholesterolemia, or hypercholesterolaemia, or cerebrovascular disorder, or cerebrovascular accident.

Oral conditions: Periodontal disease, or periodontitis, or periodontal attachment loss, or alveolar bone loss, or dental plaque, or oral hygiene.

Inclusion criteria: The reports included in the review were those that recruited participants with atherosclerosis, myocardial infarction (MI), stroke, or peripheral vascular disease. Oral conditions considered included periodontal disease (as measured by assessments of gingival inflammation, probing depth, clinical attachment loss, and/or radiographic bone loss). Our search
strategy also considered studies that tested the effect of periodontal intervention on the initiation and progression of atherosclerosis, MI, stroke, or peripheral vascular disease.

**Exclusion criteria:** The search was limited only to studies of humans.

**Outcomes:** The following outcome measures were assessed:
1. Primary outcome: increased incidence of MI or stroke associated with periodontal disease.
2. Secondary outcomes: deficient measures of heart function or surrogates of cardiovascular risk, such as measures of endothelial function, intima-media wall thickness, vascular calcification, blood lipids, or C-reactive protein levels associated with periodontal disease.
4. Adverse outcomes: intraoral adverse effects, increased rate of MI, stroke.

**Data Collection and Analysis**

Titles and abstracts of articles obtained using the above described search strategy were screened by two independent readers (FAS and SP) and checked for agreement. The full text of the articles judged by title and abstract to be relevant (by either FAS or SP) were read and independently assessed against the stated inclusion criteria.

For cohort studies that measured differences in rates of disease between the group with oral disease and the group without oral disease, weighted mean differences, relative risks or odds ratios were compared. No published randomized controlled clinical trials evaluating primary outcomes were identified during the course of this search.

Because of the heterogeneity in study design, methods of outcome measures, and target populations, no effort was made to perform a meta-analysis of the included studies.

**Ranking of Studies**

Included papers were graded according to previously reported classifications.29,30
1. Systematic review of randomized controlled clinical trials. RCTs with narrow confidence intervals.
2. Randomized controlled clinical trial. Low quality systematic review.

**RESULTS AND DISCUSSION**

Following the described search strategy, MEDLINE searching yielded 1,502 articles (1,020 in the English language). In addition, 1 article was retrieved from the MEDLINE Daily Update, 19 from the Pre-MEDLINE and 4 from CCTR. Titles and abstracts were read and the full text of all articles deemed relevant were obtained and reviewed. This process resulted in the selection of 31 articles that attempted to evaluate the association of periodontal disease to CVD, stroke, or peripheral vascular disease (Tables 1, 2, 3, and 4).

Search of the CCTR database revealed no articles of relevance to the objectives of this review.

Interest in a possible connection between poor oral health and atherosclerosis-induced heart disease began with case and case-control studies in the 1980s. Since then 4 additional case-control studies have been published. Of the 5 case-control studies (Table 1), 4 reported a positive association between indicators of poor dental health and outcomes of atherosclerosis (CVD).9-11,16 The one study reporting the absence of a positive association was of very elderly subjects.12 Taken together, these studies support a positive association between the poor oral health and the prevalence of cardiovascular events. In some cases, the evidence points to an association with periodontal disease.

Stimulated by these first case-control studies, 15 cross-sectional studies have since been published (Table 2).17-28,31-33 Of these, 11 studies support a modest association of periodontal disease with CVD, after controlling for other cardiovascular risk factors, particularly smoking. Because few studies use the same oral assessment measures, it is not possible to perform a valid meta-analysis by combining data from these studies. Most studies were retrospective in design. To date, results from a prospective, longitudinal epidemiologic study have not been reported.

In addition, 4 other studies have shown a positive association between periodontal disease and stroke,20,34-36 and another study has associated periodontal disease with peripheral vascular disease37 (Table 3). In addition to the aforementioned epidemiologic studies, several other studies14,15,38-41 have reported an association of periodontal disease with various parameters causally linked with the pathogenesis of atherosclerosis-induced disease (Table 4). These studies demonstrate elevated levels of C-reactive protein, fibrinogen, white blood cells, cholesterol, and cytokines in association with periodontal disease. Results of such studies suggest possible mechanisms that link periodontal disease to the etiology of atherosclerosis.

One of the limitations of this analysis is the recognition of the great heterogeneity between studies in assessment of oral disease, making comparison of results difficult. An internationally accepted and standardized protocol for the assessment of oral health is lacking. Limiting consideration only to studies that used clinical attachment levels as a measure of periodontal disease history (a commonly accepted measure of periodontal damage) reveals general consensus of a positive association between the extent of attachment loss and CVD.12-15
**Table 1.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Oral Assessment</th>
<th>Cardiovascular Assessment</th>
<th>Conclusions</th>
<th>Study Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simonka et al.9 1988</td>
<td>Cases: 211 males with previous heart attack. Controls: 336 age-matched patients without heart attack.</td>
<td>“KEP” index (= DMF: caries, missing, and filled teeth), CPITN index.</td>
<td>Previously diagnosed MI</td>
<td>Significant difference in CPITN and demand for periodontal surgery in patients ≥50 years old with heart attack. No difference in DMF between cases and controls.</td>
<td>3</td>
</tr>
<tr>
<td>Mattila et al.10 1989</td>
<td>Cases: 40 males ≤50 years old; 60 males and females &lt;65 Controls: 102 age- and gender-matched.</td>
<td>Dental Severity Index (sum of scores for caries, periodontal disease, periapical pathosis and pericoronitis).</td>
<td>Evidence of MI from EKG and elevated enzyme levels (creatine phosphokinase isoenzyme MB).</td>
<td>Dental health significantly worse in patients with acute MI than controls after adjustment for social class, smoking, serum lipids, and diabetes.</td>
<td>3</td>
</tr>
<tr>
<td>Mattila et al.11 1993</td>
<td>100 subjects with previous CVD. No controls</td>
<td>Sum of the number of vertical bone defects, periapical lesions, caries, pericoronitis, and furcation lesions.</td>
<td>Extent of coronary artery occlusion by angiography.</td>
<td>Significant association between dental infections and severe coronary atheromatosis in males. No association in females.</td>
<td>3</td>
</tr>
<tr>
<td>Mattila et al.13 2000</td>
<td>Cases: 85 males and females with proven cardiovascular disease. Controls: 53 age- and gender-matched.</td>
<td>Indices based on sum scores from periodontal probing, furcation lesions; radiographic examination enumerating number of carious teeth, impacted teeth, periapical lesions, vertical bone defects and furcation lesions.</td>
<td>Subjects with diagnosed clinically or angiographically proven MI.</td>
<td>Dental indices (clinical and radiographic) higher, but not significant, among CHD than controls.</td>
<td>3</td>
</tr>
<tr>
<td>Emingil et al.16 2000</td>
<td>Cases: 60 subjects with acute MI (AMI). Controls: 60 with chronic coronary heart disease (CCHD).</td>
<td>Missing teeth, restorations, PD and BOP.</td>
<td>AMI subjects were admitted to the hospital for treatment of AMI, verified by EKG and serum enzyme levels. The CCHD subjects had history of MI but not of recent AMI.</td>
<td>Logistic regression analysis showed % of sites with BOP, N of sites with PD ≥4, number of restorations, smoking status, and triglyceride levels were significantly increased in AMI subjects (P&lt;0.05). These results suggest that periodontal disease may be associated with acute MI.</td>
<td>3</td>
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</tbody>
</table>

It has been suggested that the association observed between atherosclerosis-induced disease and periodontal disease is due to etiologic factors common to both disease processes, such as lifestyle practices like cigarette smoking.20,21,24 Thus, dissection of the independent role of lifestyle factors from the effect of periodontal inflammation on atherosclerosis will require conducting of large longitudinal epidemiologic studies of never smokers in addition to large randomized controlled clinical trials of periodontal intervention to prevent the initiation and progression of atherosclerosis-induced diseases.

**REVIEWERS’ CONCLUSIONS**

Periodontal disease appears to be moderately associated with atherosclerosis-induced diseases such as coronary artery disease, stroke and peripheral vascular disease. The extent to which the initiation and/or progression of atherosclerosis is influenced by periodontal infection or inflammation is presently unknown.
### Table 2.

**Cross-Sectional and Longitudinal Studies**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Oral Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paunio et al.18 1993</td>
<td>1,384 Finnish males; 868 re-examined.</td>
<td>N missing teeth.</td>
</tr>
<tr>
<td>Joshipura et al.19 1996</td>
<td>44,119 participants of the Health Professionals Follow-up Study (58% were dentists).</td>
<td>Self-reported number of teeth, and history of periodontal disease</td>
</tr>
<tr>
<td>Beck et al.20 1996</td>
<td>203 cases; 940 controls from VA Dental Longitudinal Study component of the Normative Aging Study.</td>
<td>Alveolar bone loss measured from radiographs measured using Schei ruler; worst probing depth per tooth.</td>
</tr>
<tr>
<td>Loesche et al.21 1998</td>
<td>320 veterans ≥60 years old.</td>
<td>Number of teeth (0-14 or 15-28); probing depths, attachment level and gingival recession; plaque index; gingival bleeding. Plaque N-benzoyl-DL-arginine-2-naphthylamide enzyme score; complaint of xerostomia.</td>
</tr>
<tr>
<td>Arbes et al.22 1999</td>
<td>5,564 subjects &gt;40 years old.</td>
<td>% attachment loss of all teeth ≥3 mm (categorized as 4 levels).</td>
</tr>
<tr>
<td>Morrison et al.23 1999</td>
<td>10,368 subjects enrolled in Nutrition Canada Survey.</td>
<td>Periodontal disease classified as none, mild gingivitis, severe gingivitis, obvious pockets, loose teeth, and edentulous.</td>
</tr>
</tbody>
</table>
### Table 2. (continued)
#### Cross-Sectional and Longitudinal Studies

<table>
<thead>
<tr>
<th>Cardiovascular Assessment</th>
<th>Major Findings or Odds Ratio (OR) or Risk Ratio (RR) (95% CI)</th>
<th>Conclusions</th>
<th>Study Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to hospital for CHD treatment. Mortality due to coronary heart disease.</td>
<td>RR 1.72 (1.10-2.68) when periodontitis compared to CHD.</td>
<td>Dental disease is associated with a small increased risk of CHD.</td>
<td>4</td>
</tr>
<tr>
<td>Screening examination using questionnaires and interviews about previous disease; chest X-rays, EKG, blood pressure. Subjects with any suggestive finding were re-examined with clinical examination and diagnosis by physician. CHD defined as angina pectoris or previous MI.</td>
<td>Prevalence of ischemic heart disease was correlated with the number of missing teeth; around 10% when less than 1/2 teeth lost and around 20% when at least 1/2 teeth were lost.</td>
<td>A weak but statistically significant association between missing teeth and ischemic heart disease.</td>
<td>4</td>
</tr>
<tr>
<td>Fatal/non-fatal MI, sudden death. Subjects with revascularization procedures excluded.</td>
<td>Men with periodontal disease and with 0-10 teeth, as compared to men with 25+ teeth; RR = 1.67 (1.03-2.71). No association among men without periodontal disease, RR = 1.11 (0.74-1.68).</td>
<td>A small association between tooth loss and CHD risk no overall association between periodontal disease and CHD.</td>
<td>4</td>
</tr>
<tr>
<td>Total CHD determined as cases of non-fatal MI, angina pectoris, and CHD deaths. Stroke diagnosed by means of history and physical examination.</td>
<td>Incidence odds ratios: Bone loss and total CHD 1.5, Bone loss and fatal CHD 1.9, Bone loss and stroke 2.8.</td>
<td>Periodontal disease associated with a moderate risk of CHD/stroke.</td>
<td>4</td>
</tr>
<tr>
<td>Diagnosis of MI, bypass surgery, clinical angina, EKG, serum enzyme levels, angiography; positive response to treatment for heart disease.</td>
<td>Significant association between CHD and poor oral health in independent living subjects. OR for 1-14 teeth 2.83 (1.11-7.2); for papillary gingival bleeding score &gt;1.5-4.6 (1.32-15.97); for positive plaque BANA score 2.46 (1.13-5.38); for complaint of xerostomia 2.6 (1.02-6.62). For dependent living subjects: 1-14 teeth 6.16 (1.60-23.7); for complaint of xerostomia 2.92 (1.02-8.39).</td>
<td>Several oral health variables are risk indicators for CHD.</td>
<td>4</td>
</tr>
<tr>
<td>Self-reported MI.</td>
<td>Relative to 0% category, the unadjusted odds of heart attack increased with each higher category of attachment loss (0-33%, 33-67%, 67-95%) were 2.1 (1.1-3.9), 5.5 (3.4-9.1) and 9.8 (4.5-21.0), respectively. When adjusted for age, gender, race, etc. OR was 1.38 (0.75-2.54), 2.28 (1.18-4.39), and 3.77 (1.46-9.74).</td>
<td>Results support an association between periodontal disease and coronary heart disease.</td>
<td>4</td>
</tr>
<tr>
<td>Death attributed to coronary heart and cerebrovascular disease.</td>
<td>The relation between dental health (severe gingivitis and edentulous status) and the risk of fatal CHD and CVD was (rate ratios-RR) 2.15 (1.25-3.72) and 1.90 (1.17-3.10), respectively, as adjusted for confounding variables.</td>
<td>These data indicate that poor dental health is associated with an increased risk of fatal CHD.</td>
<td>4</td>
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(continued)
Table 2. (continued)

Cross-Sectional and Longitudinal Studies

<table>
<thead>
<tr>
<th>Reference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Beck et al.24</td>
<td>6,017 persons from the Atherosclerosis Risk in Communities Study 1996.</td>
<td>Periodontitis was defined by extent of attachment loss ≥3 mm: none/mild (&lt;10%), moderate (10% to &lt;30%), or severe (≥30%).</td>
</tr>
<tr>
<td>Jansson et al.25</td>
<td>1,393 subjects from the County of Stockholm admitted to the study in 1979. A follow-up was performed in 1997.</td>
<td>N missing teeth, apical lesions, and carious lesions. Marginal bone loss (MBL) expressed as % of the distance from apex to CEJ. MBL index was defined as the mean of the MBL values at all measurable points in an individual.</td>
</tr>
<tr>
<td>Hujoel et al.26</td>
<td>8,032 dentate adults aged 25-74 years from NHANES-I. a periodontal pocket with attachment loss; gingivitis, inflammation with no attachment loss; periodontal health, no attachment loss or inflammation.</td>
<td>Baseline periodontal status: periodontitis; a periodontal pocket with attachment loss; gingivitis, inflammation with no attachment loss; periodontal health, no attachment loss or inflammation.</td>
</tr>
<tr>
<td>Hujoel et al.27</td>
<td>4,027 people who participated in the NHANES-I.</td>
<td>Comparison of subjects with periodontitis (pockets ≥4 mm on any teeth) with edentulism.</td>
</tr>
<tr>
<td>Howell et al.28</td>
<td>22,037 male subjects in Physicians’ Health Study I.</td>
<td>Self-report of presence or absence of periodontal disease at study entry.</td>
</tr>
<tr>
<td>Katz et al.31</td>
<td>1,094 Israeli army servicemen aged 26-53 years (mean: 39 ± 5); 151 had CHD.</td>
<td>Severity of periodontal disease assessed by CPITN.</td>
</tr>
<tr>
<td>Takata et al.32</td>
<td>697 octogenarians in Fukuoka Prefecture, Japan.</td>
<td>Tooth loss and assessment of the Community Periodontal Index.</td>
</tr>
<tr>
<td>Hujoel et al.33</td>
<td>636 dentate individuals initially enrolled in NHANES-I who had both medical and dental examinations, reported a prior history of CVD, and who were followed longitudinally.</td>
<td>Inclusion: History of prior CVD as determined by a yes answer to 1 of 4 questions: “Has a doctor ever told you that you had a heart attack?” “Has a doctor ever told you that you had a stroke?” “Has a doctor ever told you that you have heart failure?” and “During the past 6 months have you used any medicine, drugs, or pills for a weak heart?” (continued)</td>
</tr>
<tr>
<td>Cardiovascular Assessment</td>
<td>Major Findings or Odds Ratio (OR) or Risk Ratio (RR) (95% CI)</td>
<td>Conclusions</td>
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<tr>
<td>Carotid artery intima-media wall thickness (IMT) ≥1 mm.</td>
<td>Severe periodontitis (OR 1.31, CI 1.03 - 1.66) was associated with IMT ≥1 mm, while adjusting for the other factors.</td>
<td>Periodontitis may influence atheroma formation.</td>
</tr>
<tr>
<td>Death due to CVD.</td>
<td>The sum of scores for number of missing teeth, apical lesions, caries lesions, and marginal bone loss was significantly correlated to fatal coronary events in subjects ≤45 years old.</td>
<td>Poor dental health and smoking are risk indicators of death due to CVD.</td>
</tr>
<tr>
<td>Death from CHD or hospitalization due to CHD, or revascularization procedures, obtained from death certificates and medical records.</td>
<td>Neither gingivitis nor periodontitis was associated with a statistically significant increased risk for CHD.</td>
<td>This study did not find convincing evidence of a causal association between periodontal disease and CHD risk.</td>
</tr>
<tr>
<td>Death from CHD, or hospitalization due to CHD, or revascularization procedures, obtained from death certificates and medical records.</td>
<td>Confirmed elimination of chronic dental infections (by full-mouth dental extraction) did not lead to a decreased risk of experiencing a CHD event.</td>
<td>Reduction in periodontal inflammation by tooth extraction will not prevent CHD.</td>
</tr>
<tr>
<td>A cardiovascular event was confirmed after examination of all information by an end points committee blinded to participants’ periodontal disease status. Nonfatal stroke was defined as a typical neurologic deficit, either sudden or rapid in onset, that lasted &gt;24 hours and was attributed to a cerebrovascular event. Cardiovascular death confirmed by review of death certificates, hospital records, and observers’ impressions.</td>
<td>No statistical association between cardiovascular death or stroke and self-reported periodontal disease at baseline, compared to those who did not.</td>
<td>Self-reported periodontal disease is not an independent predictor of subsequent cardiovascular disease.</td>
</tr>
<tr>
<td>History of MI and/or anginal syndrome with angiographic evidence of significant coronary disease, or suffer from atherosclerotic risk factors; i.e., diabetes (fasting glucose).</td>
<td>A significant association between CPITN score 4 and hypercholesterolemia.</td>
<td>The generation of higher cholesterol blood levels is proposed as a possible link between chronic periodontal inflammation and atherosclerosis.</td>
</tr>
<tr>
<td>Abnormal ECG findings.</td>
<td>Individuals with &lt;20 teeth had increased prevalence of ST depression and T-wave abnormalities in ECG.</td>
<td>Tooth loss may be a predictor of abnormal ECG findings in the very elderly.</td>
</tr>
<tr>
<td>Periodontal disease was defined as: periodontitis: presence of ≥4 with pockets and attachment loss, n = 236; gingivitis n = 186; and periodontal health n = 214. Individuals with gingivitis had an overt area of inflammation which may completely circumscribe the tooth and which may have been associated with pseudopockets.</td>
<td>No significant differences observed between CHD and periodontitis or gingivitis.</td>
<td>Periodontal disease does not increase risk of CHD in subjects with preexisting heart disease.</td>
</tr>
</tbody>
</table>
Table 3.

Studies Relating Human Oral Health to Stroke (Cerebrovascular Accident or CVA) and Peripheral Vascular Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Oral Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syrjanen et al.34 1989</td>
<td>Case-control study of 40 patients with ischemic cerebral infarction under the age of 50, and 40 randomly selected community controls matched for gender and age.</td>
<td>Total dental index that measured number of carious lesions, severity of periodontitis, N periapical lesions and pericoronitis. The presence of subgingival calculus or suppuration in the gingival pockets was measured.</td>
</tr>
<tr>
<td>Beck et al.20 1996</td>
<td>203 cases and 940 controls from VA Dental Longitudinal Study component of the Normative Aging Study.</td>
<td>Alveolar bone loss measured from radiographs measured using Schei ruler; worst clinical PD per tooth.</td>
</tr>
<tr>
<td>Loesche et al.35 1998</td>
<td>Cross-sectional study of 401 veterans ≥60 years of age.</td>
<td>N teeth (0-14 and 15-28); PD, attachment level, and gingival recession; plaque index; gingival bleeding; evaluation of salivary flow and xerostomia.</td>
</tr>
<tr>
<td>Wu et al.36 2000</td>
<td>9,962 participants enrolled in NHANES-I and follow-up study.</td>
<td>Periodontal status was grouped into one of the following: 1) no periodontal disease; no teeth with periodontal disease, or 1 tooth with mild gingivitis if ≥20 teeth; 2) gingivitis; ≥1 tooth with mild gingivitis or a worse condition that did not fit category 1 or 3; 3) periodontitis; ≥4 or more teeth with overt pockets or worse conditions; and 4) edentulosity (both arches edentulous or all teeth were roots).</td>
</tr>
<tr>
<td>Mendez et al.37 1998</td>
<td>Assessment of a relationship between PVD and periodontal disease by analyzing data from the Normative Aging Study and Dental Longitudinal Study of the US Department of Veterans Affairs; 80 individuals with PVD were compared with 1,030 control subjects. Multivariate logistic regression analysis was used.</td>
<td>Radiographic measures of alveolar bone loss estimated from intraoral periapical films taken at baseline using Schei ruler.</td>
</tr>
</tbody>
</table>

Additional large-scale longitudinal epidemiologic and interventional studies are necessary to validate this association and to determine if the association is causal.

Presently, insufficient evidence is available to justify periodontal intervention to prevent the onset or progression of atherosclerosis-induced diseases.

FUTURE DIRECTIONS FOR RESEARCH

Studies to date provide equivocal evidence that periodontal disease has a causal link to atherosclerosis. Further research must be conducted to definitively establish the role of periodontal disease in the etiology of atherosclerosis. Randomized controlled clinical trials that evaluate the effects of periodontal intervention (that may include mechanical, chemical, or host modulatory approaches) in the prevention of atherosclerotic disease as well as in the management of patients suffering the effects of atherosclerosis-induced diseases (e.g., myocardial infarction, stroke) are necessary to prove or disprove this link.

REFERENCES

**Table 3. (continued)**

Studies Relating Human Oral Health to Stroke (Cerebrovascular Accident or CVA) and Peripheral Vascular Disease

<table>
<thead>
<tr>
<th>Stroke/PVD Assessment</th>
<th>Conclusions</th>
<th>Study Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis made by aorto-cervical angiography or by detection of brain stem infarction or cardiac emboli.</td>
<td>Poor oral health was more common in subjects with ischemic cerebrovascular disease in patients &lt;50 years of age.</td>
<td>3</td>
</tr>
<tr>
<td>Stroke diagnosed by means of history and physical examination.</td>
<td>Incidence OR for bone loss and stroke 2.8. Periodontal disease associated with a moderate risk of CHD/stroke.</td>
<td>3</td>
</tr>
<tr>
<td>Diagnosis of stroke (CVA) determined from hospital records, patient interview, CAT scans, and physical and neurologic examinations.</td>
<td>21% of the teeth in subjects with CVA had attachment loss &gt;6 mm compared to 12% in subjects without CVA (P = 0.028). Dentate subjects with CVA had more plaque and gingival bleeding than dentate subjects without CVA. The presence of 15-28 teeth and increased proportion of teeth with attachment loss &gt;6 mm were significantly related to CVA. Poor oral health and dental neglect are associated with CVA.</td>
<td>4</td>
</tr>
<tr>
<td>Incident cases of CVA meeting at least 1 of the following criteria: death certificate with cause of death due to CVA or 1 or more hospital/nursing home stays during the follow-up period with discharge</td>
<td>Compared with no periodontal disease, the relative risks (95% confidence intervals) for incident nonhemorrhagic stroke were 1.24 (0.74-2.08) for gingivitis, 2.11 (1.30-3.42) for periodontitis, and 1.41 (0.96-2.06) for edentulousness.</td>
<td>4</td>
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<td>Subjects with periodontal disease at baseline had a 2.27 increased risk of developing PVD (95% CI 1.32-3.9; P = 0.003) after excluding other vascular conditions from the control group and excluding stroke from the case group.</td>
<td>Periodontal disease emerged as a significant independent risk factor for PVD in a multivariate analysis that adjusted for other established risk factors.</td>
<td>4</td>
</tr>
</tbody>
</table>


### Table 4.

**Relationships of Markers of Atherosclerosis Associated with Human Periodontal Disease**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Outcome</th>
<th>Conclusions</th>
<th>Study Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kweider et al.38 1993</td>
<td>Case control. Cases: 50 consecutive patients attending dental hospital. Controls: 50 subjects with healthy periodontium recruited from hospital patients and staff.</td>
<td>Dental indices (plaque index, gingival index, CPITN) correlated significantly with fibrinogen and WBC count (GI and fibrinogen K = 3.17 and GI and WBC K = 3.38).</td>
<td>Inflammatory dental disease may influence fibrinogen level and WBC count.</td>
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<td>Ebersole et al.15 1997</td>
<td>40 subjects with periodontitis (radiographic evidence of bone loss, pockets &gt;5 mm, bleeding on probing) were compared to 35 normal subjects (who could exhibit mild to moderate gingivitis with pockets &lt;4 mm).</td>
<td>C-reactive protein (CRP) and haptoglobin (Hp) were significantly increased in serum from periodontal patients compared to healthy controls (P &lt;0.05).</td>
<td>Localized periodontal infections result in increased inflammation and tissue loss in the periodontium and elicit systemic host changes.</td>
<td>4</td>
</tr>
<tr>
<td>Wakai et al.39 1999</td>
<td>Cross-sectional 517 males and 113 females 23-83 years old.</td>
<td>Poor periodontal status (as measured by CPITN) strongly associated with high WBC count and CRP. Total cholesterol and triglyceride not associated with periodontal status.</td>
<td>Results suggest an association between periodontal status and associated factors for atherosclerosis.</td>
<td>4</td>
</tr>
<tr>
<td>Loos et al.14 2000</td>
<td>Case-control. Cases: 107 consecutive periodontal patients. Controls: 43 subjects with healthy periodontium.</td>
<td>Patients with periodontitis had higher median CRP levels than periodontally healthy controls (P = 0.030). Subjects with periodontal disease were more frequently seropositive for interleukin 6, and plasma IL-6 levels were higher than in periodontally healthy controls.</td>
<td>Periodontitis is associated with higher levels of CRP, IL-6, and neutrophils and these inflammatory factors potentially increase the risk for cardiac events.</td>
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</tr>
<tr>
<td>Wu et al.40 2000</td>
<td>10,146 subjects enrolled in the Third National Health and Nutrition Examination Survey and its follow-up study.</td>
<td>Significant associations between indicators of poor periodontal health status (gingival bleeding index, calculus index, periodontal pocket depth, attachment loss) and increased CRP and fibrinogen. Weak or no association between periodontal status and total cholesterol or HDL.</td>
<td>CRP and fibrinogen are possible intermediate factors that may link periodontal disease to elevated cardiovascular risk.</td>
<td>4</td>
</tr>
<tr>
<td>Noack et al.41 2001</td>
<td>Cross-sectional cohort study of 174 subjects randomly selected from a larger cohort of 1,250 subjects. 59 subjects had moderate periodontal attachment loss, 50 had severe attachment loss and 65 periodontally healthy subjects served as controls.</td>
<td>Statistically significant increase in CRP in subjects with periodontitis when compared to healthy controls (P = 0.036).</td>
<td>Positive correlation between CRP and periodontal status may be a pathway in the association periodontal disease and CVD.</td>
<td>4</td>
</tr>
</tbody>
</table>


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APPENDIX A

CONSENSUS REPORT

Introduction

Both periodontal and cardiovascular diseases are relatively common, chronic, multifactorial conditions. The concordant linkages or associations between these coincident conditions may reflect chance occurrence, the sharing of a common antecedent susceptibility or resistance traits, common behaviors or exposures, or the influence of one condition on the other. Furthermore, both conditions have heterogeneous clinical presentations and etiological and modifying components may or may not be uniformly expressed clinically, based upon the genetic background of the individual. The initial observation that the prevalence of cardiovascular disease among chronic periodontitis patients was higher than the general population was reported over a decade ago suggesting that these two conditions tend to cluster or self-aggregate within the population. Upon first consideration, it would appear that these linkages of both periodontal disease and car-
diovascular disease within subjects might easily be explained by the presence of common behaviors or traits that increase the risk for both conditions, such as smoking or obesity. Thus, the challenge of any study design and analytical experimental approach aimed at quantifying the relative contribution of periodontal disease to cardiovascular disease is that the study needs to include a wide range of additional risk factors or markers that enable one to dissect out and quantify that portion of the risk that is specifically attributable to periodontal disease. That is, the effects of periodontal disease need to be considered in the presence of full measurements of other confounding or effect-modifying variables, being as inclusive as possible. For this reason, studies must usually be fairly large and epidemiologic in nature, usually requiring at least 10 cases in each subcell to adequately adjust or “statistically correct for” each possible risk factor that needs to be considered as a possible modifier of either periodontal disease or cardiovascular disease. As a consequence the initial analyses showed associations, which could not be easily explained away by common risk factors, that were based upon large heart studies or general health studies that also had periodontal data.

It is important to note that in the consideration of the available data the Section members and the reviewers were ever cognizant of the central importance of examining for and evaluating the quality of the data with regards to these critical issues of assessing the potential contribution of confounders and covariates. It is in this context that the evidence for an association between periodontal disease and systemic conditions, such as cardiovascular disease, pneumonia, and adverse pregnancy outcomes has been uniformly and systematically considered. Furthermore, it has now been acknowledged that the manner in which periodontal disease is defined as a systemic exposure; e.g., as a condition that may contribute risk for CVD, may differ from traditional classifications of periodontal disease. These traditional classifications use signs and symptoms (such as bleeding scores) as an index of exposure to quantify the risk for a tooth-related outcome, for example an increase in probing depth or bone loss and not a systemic disease outcome. As yet another example, bleeding sites and probing depths may be a better reflection of systemic exposure than attachment and bone loss, depending on the outcome of interest. Thus, the definition of periodontal disease which serves to define a periodontal case as a systematic exposure is a simplified, clinical measurement representation of the triad of periodontal disease components: periodontal infection, inflammation, and clinical signs. For this reason, the diversity in the definitions of periodontal case status that has been used to define periodontal exposure among different studies is not a failure to recognize or apply traditional, uniform definitions, but rather is a data-driven reassessment of the changing definitions or clustering of clinical signs that best describe the relationships.

Despite these conceptual limitations that require a paradigm shift in considering periodontal disease as a possible etiologic contributor to cardiovascular disease, the body of evidence continues to accrue supporting a modest association even after thoughtful and complete statistical methodological correction or adjustment for other risk factors, such as smoking. However, residual confounding may still be present in that these methods have not adequately captured the appropriate measure of periodontal disease as an exposure that increases the risk of a given systemic disease or condition. But this is always a characteristic of epidemiologic, observational, and case-control study designs. It is important to note that overcorrection for confounders can easily occur in these analytical approaches, as well. For example, the effects of cholesterol on the risk for heart disease in large data sets can be easily missed or nullified if non-relevant or non-exclusive variables are included in the adjustments. These methodological issues, while seemingly tangential to the current Consensus Report, highlight the central issues that were considered as pros and cons for the oral and systemic disease linkages. This Section carefully deliberated the quality and quantity of the data on which we are seeking to reach consensus, as to whether these reported associations between periodontal disease and systemic conditions such as CVD, pneumonia, and adverse pregnancy outcomes occur by chance as a result of common underlying risk traits, behaviors, or exposures, or whether these associations survive as true linkages independent of these potential confounders and whether the increased risk is indeed attributable to periodontal disease.

Members of the Section read and studied the review titled “Associations Between Periodontal Disease and Risk for Atherosclerosis, Cardiovascular Disease, and Stroke. A Systematic Review,” by Frank A. Scannapieco, Renee Bush, and Susanna Paju. The focused PICO question addressed by this evidence-based systematic review is: “Does periodontal disease influence the initiation/progression of atherosclerosis and therefore cardiovascular disease, stroke, and peripheral vascular disease?”

1. Does the Section agree that the evidence-based systematic review is complete and accurate?
Yes. Members of the Section unanimously agreed that the systematic review was complete and accurate as of April 2002.
2. Has any new information been generated or discovered since the evidence-based search cut-off date?

Yes, members of the Section identified several publications that directly or indirectly dealt with the topic of the current systematic review.3-13

Authors of this review made the decision not to perform a meta-analysis on the existing studies due to the small number of publications that specifically addressed the focused PICO question. In addition, existing studies have disparate study design characteristics and use measures of exposure and outcomes that would have limited the applicability and generalizability of the meta-analysis. However, other authors using other a priori study inclusion criteria and who addressed other questions have analyzed and published 2 meta-analyses exploring the relationship between periodontal disease parameters and cardiovascular diseases.3,4

One of these meta-analyses by Janket et al.2 included 9 cohort studies and concluded that periodontal disease is positively associated with an increased risk of future cardiovascular diseases. In an analysis stratified to individuals of ≤65 years of age the relative risk (RR) was 1.44 (95% CI, 1.20 to 1.73). When outcome was restricted to stroke only, the RR was 2.85 (95% CI, 1.78 to 4.56).

There is additional evidence from large epidemiologic studies that periodontal disease is associated with serum inflammatory markers that are considered significant surrogate markers of cardiovascular risk. Slade et al. have reported that extensive periodontal disease and body mass index (BMI) are jointly associated with increased C-reactive protein (CRP) levels.5 In this cross-sectional study of 5,562 subjects, periodontal disease (defined as ≥30% of sites with probing depths ≥4 mm) was associated with increased serum CRP concentration when adjusted for age, sex, diabetes, cigarette smoking, and use of NSAIDs. Matilla et al. in a pilot study of 35 subjects demonstrated that periodontal therapy reduced serum CRP levels.6

Malthaner et al. reported no significant differences between periodontal disease parameters and coronary artery disease (CAD) as assessed by angiogram.7 Beck and Offenbacher have raised questions regarding whether current clinical measures of periodontal disease are sufficient to reflect the infectious and inflammatory burden that periodontal disease poses as an exposure for CVD risk.2 In light of the increasing evidence that periodontal infections can have systemic effects, these authors suggest that the definitions of periodontal disease as a systemic exposure be reconsidered to reflect extent and severity, temporality, and systemic dissemination of the oral infectious and inflammatory burden.2 For example, Craig et al. demonstrated that antibodies to Porphyromonas gingivalis were positively associated with serum CRP levels (>2.08 mg/L) (OR = 5.6).8 In addition, multiple sites with periodontal disease progression were associated with an increased risk for high CRP with an OR of 14.1.

Buhlin et al. reported a significant association between self-reported bleeding gums, the presence of dentures and cardiovascular disease.9 Hung et al. in a prospective 12-year study on 45,136 males demonstrated that periodontal disease contributed to the risk of peripheral vascular disease with a RR of 1.41 (95% CI, 1.12 to 1.77) and for any tooth loss during the follow-up period the RR was 1.39 (95% CI, 1.07 to 1.82) controlling for traditional risk factors for peripheral artery disease.10 López et al. in a case-control study of 86 adults demonstrated a positive association between mean clinical attachment level (OR = 3.17; 95% CI, 1.31 to 7.65), mean probing depth (OR = 8.64; 95% CI, 1.22 to 61.2) and the diagnosis of coronary heart disease (CHD).11 Joshipura et al. found an association between self-reported periodontal disease and stroke in a study of 41,380 subjects followed for 12 years.12 They reported an adjusted hazards ratio (HR) of 1.57 (95% CI, 1.24 to 1.98) relating tooth loss and higher rate of ischemic stroke, and an association was also seen between baseline periodontal disease history and ischemic stroke (HR = 1.33; 95% CI, 1.03 to 1.70).

In addition to the relationship between periodontal disease and atherosclerotic changes and ischemic events, new findings indicate a potential relationship with cardiac myopathy. Angeli et al. in a study of 104 patients with essential hypertension showed an association between severity of periodontitis and left ventricular mass.13

3. Does the Section agree with the interpretations and conclusions of the reviewers?

Yes, the data for an association between periodontal disease and atherosclerosis-induced disease are largely due to case-control and epidemiologic studies, with few prospective studies and are often limited to secondary analyses of existing data sets. Measures of periodontal disease vary considerably across studies, often relying on variable and rather inexact or indirect assessments to define case status, such as self-reported disease or missing teeth as indices of periodontal disease as an exposure. Clearly the results, although moderate in nature, often show a positive association and those studies with more complete periodontal data appear to demonstrate stronger associations. Caution in the interpretation of these associations appears warranted, as confounding factors such as smoking may obfuscate these relationships. However, the high prevalence of periodontal disease in the population may make these
modest associations potentially important in a public health context. To date it is unclear as to whether periodontal disease as an exposure can contribute to the initiation of vascular atheromatous plaques, atheroma maturation, or the subsequent rupture that precipitates cardiovascular disease events. Pilot studies suggest that periodontal therapy may have the potential to reduce levels of surrogate serum markers of cardiovascular disease, such as CRP. However, large-scale intervention trials examining the effects of periodontal therapy on surrogate markers, or atheroma formation, or ultimately the direct demonstration of reduction in cardiovascular events have not been conducted. This represents a critical deficit in our current knowledge base and needs to be addressed in order to establish the medical necessity for periodontal care.

4. What further research needs to be done relative to the focused questions of the evidence-based review?

Scientifically, in order to elucidate whether the relationship between cardiovascular and periodontal disease is causal in nature we need data from controlled interventional trials rather than observational studies. For example, one observational study comparing CVD rates of edentulous to dentate subjects concluded that reduction in periodontal inflammation by tooth extraction (presumed due to periodontal disease) will not prevent CVD. Such approaches are unable to determine the extent to which periodontal disease contributes to tooth loss as compared to other causes.

We recommend that large-scale multi-center placebo-controlled RCTs be conducted to determine whether the treatment of periodontal infection reduces the risk of cardiovascular events with mortality as the primary outcome. One multi-centered pilot study is currently underway to examine the effects of intervention on event rate. Intervention studies could include a number of periodontal treatment modalities to control infection and inflammation.

Additional studies are recommended to determine whether the prevention, presence, progression or treatment of periodontal infection and inflammation reduces the biological markers of cardiovascular disease risk, atheroma initiation, progression, and incidence of CVD events. These studies would not only permit assessments of effects of periodontal treatment on the primary outcomes, but also would provide insights into the mechanisms in the causal pathways.

Because of the high prevalence of periodontal disease and strength and consistency of the association, it may serve as a confounder in other studies of CVD risk and response to therapy. Therefore, we strongly recommend that periodontal assessments should be a component of cardiovascular studies. It is recommended that efficient, inexpensive, and validated tools be developed to assess periodontal disease as a systemic exposure for such large-scale trials.

5. How can the information from the evidence-based review be applied to patient management?

We concur with the current systematic review. It is consistent with the 2 recent meta-analyses that found a statistically significant association between CVD and periodontal disease. Furthermore, the association of periodontal disease with ischemic stroke appears to be stronger than periodontal disease and coronary heart disease.

Pilot studies suggest periodontal treatment can reduce risk factors for coronary heart disease, such as serum CRP. However, RCTs are needed before any definitive recommendations can be made regarding the treatment of periodontal diseases to modulate heart disease.

A. There is evidence to suggest that periodontal disease is associated with cardiovascular disease, however causality is unclear.

Level of Evidence: Moderate.

Rationale: Even though there are no level I RCTs, the level of evidence was rated as "moderate" because there are 24 level II studies (with some inconsistencies) that demonstrate moderate associations between CVD and periodontal disease. The conclusions of 2 recently published meta-analyses are consistent with the current systematic review and this conclusion.

B. There is currently insufficient evidence to show that treatment of periodontal disease reduces the risk of heart disease.

Level of Evidence: Insufficient.

Rationale: There are no level I RCTs or other studies to show that treatment of periodontal infections lowers the risk of developing adverse cardiovascular (e.g., myocardial infarction) or cerebrovascular (e.g., stroke) events.

Concluding Remarks

In the opinion of members of this Section, patients and health care providers should be informed that periodontal intervention may prevent the onset or progression of atherosclerosis-induced diseases. This opinion is based on 1) the strength and consistency of the association between periodontal disease and CVD; 2) the overall benefits of oral health; and 3) the negligible risk associated with periodontal therapy.

REFERENCES


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