期颐与动脉粥样硬化相关的疾病

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第1页

系统性回顾

期颐与动脉粥样硬化相关的疾病

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目的。本文回顾了评估期颐与慢性炎症性期颐疾病的关联，以及动脉粥样硬化诱导疾病、心血管疾病及其并发症的可用研究，使用基于证据的标准。

方法。这项研究基于2001年1月至2006年4月Medline数据库的文献综述，包括特定时期的文献综述，系统性综述，综述性文献和元分析，研究了期颐与心血管疾病的临床资料的关联。

结果。在临床方面，期颐与心血管疾病的关联是基于2个随机对照试验，5个系统性综述，5个综述性文献和2个元分析。期颐与心血管疾病的关联是有限的。

结论。支持期颐与心血管疾病的关联的现有证据是有限的。期颐与心血管疾病的关联是否重要尚不明确。

[Int Angiol 2007;26:197-205]

关键词：动脉粥样硬化 - 心血管疾病 - 期颐与心血管疾病的关联

心血管疾病，动脉粥样硬化诱导疾病及其并发症，如中风，短暂性脑缺血发作，冠状动脉和周围血管疾病，是较常见的及严重的在发达国家。

它，不令人惊讶的是，心血管疾病和动脉粥样硬化是期颐死亡的主要原因。1

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ease and atherosclerosis, as the independence of these associations from confounding factors has not been consistently established. Thus, it is possible that these associations may be partly or completely explained by risk factors common to oral and cardiovascular disease.

Indeed, the multi-factorial causation of periodontal and cardiovascular diseases, coupled with the large number of risk factors and risk indicators that may impact the severity and extent of disease, makes the determination of periodontal-cardiovascular disease association extremely difficult. Moreover, there has been concern expressed about the conflicting and inconsistent results among the studies reported, and there has been a great deal of discussion concerning the reasons for these differences. The literature to date suggests that further studies are needed to corroborate the associations between periodontitis and cardiovascular disease and much more work is needed to rule out the confounders.

This article reviews the available studies linking periodontitis with cardiovascular diseases, atherosclerosis related diseases and their complications, using standard evidence-based criteria. The aim of this article is to identify all literature pertinent to this issue, to critically evaluate it and understand the current state of knowledge on this subject.

Objective

We attempted to answer the following focused question: does periodontal disease influence the initiation/progression of atherosclerosis and, therefore, cardiovascular disease, stroke and peripheral vascular disease?

Materials and methods

Search protocol

This study is based on a literature search using Medline medical database, covering the period from 2001 to April 2006 and applying specific inclusion criteria. The search strategy was defined to include randomized controlled trials, systematic reviews, narrative reviews and meta-analyses, which investigated the relationship of periodontal and cardiovascular diseases with clinically derived documentation.

Key words

Arteriosclerosis or atherosclerosis, cardiovascular diseases, cerebrovascular disorders, or heart diseases, or carotid artery diseases or peripheral vascular diseases. Oral conditions: periodontal disease or periodontitis.

Inclusion criteria

The reports included in this review were those that recruited participants with atherosclerosis and periodontal diseases. Our search strategy considered studies that investigated whether individuals with periodontal disease as compared to individuals without periodontitis, had increased risk of atherosclerosis and cardiovascular diseases. The critical evaluation of the studies was performed based on the Impact Factor of the journal, on which they were published.

Exclusion criteria

The search was limited only to articles that studied the focused question from the clinical point of view. Animal, laboratory studies, serological and cell culture studies that examined the periodontal and cardiovascular disease association focusing on etiopathogenetic or biological mechanisms, on various inflammatory and immunological mediators and on detection of bacterial pathogens in atherosclerotic plaques, were not included.

In spite of the fact that very specific and narrow inclusion criteria might be accompanied by the risk of being so exclusive that relevant data is excluded, they allow greater homogeneity and produce a review relevant to clinical aspects. It is beyond out of doubt that studies, which examine the biological mechanisms of interaction between periodontal and cardiovascular diseases, explain the possible relationship and provide the biological mechanisms underlying the association. However, if the inclusion criteria were so broadened, there would be greater heterogeneity between studies, making comparison of results difficult.

Results

Types of studies reviewed

Following the described search strategy, Medline searching revealed 126 articles. The critical evaluation of the 126 studies, which was based on
### Table I.—The journals and their impact factors.

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Journal</th>
<th>Impact Factor</th>
<th>Total cites</th>
<th>Immediacy index</th>
<th>Articles</th>
<th>Cited half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Howell et al.⁵</td>
<td>J Am Coll Cardiol</td>
<td>9.2</td>
<td>43 957</td>
<td>2.134</td>
<td>561</td>
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<tr>
<td>2003</td>
<td>Ide et al.⁶</td>
<td>J Clin Periodontol</td>
<td>2.225</td>
<td>6 181</td>
<td>0.348</td>
<td>210</td>
<td>8.5</td>
</tr>
<tr>
<td>2001</td>
<td>Beck et al.⁷</td>
<td>Ann Periodontol</td>
<td>2.577</td>
<td>1 201</td>
<td>1.885</td>
<td>26</td>
<td>5.8</td>
</tr>
<tr>
<td>2002</td>
<td>Kolliveti et al.⁸</td>
<td>Eur J Oral Sci</td>
<td>1.784</td>
<td>1 381</td>
<td>0.205</td>
<td>78</td>
<td>5.4</td>
</tr>
<tr>
<td>2002</td>
<td>Joshipura⁹</td>
<td>J Am Dent Assoc</td>
<td>0.935</td>
<td>3 550</td>
<td>0.299</td>
<td>134</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2002</td>
<td>Madianos et al.¹⁰</td>
<td>J Clin Periodontol</td>
<td>2.225</td>
<td>6 181</td>
<td>0.348</td>
<td>210</td>
<td>8.5</td>
</tr>
<tr>
<td>2003</td>
<td>Scannapieco et al.¹¹</td>
<td>Ann Periodontol</td>
<td>2.377</td>
<td>1 201</td>
<td>1.885</td>
<td>26</td>
<td>5.8</td>
</tr>
<tr>
<td>2001</td>
<td>Garcia et al.³</td>
<td>Periodontol 2000</td>
<td>2.377</td>
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<td>1.885</td>
<td>26</td>
<td>5.8</td>
</tr>
<tr>
<td>2002</td>
<td>Genco et al.¹²</td>
<td>J Am Dent Assoc</td>
<td>0.935</td>
<td>3 550</td>
<td>0.299</td>
<td>134</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2002</td>
<td>Hujoel ¹³</td>
<td>J Am Dent Assoc</td>
<td>0.935</td>
<td>3 550</td>
<td>0.299</td>
<td>134</td>
<td>&gt;10</td>
</tr>
<tr>
<td>2003</td>
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<td>Periodontol 2000</td>
<td>2.377</td>
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<td>1.885</td>
<td>26</td>
<td>5.8</td>
</tr>
<tr>
<td>2003</td>
<td>Seymour et al.¹⁵</td>
<td>J Clin Periodontol</td>
<td>2.225</td>
<td>6 181</td>
<td>0.348</td>
<td>210</td>
<td>8.5</td>
</tr>
<tr>
<td>2004</td>
<td>Meurman et al.¹⁶</td>
<td>Crit Rev Oral Biol Med</td>
<td>3.933</td>
<td>1 440</td>
<td>0.348</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>Oral Radiol Endod</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Khader et al.¹⁸</td>
<td>J Periodontol</td>
<td>1.784</td>
<td>8 401</td>
<td>0.104</td>
<td>299</td>
<td>9.3</td>
</tr>
</tbody>
</table>

### Table II.—The 15 included studies, their study type and their concluding remarks.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type</th>
<th>Sample size/types of studies reviewed</th>
<th>Association/concluding remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howell et al.⁵</td>
<td>RCT</td>
<td>22 071 subjects</td>
<td>Weak</td>
</tr>
<tr>
<td>Ide et al.⁶</td>
<td>RCT</td>
<td>9 subjects/levels of vascular markers</td>
<td>No significant changes</td>
</tr>
<tr>
<td>Beck et al.⁷</td>
<td>Systematic review</td>
<td>Longitudinal studies</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Kolliveti et al.⁸</td>
<td>Systematic review</td>
<td>Ecological studies</td>
<td>Causal relationship</td>
</tr>
<tr>
<td>Joshipura⁹</td>
<td>Systematic review</td>
<td>Epidemiologic studies</td>
<td>Weak</td>
</tr>
<tr>
<td>Madianos et al.¹⁰</td>
<td>Systematic review</td>
<td>Cross-sectional, case-control, cohort studies and clinical trials</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Scannapieco et al.¹¹</td>
<td>Systematic review</td>
<td>Longitudinal, case-control and cohort studies</td>
<td>Modest association</td>
</tr>
<tr>
<td>Garcia et al.³</td>
<td>Narrative</td>
<td>Longitudinal studies</td>
<td>Weak</td>
</tr>
<tr>
<td>Genco et al.¹²</td>
<td>Narrative</td>
<td>Longitudinal, case-control, cross-sectional, clinical, animal and laboratory studies</td>
<td>Moderate association</td>
</tr>
<tr>
<td>Hujoel ¹³</td>
<td>Narrative</td>
<td>9 cohort studies</td>
<td>Weak</td>
</tr>
<tr>
<td>Hujoel et al.¹⁴</td>
<td>Narrative</td>
<td>Case-control, cross-sectional, prospective, cohort studies</td>
<td>Weak</td>
</tr>
<tr>
<td>Seymour et al.¹⁵</td>
<td>Narrative</td>
<td>Descriptive, cross-sectional, case-control, longitudinal studies</td>
<td>Modest association</td>
</tr>
<tr>
<td>Meurman et al.¹⁶</td>
<td>Narrative</td>
<td>9 cohort studies</td>
<td>Modest association</td>
</tr>
<tr>
<td>Janket et al.¹⁷</td>
<td>Meta-analysis</td>
<td>7 cohort studies and 4 studies of other design</td>
<td>Modest association</td>
</tr>
<tr>
<td>Khader et al.¹⁸</td>
<td>Meta-analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Randomized controlled trials

Howell et al. examined whether self-reported periodontal disease is associated with subsequent risk of cardiovascular disease, using prospective data from Physicians’ Health Study I, a randomized, double-blind placebo-controlled trial of aspirin and β-carotene in the prevention of cancer and cardiovascular disease among 22,071 US 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 response option being periodontal disease. Follow-up questionnaires asked: ‘Since you filled out the last questionnaire (about 12 months ago), have you been newly diagnosed as having any of the following conditions?’ with one response option being periodontal disease. The study outcomes were diagnoses of non-fatal myocardial infarction, nonfatal stroke and death due to cardiovascular disease. The results included data up to 1995, which resulted in an average follow-up time of 12.3 years. In analyses adjusting only for age and treatment assignment, men who reported periodontal disease at baseline, compared to those who did not, had slightly elevated, but statistically nonsignificant, increased risk of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death (relative risk [RR]: 1.13; 95% confidence interval [CI]: 0.99-1.28). After further adjustments for possible cardiovascular risk factors, such as cigarette smoking, alcohol use, body mass, physical activity, history of angina and parental history of myocardial infarction, all RRs were attenuated near the null value of 1 (95% CI: 0.88-1.15), which represents no association at all.

Howell et al. concluded that self-reported periodontal disease is not an independent predictor of subsequent cardiovascular disease in middle-aged men. However, the authors have admitted that several limitations of the study need to be considered. As the diagnosis of periodontal diseases relied on participant reports, and not on oral examinations of study participants, some reports of periodontal disease may have been error, and some true cases of periodontal disease may have been missed. Besides that, periodontitis is a disease of insidious onset as affected individuals may not be aware of any symptoms in the earlier stages of disease development. As a result, the chronic infection of periodontitis may progress symptom-free for many years prior to initial diagnosis or clinical manifestation. Finally, using certain population such as health professionals results in a homogenous group of people and inherently controls for socioeconomic status and healthy behavior, factors that otherwise are difficult to measure, but restricts the results, as such sample cannot represent the general population.

Ide et al. carried out a small randomized controlled trial, in which the circulating levels of cardiovascular and systemic inflammatory markers were compared among individuals, who were randomized to either immediate (test: n=24) or delayed treatment (control: n=15). Venous blood was taken before and 6 weeks after completion of treatment for both groups and was analyzed to determine serum and plasma fibrinogen, C-reactive protein, sialic acid, tumor necrosis factor-α (TNF) and interleukin-6, -1b. Periodontal examination included probing depth, loss of attachment, plaque scores and bleeding scores. The authors observed that the impact of periodontal treatment on the levels of the systemic markers was not significant. However, within the limitations of this study, there are several points to consider when interpreting the results. Although the researchers excluded current smokers and as far as possible subjects with any other inflammatory condition and thus confined the confounding factors, they did not assess the effects of obesity, hypertension, education or cholesterol, confounders that may have influenced the results. Besides the size of the sample, which might have been too small to reveal significant changes in the levels of any of the systemic markers, there was also a very short follow-up period.

Systematic reviews

Beck et al. reviewed 8 longitudinal studies on the periodontal disease-cardiovascular disease association. Since no randomized controlled trials have been conducted, longitudinal studies represent the highest level of evidence available. Beck et al. concentrated on 3 studies published during 2000-2001 and discussed a number of limitations that would also apply to other papers. The authors submitted that the majority of the longitudinal studies on periodontal disease and car-
diovascular diseases, reported to 2001, have been secondary analyses of available data that were not designed to test the hypothesized association. Longitudinal studies were not initially designed to actually test the association of interest, but almost all were restricted to clinical measures of periodontitis to index the exposure and lacked measures of infectious burden and host response. While most studies were retrospective in design, all of them, except the Mattila et al.'s study, were designed with periodontal disease being the clinical outcome of interest, not as an exposure. Furthermore, the longitudinal studies used a variety of cardiovascular clinical events to index the outcome and did not include subclinical measures of atherosclerosis. An additional limitation underlying the study was the inability to monitor changes in disease status. Having a baseline measure of the exposure may bias the periodontal-cardiovascular disease association, possibly toward no association.

The authors concluded that there was not enough evidence to state that periodontal infection is a cause of cardiovascular disease. As the majority of studies on periodontal and cardiovascular disease might no longer be viewed as 'state-of-the-science', further research is needed. Only if research enters the next phase of investigation by conducting molecular epidemiology studies that are appropriately designed, will we understand the molecular and cellular mechanisms involved.

Kolltveit et al. systematic review was based on a literature search covering the period from 1989 to October 2000. Based on predefined inclusion criteria, including consideration of possible confounders in multivariate analyses, properly selected controls for case-control studies, and sufficient sample size for cross-sectional studies, the authors selected a number of studies to conclude that a causal relationship between periodontitis and atherosclerosis-related diseases appeared possible. Kolltveit et al. supported their findings by using data published by World Health Organization (WHO), which demonstrated in a figure, a comparison between prevalence of severe periodontal disease in 35-44 years old and non-standardized total mortality rates of myocardial infarction and ischemic heart disease in several European countries. An interesting conformity of the two distribution curves could be observed and the authors concluded that the documented correlation may indicate a causal relationship between periodontitis and atherosclerosis-related diseases. Müller analyzed critically the Kolltveit et al. systematic review, and illustrated one of the most important confounding factors in the analysis of the periodontitis and atherosclerosis related disorders association, which is smoking. In addition to Kolltveit et al. findings, Müller also used data published by WHO to generate another graph. It was striking that prevalence of severe periodontal disease in different European countries was significantly correlated not only with total mortality rates of myocardial infarction and ischemic heart disease, but also with prevalence of smoking among male adults ($r=0.55$, $P<0.01$). In most studies, smoking status is only crudely defined as current, former or never, without taking into account smoking intensity, the number of cigarettes smoking per day, age at start of smoking and age at cessation of smoking. It is likely that studies will yield a positive association between periodontitis and cardiovascular disease, if smoking is not adequately adjusted for.

The article of Joshipura is a critical review of the epidemiologic studies linking or disassociating oral conditions with stroke and peripheral vascular disease. After the critical evaluation of the published literature, the author concluded that there may be a causal relationship which may be explained by common risk factors or by potential causal pathways.

Madianos et al. examined the relation of periodontal disease and increased risk for coronary heart disease and preterm and/or low birth weight deliveries. As long as the related evidence linking periodontitis with preterm and/or low birth weight deliveries is beyond the scope of this paper, only the evidence suggesting association between periodontal disease and coronary heart disease will be included in the present study. Based on a good search strategy, hand searching in 4 journals, using eligibility criteria for study inclusion, quality assessment and quantitative measures of exposure and outcomes, the authors investigated the periodontitis-coronary heart disease association in 21 studies. Since no clinical trials were found, the evaluation was based on observational studies. The authors concluded that the evidence linking periodontitis with an increased risk for coro-
nary heart disease is limited and suggested that the reasons for the conflicting reports had to be sought in the extensive heterogeneity of the included studies. One of the major findings of this review was the lack of proper assessment of exposure in the majority of the studies. Study quality assessment revealed that only 6 studies employed what authors considered to be adequate measures of periodontal disease (based on full mouth probing or radiographic assessment). The rest of the studies used a wide range of measures varying from partial mouth probing assessment to non-probing assessment and questionnaires. Another source of potential misclassification in cohort studies with long follow-up time was the lack of repeated measurement of periodontal status, as it may change towards either direction over time.

Scannapieco et al. reviewed existing data on the association between chronic inflammatory periodontal disease and the risk for atherosclerosis, cardiovascular disease and stroke and its clinical manifestations. It should be emphasized that there were no data from randomized controlled interventional studies. The majority of the included studies supported a modest association of periodontitis with cardiovascular diseases. However, after controlling for cardiovascular risk factors, there was insufficient evidence available to justify periodontal intervention to prevent the onset or progression of atherosclerosis-induced diseases. This review concluded that periodontal disease might be moderately associated with atherosclerosis-induced diseases, such as coronary artery disease, stroke and peripheral vascular disease. Finally the authors suggested that the association observed between atherosclerosis-induced disease and periodontal disease is due to etiological factors common to both diseases, such as lifestyle practices and cigarette smoking.

**Narrative reviews**

Garcia et al. carried out a detailed analysis of the relationship between periodontal disease and systematic health. They concluded that unless clinical intervention studies demonstrated a beneficial effect of periodontal treatment on cardiovascular risk reduction, the nature of the association would remain undefined and no causal relationship would be established. The exact nature of periodontitis-cardiovascular disease association will be determined, if it is shown that periodontal treatment and prevention leads to decreased risk of cardiovascular disease. It has become clear in Garcia et al. study that although the weight of current evidence does not support the existence of a causal relationship, further research is necessary to determine whether there are beneficial effects of periodontal treatment on this important medical condition.

Genco et al. summarized the longitudinal, case-control and cross-sectional studies and findings from clinical, animal and basic laboratory studies, regarding the possible connection between periodontal disease and heart disease. They concluded that the accumulation of epidemiologic in vitro clinical and animal evidence suggested a moderately association, but not a causal relationship, between periodontal infection and heart disease. The authors attempted to interpret the inconsistent study findings and noted that the basic reasons why some studies had found positive associations whereas others had not were differences in the way studies had been conducted, differences in ages of the participating subjects, smoking status not adequately adjusted for, lack of control of confounding factors, residual confounding, overcontrol of confounders, the outcome measure being studied, the way the outcomes and the exposures were measured.

Genco et al. pointed out that the measures used to assess periodontal disease did appear to be related to the strength and significance of the reported associations. It had been estimated that studies, which assessed the periodontal status by clinical probing measures or bone loss, found significant associations, whereas studies, which used self-reported periodontal disease, had negative findings. In one study that did not specify the measure used, probably nonprobing, it was found a significant association. With regard to further research, Genco et al. suggest that it should be investigated whether a possible clinically meaningful reduction in heart disease will be achieved by the prevention or treatment of periodontal disease.

Hujoel concluded that current evidence supporting a causal association between chronic periodontitis and coronary heart disease had been weak. Summarizing data from 9 cohort studies,
the author noted that conclusions from individual studies depended on study characteristics. According to author's opinion, one plausible explanation for the studies reporting significant periodontitis and coronary heart disease associations might be lack of control for smoking history. Furthermore, he came into conclusion that chronic periodontitis was not at all or was weakly associated with coronary heart disease when summary risk was estimated in studies controlling for health awareness (2 of 9 studies) or in studies with a sufficient number of events (3 of 9). In case of positive results from small studies, author implied that they had a high chance of being false-positive results, and explained that this is due to the lack of power, publication bias and 'investigator's enthusiasm.' Lastly, Hujioel implied that even if convincing evidence regarding the periodontitis coronary heart disease link would come to light in future, it would not necessarily mean that periodontal treatment should be recommended to lower coronary heart disease risk.

Hujioel et al. suggested that the observed periodontitis-systemic disease associations are, in part, a result of confounding by smoking. Smoking is referred to as confounder, as it is impossible to distinguish the effect of smoking on periodontitis from the effect of smoking on systematic diseases. Smoking spuriously inflates the association between periodontitis and smoking related diseases, because it is causally related to both, regardless of whether periodontitis and the systematic disease are causally related to each other. Therefore, the comparison between individuals with and without periodontitis with respect to the occurrence of systematic disease is said to be biased because of the unequal distribution of smoking in two groups. It is important to note that statistical adjustments could be used to eliminate some, but not all, the bias caused by the higher prevalence of smokers among individuals with periodontitis. The bias caused by smoking explains why in studies that provided a good adjustment for smoking dose, periodontitis was not significantly associated with coronary heart disease compared to studies that either did not adjust for smoking or adjusted crudely, which found that periodontitis was significantly associated with coronary heart disease. The authors indicate that the dental infections occur coincidentally with, but are not causal for, increased cardiovascular risk and recommend that a systematic evaluation of the periodontitis-systemic disease associations should be conducted among healthy never smokers.

Seymour et al. investigated the possible association between periodontal disease and coronary artery disease by reviewing the results of related studies. Apart from describing the studies published till 2003, the authors highlighted the potential biases that might have contributed to the variability in the results. Thus, the major problems involved the differences and the way in which dental data had been recording, the accuracy and reliability of the available clinical data and the way in which covariables were managed. Taking into account these conditions, they assume that any impact of periodontitis on coronary health is less than suggested by earlier studies and whether periodontal disease is a significant risk factor for coronary artery disease is needed to be substantiated by intervention studies.

In the Meurman et al.'s review, the accumulated, till 2004, data were critically evaluated and summarized. Strength of scientific evidence was thoroughly examined according to the 5 Bradford criteria for causality: temporal relationship, dose response, strength for association, consistency and biological plausibility. It is well recognized that the application of these criteria, while suitable to guide one's thinking, will not provide a definitive answer. Conclusions reached by descriptive and cross-sectional studies were questioned and a causal inference could not be made because of the study design. While analyzing the results from longitudinal studies, the authors observed that although two groups of investigators had analyzed the same National Health And Nutrition Examination Survey (NHANES) data, they reported contradictory results. They assumed that the disparity was originated from the degree of adjustment carried out with covariates, and reported that the adjustment of confounding was excessive in the study by Hujioel et al. The authors completed their review by utilizing the results of a meta-analysis, conducted by the same group of investigators. The authors did claim that despite of the small statistical effect size, periodontal disease may contribute to the pathogenesis of cardiovascular disease.
Meta-analysis

A recent published meta-analysis of the association between periodontal disease and risk of cardiovascular disease/stroke included 9 reports of cohort studies. The majority of these reports were prospective in design, meaning that the assessment of periodontal disease was made prior to the occurrence of the event of interest. The summary RR found in the meta-analysis was 1.19 (95% CI: 1.08 to 1.32), indicating a small but significant association between periodontal disease and cardiovascular disease/stroke. When the authors restricted the outcomes to stroke only, the RR was 2.85 (95% CI: 1.78 to 4.56). They concluded that periodontal disease was associated with a 19% increase in risk of future cardiovascular disease. They further imply that as 40% of population has periodontal disease, the modest increase of risk between subjects with or without periodontal disease may have a profound public health impact.

However, it is noteworthy, that three of the reports actually represented different analyses of the same cohort (NHANES I Epidemiologic Follow-Up Study—NHEFS). Janket et al. demonstrated that the type of periodontal disease assessment explained some of the heterogeneity between studies. Hence, four studies used R Clausen's periodontal index, an index that relies on visual examination of the periodontium, rather than periodontal probing; two studies, conducted on physicians and other health professionals, used subjects' self-report to ascertain periodontal disease status; and one study was published as an abstract only. Only this latter study and another one actually used a quantitative measure of periodontal disease history for exposure assessment.

Khader et al. conducted a meta-analysis to examine the relationship between periodontal diseases and coronary heart and cerebrovascular diseases in 11 observational studies. Eight studies were included in the meta-analysis to analyze the relationship between periodontitis and coronary heart disease. After adjusting for possible confounders, the data showed that subjects with periodontitis had an overall risk of coronary heart disease of 1.15 times (95% CI 1.06 to 1.25; P=0.001). The relationship between periodontitis and the risk for cardiovascular disease was explored in 6 studies. As compared to healthy people, subjects with periodontitis had an overall adjusted RR of cardiovascular disease of 1.13 (95% CI 1.01 to 1.27; P=0.032). Though findings indicated that periodontal infections increased the risk for coronary heart and cerebrovascular disease, this group of investigators reported that the meta-analysis provided no evidence for the existence of strong associations between periodontitis and coronary heart and cerebrovascular disease.

Furthermore, the authors admitted that the results should be interpreted with caution, because it is a meta-analysis of observational studies. One should be conservative in interpreting data from meta-analyses, because such studies yield estimations of associations that may deviate from true underlying relationships beyond the play of chance. On the contrary this may be due to the effect of confounding factors, the influences of biases, or both. In addition, the possibility of publication bias cannot be excluded, in spite of the fact there was no heterogeneity among the studies.

Conclusions

The cumulative evidence presented above suggests that there is a significant, although modest, association between periodontal disease and atherosclerosis-related diseases. However, the reliability of the currently available evidence based on observational studies is questioned and consequently the systematic reviews, narrative reviews and meta-analyses utilized data from such studies are insufficient to accurately estimate the strength of the association. In addition, a number of legitimate concerns have arisen about the nature of the relationship, as the overall evidence regarding the periodontal-atherosclerosis relationship is not strong and the association may or may not be causal. It is important to point out that the reported associations should be interpreted with caution, as confounding factors, such as smoking may obfuscate these relationships.

The strongest evidence for the role of periodontal disease as a risk factor for atherosclerosis-related diseases is likely to come from well-controlled intervention studies. Although research into this relationship is still in its early stages, randomized controlled clinical trials that evaluate the effects of periodontal intervention in the prevention of atherosclerotic disease, as well as in the management of patients suffering the effects of atherosclerosis-
induced diseases, are necessary to prove or disprove this link. To date, it is unclear as to whether treatment of periodontal infection reduces the risk of developing heart diseases. Taking into account the strength and consistency of the association between periodontal and cardiovascular diseases, the overall benefits of oral health and the negligible risk relative to periodontal therapy, patients and health care providers should be informed that periodontal intervention may prevent the onset or progression of atherosclerosis-induced disease. The future of dental practice will be dramatically altered if subsequent research confirms that periodontal disease is a true risk factor for atherosclerosis-related diseases and that the initiation or progression of these medical conditions can be reduced by periodontal treatment.

References