



Oral and General Health - Exploring the Connection

Research Review December 2009

Associations between Periodontal Disease and Atherosclerotic Cardiovascular Diseases (CVD)

PROFESSIONAL VERSION

The research for this report was generously provided by Delta Dental Plans Association and performed by the University of Michigan by George W. Taylor, Wenche S. Borgnakke, Patricia F. Anderson and Carol Shannon. DDPA 2009

ORAL AND SYSTEMIC HEALTH CONNECTIONS

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I. Introduction

This report will focus on evidence for the association between periodontal disease and cardiovascular diseases (CVD). Evidence has emerged during the last twenty years regarding the association between periodontal disease and CVD. The number of publications on the subject in the form of literature reviews, meta-analyses, editorials, and opinions, as well as articles in the popular press and stories in news media, greatly outnumbers the actual number of original research reports. The goal of this report is to focus principally on evidence published since the mid-2000s, but will also feature some of the earliest studies in each of the areas.

Following this introduction, the remainder of the report is organized as follows: Section II presents a methodological overview of the report's preparation, first defining periodontitis and CVD, then briefly describing the general strategy for selecting articles for review and the framework used to consider the level of evidence in rating reports. These topics are briefly described in the report's main body of text and more thoroughly presented in the Appendix. Next, the report considers evidence linking periodontal disease and CVD from several perspectives: observational epidemiologic studies evaluating primary CVD endpoints assessed in meta-analyses or described in published reports of cohort, case control and cross-sectional studies (Section III); intervention studies and observational epidemiologic studies focusing on secondary CVD endpoints (Section IV); intervention studies (Section V) and laboratory-based studies (Section VI) elucidating mechanisms linking periodontal disease and CVD; health services research investigating the relationship between periodontal treatment and CVD medical care costs (Section VII); and organizational consensus statements and recommendations regarding the application of current evidence (Section VIII). In the Appendix, Tables 3A (intervention studies) and 3B (etiologic observational studies) provide a comprehensive overview of the body of evidence published since January 1st, 2007, displaying the full reference citation for each report, the study design, and position in the hierarchy of evidence.

II. Methods

II. A. Definitions

Periodontitis is a bacteria-induced, localized, chronic inflammatory disease that destroys connective tissue and bone supporting the teeth. According to a position paper by the American Academy of Periodontology on the epidemiology of periodontal diseases, citing 199 references, some 5% to 20% of any population suffers from severe, generalized periodontitis, although mild to moderate periodontitis affects a majority of adults¹. The World Health Organization estimates that advanced disease with periodontal pockets of at least 6mm affects 10% to 15% of adults in all regions of the world².

Cardiovascular disease (CVD) is the broad term used to categorize any abnormal condition characterized by dysfunction of the heart and blood vessels. Including the qualifying term *atherosclerotic* (Greek: athero = gruel (thin cereal) or paste and sclerosis = hardness) is meant to exclude conditions, such as congenital heart valve deformities, that are not due to arterial disease in which raised areas of degeneration and cholesterol deposits plaques form on the inner surfaces of the arteries obstructing blood flow. The acronym “CVD” used hereafter in this report refers to atherosclerotic CVD. *Peripheral arterial disease (PAD)*, also known as *peripheral vascular disease (PVD)* or *peripheral artery occlusive disease (PAOD)*, pertains to all diseases caused by the obstruction of large arteries in the arms and legs. *Coronary heart disease (CHD)* – also called *coronary artery disease (CAD)*, *coronary arteriosclerosis*, *coronary atherosclerosis*, or simply: *heart disease* -- is a subset of CVD that involves dysfunction of the arteries supplying blood to the muscle tissue of the heart, thereby depriving the heart of sufficient amounts of blood. CHD could involve blockage in the blood vessels (thrombosis) and can lead to acute myocardial infarction (heart attack) when sufficiently severe. CHD also includes unstable angina pectoris (angina). *Non-hemorrhagic stroke* is another potentially fatal type of CVD in which the atherosclerotic arterial changes cause decreased blood flow to the brain, and is often combined with thrombosis.

CVD is the leading cause of mortality in the United States³⁻⁵ and other industrialized countries and is among the major causes of death worldwide⁶. In the US, CVD accounts for 40% of all deaths each year⁹; over three-quarters of a million people die each year from CVD (heart disease and stroke). Millions of others live with the disease and its often quality of life diminishing sequelae. In 2009, cardiovascular diseases are projected to cost more than \$475.3B, including health care services and medications (\$313.8B) and lost productivity (\$161.5B)⁴, excluding allocation of any monetary value to the immense community care-giving and human suffering in patients and their families..

CVDs include major or “hard” CHD events, such as myocardial infarction (MI), coronary death, stroke, and death due to cerebrovascular disease, as well as “soft” cardiac outcomes, such as revascularization or onset of angina pectoris, that are less life threatening⁸.

The traditional risk factors for CVD have been known for several years. The prominent and widely used Framingham risk score profile for general cardiovascular events encompasses the following sex-specific predictors: age, diabetes status, smoking, treated and untreated systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, and body mass index (BMI) replacing lipids in a simpler model^{10, 11}.

However, these factors explain only about half the deaths from CVD³, and almost half of all heart attacks occur in patients without the classic Framingham study risk factors. For example, about 40% of CHD deaths occur in people with cholesterol levels that are lower than the population average¹². Therefore, medical researchers' attention has focused in recent years on identifying additional risk factors that are non-traditional, but may play major roles in explaining some of the variability in CVD risk.

II. B. General Strategy for Selecting and Rating Reports

A detailed description of the search strategy and process of selecting publications for this report can be found in the Appendix, along with a table displaying the levels of evidence applied. Briefly, the literature search strategy team consisted of two content expert investigators and a medical librarian expert in systematic review search methodologies. Initially, the former identified a set of sentinel articles based on their knowledge of the literature. This formed the basis of the initial search strategy, suggesting relevant Medical Subject Headings (MeSH) and text words or phrases for the search. This initial search strategy was reviewed and revised in an iterative process that was validated by testing the search results for inclusion of the sentinel articles. The process culminated in a MEDLINE search strategy that identified 659 citations pertaining to periodontitis and cardiovascular disease published from 2005 until the present. Additional citations came from hand-search of relevant journal lists of contents, from references cited in relevant reports, and from the authors' weekly automated searches of by National Center for Biotechnology Information (NCBI) until and including October 26, 2009. The content experts ultimately selected 290 articles to consider in greater depth for this report. The most illustrative and recent publications of these 290 articles were selected for this report, along with articles included to provide a historical perspective of the area of research.

In evaluating the level of evidence for each study, we used an evidence hierarchy adapted from the Australian Government's National Health and Medical Research Council's^{47,48} (NHMRC) designation of 'levels of evidence' according to type of research question (Appendix Item 2). In the NHMRC hierarchy, there are two pathways: one if the study is interventional and another if the study is an observational investigation of etiology. If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should

be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure or withhold recognized effective therapy), then the ‘Etiology’ hierarchy of evidence should be utilized. In the hierarchy of strength of evidence for Interventions found in the literature, the highest level is well-conducted systematic reviews and meta-analysis of well-designed, randomized clinical trials (RCTs). For etiological questions addressed in observational studies, meta-analyses of cohort studies or individual cohort studies are the highest levels of evidence.

III. Observational Epidemiological Studies Linking Periodontal Disease and CVD, Focusing on Primary CVD Endpoints, to Address the Question: “Should Periodontitis Be Considered an Independent Risk Factor for CVD?”

III. A. Systematic Reviews and Meta-analyses

In the NHMRC’s hierarchy of evidence using the etiologic pathway (vs. the intervention pathway) the highest levels of evidence are meta-analyses and cohort studies. A meta-analysis conducted by Janket and colleagues¹⁸ of nine cohort studies concluded there is a significant association between clinical periodontal disease and cardiovascular disease with an adjusted odds ratio (OR) of 2.85 for stroke and 1.19 for CVD. The relative risk was higher, namely 1.44, for cardiovascular events in individuals up to 65 years of age. This increased risk for stroke and CVD may have profound public health impact due to the prevalence of periodontal disease, mentioned earlier, classifying it a relatively common chronic disease.

A report of several systematic reviews and meta-analyses performed by Bahekar and colleagues evaluated whether periodontitis is associated with increased risk of coronary heart disease¹⁹. Meta-analysis of five prospective cohort studies involving 86,092 subjects indicated a 1.14 times higher risk for developing CHD in people with periodontitis. The meta-analysis of case-control studies encompassing 1,432 subjects also showed a 2.22 fold greater risk for CHD among individuals with periodontal disease. The meta-analysis of cross-sectional studies on 17,724 subjects indicated the prevalence of CHD was significantly greater among those with periodontitis (OR=1.59)¹⁹. The overall conclusion from the report of these meta-analyses by Bahekar and colleagues was periodontitis may be a risk factor for CHD; they found both prevalence and incidence of CHD to be significantly increased in people with periodontitis.¹⁹

Humphrey and colleagues performed a systematic review and meta-analysis of seven prospective cohort studies on periodontal disease and incidence of coronary heart disease – The reviewed studies were conducted in the US, Canada and Finland on cohorts of 175 to 170,000 men and women with follow-up periods ranging from five to 21 years. The selected studies were population-based prospective studies assessing periodontal disease, Framingham risk factors, and coronary heart

disease incidence in the general adult population without known CHD. This meta-analysis was performed as an aid for the US Preventive Services Task Force (USPSTF) in evaluating the clinical usefulness of screening for non-traditional risk factors for CHD. It concluded “periodontal disease is a risk factor or marker for CHD that is independent of traditional CHD risk factors, including socioeconomic status”²⁰. The results suggested periodontal disease confers an approximately 24-35% increase in risk for CHD. It is noteworthy the seven studies included in this meta-analysis were the same as those evaluated by the Task Force regarding cardiovascular diseases in general, as will be described in more detail in a succeeding section, except for one additional study published in 2004 using self-reported history of periodontal disease and number of teeth.

III. B. Cohort, Case-control, and Cross-sectional Studies

A large prospective cohort study in Stockholm, Sweden followed 1,393 individuals for 27 years and found oral health at baseline was significantly correlated with fatal coronary events³⁵. This study concluded oral health was a risk factor for death due to CVD, especially in combination with smoking, another risk factor.

Case-control studies follow cohort study designs in the evidence hierarchy of evidence for the etiology pathway in the NHMRC’s hierarchy of evidence. A meta-analysis of five case-control studies including 1,423 subjects showed a more than two-fold risk of developing coronary heart disease in periodontitis patients¹⁹. A population-based case-control study with 574 cases (131 women) and 887 controls provided evidence of an association between periodontal disease and incident myocardial infarction in both genders, with women being more susceptible (OR=2.08 versus 1.34 for men, after adjusting for confounders). Importantly, this association appeared to be independent of the potential confounding effect of smoking³⁶.

Cross-sectional studies provide the lowest level of evidence to be included in this report. A meta-analysis of five such studies comprising 17,724 individuals concluded the prevalence of CHD was significantly greater among periodontitis patients¹⁹.

IV. Intervention Trials and Observational Epidemiological Studies Linking Periodontal Disease and CVD, Focusing on Secondary CVD Endpoints, to Address the Question: “Should Periodontitis Be Considered an Independent Risk Factor for CVD?”

The previous section discussed investigations of the association of periodontal disease in the occurrence of cardiovascular disease events, considered primary endpoints. Another approach to investigating the relationships between periodontal disease and cardiovascular disease is to study relationships between periodontitis and secondary outcomes, recognized as risk factors causally related to CVD. In the following sections, we will highlight the most recent reports published on

such associations between periodontal disease and endothelial function and carotid atherosclerosis, respectively, as these conditions are accepted risk factors for CVD.

IV. A. Endothelial function

Endothelium refers to the cells that line the inner surface of all blood vessels. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces. A key feature of endothelial dysfunction is the inability of arteries and arterioles to dilate fully in response to an appropriate stimulus, which creates a detectable difference in subjects with endothelial dysfunction versus a normal, healthy endothelium. Endothelial dysfunction is thought to be a key event in the development of atherosclerosis and predates clinically obvious vascular pathology by many years. Endothelial dysfunction is considered to be the first inflammatory change of the vascular endothelium leading to arteriosclerosis. Endothelial dysfunction has also been shown to be of prognostic significance in predicting vascular events including stroke and heart attacks.

IV. A. 1. Clinical trials and other intervention studies

In a recent narrative review article accepted for publication in April 2009, Tonetti⁴⁹ provides an update on intervention trials, including the following regarding periodontitis and endothelial dysfunction: an early case-control study³⁷, two pilot studies^{27,38}, and his own group's treatment study published in 2007^{39,40}.

Seinost and colleagues in Austria were the first to provide evidence of functional improvement in cardiovascular status after periodontal treatment³⁸. They reported that periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. Baseline diameter of the brachial artery was comparable between the cases and the controls and did not change after periodontal treatment. Flow-mediated dilation (FMD) was significantly lower in periodontitis cases prior to treatment than in controls. Three months after periodontal treatment, FMD significantly improved and returned to values comparable to those of the healthy controls.

The Tonetti-D'Aiuto group found, in an RCT, that intensive periodontal treatment resulted in acute, short-term systemic inflammation and endothelial dysfunction. However, six months after therapy, the benefits in oral health were associated with improvement in endothelial function^{39,40}.

Improvement in endothelial dysfunction in patients with mild to moderate periodontitis was also reported to be observed up to a year after non-surgical treatment in the previously mentioned single-arm intervention study published in 2009²⁹. Tonetti concluded in his review that the evidence supports the current thought that periodontitis causes systemic inflammation and endothelial dysfunction. Yet, he also emphasized the limited generalizability of current evidence based on the predominance of intervention reports focused on severe periodontitis treated in otherwise

systemically healthy individuals. The need remains to assess this association in individuals with less severe periodontitis who also have other systemic diseases such as some form of CVD.

IV. B. Carotid atherosclerosis / Carotid intimal-media thickness (IMT)

Intimal-media thickness (IMT) is a measurement of the thickness of artery walls. Increased carotid intimal-medial wall thickness is a measure of subclinical atherosclerosis. External ultrasound is usually the method used to both detect the presence and to track the progression of atherosclerotic disease in humans.

IV. B. 1. Clinical trials and other intervention studies

A recent single-arm, non-randomized treatment study from Italy²⁹, as mentioned previously, reported significant improvement in reduction of the *carotid intima-media thickness* (IMT) after non-surgical treatment of mild to moderate periodontitis in otherwise healthy individuals. The diminution in carotid IMT was detected in multiple sites along the carotid axis, was observed after six months, and persisted one year after treatment. There have been no RCTs reported on the effects of periodontal treatment on carotid IMT, however the evidence provided by this study, taken together with the evidence derived from the cross sectional studies to be described in the succeeding paragraph, supports a plausible relationship between periodontal disease and carotid IMT.

IV. B. 2. Cross-sectional studies

In 1999, the Beck-Offenbacher group reported preliminary results of the Dental Atherosclerosis Risk in Communities (DARIC) study along with a review of five longitudinal studies showing oral conditions being associated with the onset of CHD⁴¹. Their data indicated that periodontal disease is associated with carotid IMT.

Desvarieaux and colleagues provided evidence of a direct relationship between the periodontal disease pathogenic microbiota and subclinical atherosclerosis⁴², measured by IMT, . They found individuals with greater quantities of of periodontal pathogenic bacteria to have higher mean IMT than individuals with lower quantities of periodontal pathogens. This relationship was independent of C-reactive protein. Interestingly, this report also showed there was no association between non-pathogenic bacteria present in the periodontal microflora and greater IMT. The findings from these earlier cross-sectional studies, taken together with the promising results from the recent intervention study²⁹ support the hypothesis that oral infections may contribute to cardiovascular disease morbidity.

V. Intervention and Observational Studies Elucidating Mechanisms Linking Periodontal Disease and Cardiovascular Disease

V. A. Inflammation

Twenty years ago, a group of Finnish cardiologists²¹ were the first to explore the relationship between oral health and myocardial infarction (MI). Since then, the majority of epidemiologic studies have shown significant associations between periodontitis and MI and stroke. Matilla's group speculated that endotoxins from Gram-negative bacteria could be related to this association²¹. Advances in basic science have established a fundamental role for inflammation in mediating all stages of atherosclerosis, from initiation through progression and, ultimately, the thrombotic complications of this disease. Hence, atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response²². Since 1990, appreciation of the role of inflammation in atherosclerosis has burgeoned. It is currently accepted that atherosclerosis occurs in response to injury of the vascular endothelium and that the nature of the process is inflammatory^{22, 23}. In cardiology, the hypothesis that chronic infections may contribute to atherogenesis has been confirmed by studies reporting individuals exposed to chronic infections have two to three times higher odds of having carotid atherosclerosis²⁴. It is believed that pathogens might have both an effect of the vascular system as well as acting as a source of systemic inflammation, triggering the atherosclerotic process.

V. B. C-Reactive Protein (CRP) and Other Inflammatory Markers

As will be described in more detail in a succeeding section, the U.S. Preventive Services Task Force pointed to CRP as the most documented novel CVD risk factor for CHD, and several reports in that regard have been published. It is understood that CRP and CVD are significantly related. Studies have also linked CRP to periodontal disease, and it is gaining more acceptance that the relationship between periodontopathy and CVD is based on inflammation, at least as one major mechanism. Ebersole and Machen were the first researchers to report an association between periodontal disease and significantly higher levels of the acute-phase inflammatory markers C-reactive protein and haptoglobin²⁵. Their pilot intervention study showed non-surgical periodontal treatment with adjunctive non-steroid anti-inflammatory medication lowered the levels of these acute-phase inflammatory reactants. Additionally, while there was no change in CRP in the non-surgical periodontal treatment group receiving placebo, there was a significant reduction in haptoglobin levels at 12 months in the non-surgical periodontal treatment group receiving placebo. That report concluded, "... either these molecules are formed locally and distributed to the serum, or these presumably localized infections impact upon the systemic components of the host protective response"²⁵. In another earlier treatment study (RCT), D'Auito and colleagues showed scaling and root planing to significantly decrease serum levels of both CRP and interleukin-6 (IL-6)²⁶ one month following periodontal therapy. IL-6 is not only a potent inflammatory inducer of hepatic CRP synthesis, but is also an activator of endothelial inflammation. Thus, IL-6 could contribute to the

endothelial dysfunction observed in periodontal patients. D'Auito and colleagues concluded periodontitis may add to the systemic inflammatory burden in affected individuals.

Recently, a systematic review and meta-analyses on the association between CRP and periodontitis was conducted by Paraskevas and colleagues²⁸. The majority of the 18 studies reviewed reported higher CRP levels in periodontitis than in controls, and subjects with periodontitis often had CRP values of over 2.1 mg/l. The authors found strong evidence that plasma CRP is elevated in people with periodontitis compared to controls. Their meta-analysis of ten cross-sectional studies indicated the weighted mean difference of CRP between subjects with and without periodontal disease was 1.56 mg/l. This is a sizeable difference that needs to be evaluated in the light that the normal level, in absence of inflammation, is less than 1mg/l. Furthermore, it has been suggested that individuals with CRP serum levels of over 1mg/l could be identified as having high risk for developing coronary artery disease (CAD), whereas they would be classified as being at intermediate risk by global risk assessment according to the Framingham risk scores¹².

The pilot *multicenter* Periodontitis and Vascular Events (PAVE) study included a pilot RCT to investigate the role of periodontal treatment in a secondary cardiac event prevention model. The study randomized 303 people with a history of a coronary event, including MI, coronary artery bypass graft surgery, or coronary artery transluminal angioplasty, to either community care or protocol provided scaling and root planing to evaluate effects on periodontal status and systemic levels of high-sensitivity C-reactive protein.³²⁻³⁴ The investigators did not find a significant reduction in mean CRP or a reduction in the proportions of individuals with high CRP (i.e. >3 mg/l) in the treatment group compared to the community care group at six months in their intent-to-treat analysis. Because 48% of the community care control group received one or more preventive or periodontal treatments during the 6-month study period (i.e. prophylaxis, scaling and root planing, or periodontal surgery) the investigators also conducted secondary analyses. The participants were subsequently regrouped into those who received any periodontal treatment and those who received no treatment, irrespective of original group assignment. The secondary analyses showed no change in CRP following any periodontal treatment among the 73 obese individuals. However, the investigators found a significantly lower proportion of participants with CRP ≥ 3 mg/l at 6 months among the non-obese participants who received any form of periodontal treatment, regardless of assignment to the community care group or the experimental protocol group. The investigators concluded their results suggested that periodontal therapy may lower hs-CRP levels among non-obese cardiovascular patients if the initial levels are >3mg/l, and it may prevent a drift to levels >3mg/l for those who are in the intermediate range of 1 to 3 mg/l. Periodontal therapy did not appear to diminish CRP levels among individuals with CRP levels <3 mg/l. The report's authors

suggested the chronic burden of CVD contributes as an inflammatory process and may alone serve to keep a mild elevation of hs-CRP present, irrespective of the added burden of periodontal disease. Obesity acts to increase hs-CRP levels and to possibly nullify any periodontal treatment effects. This pilot study provided important insights into the design and interpretation of future observational and interventional studies on the effects of periodontal disease and its treatment on cardiovascular disease risk.

A single-arm (non-RCT) treatment study published in 2009 by Piconi and colleagues found that non-surgical periodontal treatment (of thirty-five otherwise healthy individuals who had mild to moderate periodontal disease) resulted in a significant reduction of the total oral bacterial load and a significant amelioration of inflammatory biomarkers²⁹. The investigators also observed significant diminution of intimal-media thickness after the periodontal therapy. Inflammatory alterations associated with the formation of atherosclerotic plaques were detected in those with mild to moderate periodontitis, but were positively influenced by periodontal treatment. The design of this study did not include a randomized control group, hence there must be caution in ascribing the results entirely to the periodontal therapy. However, the investigation included a comprehensive assessment of inflammation-related markers of atherogenesis. Hence, the results of this study provide further insights into the potential role of periodontal infection in the pathogenesis of atherosclerosis.

Another single-arm treatment study published in 2009 by Behle and colleagues investigated the effect of comprehensive periodontal therapy on the levels of multiple systemic inflammatory biomarkers in thirty patients with severe periodontitis. This study found highly heterogeneous systemic inflammatory responses that correlated poorly with clinical, microbiological and serological periodontal outcomes. The investigators concluded periodontal therapy resulted in an overall reduction of systemic inflammation, particularly immediately after completion of therapy, however the responses were inconsistent across subjects and were largely not sustainable³⁰. It should be noted this study showed significant reduction of several biomarkers immediately post-treatment and three markers at the 10-week follow-up visit that have all been reported to play a role in atherogenesis. Once again, the absence of a randomized control group calls for caution in ascribing the results entirely to the periodontal therapy. This report contributes in supporting the potential for periodontal therapy to promote an anti-atherogenic phenotype and yet emphasizes the need for rigorous controlled trials and further investigation of the determinants of the heterogeneous responses.

VI. Laboratory-based Studies Elucidating Mechanisms Linking Periodontal Disease and CVD

VI. A. Periodontal Pathogens in Atheromatous Plaques

In early 2009 investigators reported for the first time that infection with a periodontal pathogen induces a prothrombotic response in human aortic smooth muscle cells (HASMC)⁴³. The investigators showed that only whole, viable *Porphyromonas gingivalis* bacteria were able to induce prothrombotic effects in HASMC, and not the heat-killed version nor its non-invasive mutant. This report helps to explain how periodontal infections and atherosclerosis-related vascular disease may be linked. It adds to our understanding of how one periodontal pathogen, *Porphyromonas gingivalis*, could be involved in pathways associated with atherosclerotic plaque progression and instability.

VI. B. Shared Genetic Susceptibility Locus for Coronary Heart Disease and Periodontitis

Published in February 2009, an investigation at the molecular level (i.e. a candidate-gene association study) demonstrated that CHD and periodontitis are genetically related by at least one susceptibility locus. Both CHD and periodontitis are known to have a genetic basis; share similar risk factors such as smoking, diabetes, and gender; and are characterized by a chronic inflammatory process. Interestingly, the finding of shared genetic susceptibility did not appear to be modified by the common environmental and behavioral risk factors known to increase the susceptibility for CHD and/or periodontitis. Hence, the authors conclude the association between these common inflammatory complex diseases could be partially due to a shared genetic cause. This report provides new insight into the underlying partially shared pathogenic mechanisms of these complex common diseases⁴⁴.

VII. Health Services Research Linking Periodontal Disease and CVD, Addressing the Question: “Can Treatment of Periodontitis Help Reduce the Medical Care Costs?”

Another perspective in evaluating the association between periodontal disease and systemic disease involves assessing medical care costs as a health care outcome. Evidence on the ability for periodontal treatment to influence medical care costs of systemic diseases is scant and may be limited to one publication in the scientific literature. Albert and colleagues’ two-year retrospective examination of a large insurance company database revealed a possible association between periodontal treatment and per member per month (PMPM) medical costs⁴⁶. The findings suggest that periodontal treatment (a proxy for the presence of periodontitis) may have an impact on the PMPM medical costs and retrospective risk scores (markers for total health burden risk) for the chronic conditions coronary heart disease and cerebrovascular disease. However, the authors point out that claims data are limited in information other than medical diagnoses and dental and medical services rendered. They and suggest additional research is needed to take confounding and mediating factors into account, such as smoking habits, and other important individual characteristics. At this time there are no definitive conclusions that may be drawn from this emerging evidence and approach to examining periodontal disease-CVD relationships.

VIII. Consensus Statements and Policy Recommendations

VIII. A. The American Journal of Cardiology and Journal of Periodontology Editors’

Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease

In July, 2009, an unusual publication appeared simultaneously in two major journals, namely a consensus report authored by both editors of the American Journal of Cardiology and Journal of Periodontology¹³ in collaboration with experts in the field of the association between periodontitis and atherosclerotic CVD. This document reports the results of a gathering of these leading experts in the fields on January 9, 2009. The publication aims to provide health professionals, especially cardiologists and periodontists, a better understanding of the link between atherosclerotic CVD and periodontitis. Unique are its further attempts to provide an approach to reduce the risk for CVD events in patients with periodontitis, based on the current evidence in the scientific literature. Confidence and evidence levels are assigned to each clinical recommendation for each of five categories: 1) Patient Information, 2) Medical and Dental Evaluation, 3) Risk Factor Treatment: Abnormal Lipids, 4) Risk Factor Treatment: Cigarette Smoking, and 5) Risk Factor Treatment: Hypertension. The consensus panel also describes recommendations for ten future research questions aimed at shedding light on the periodontitis-atherosclerosis relationship to define the mechanisms linking the two diseases and how patients with periodontitis should best be managed to reduce their risk for CVD. The report concluded a direct causal relationship between periodontitis and atherosclerotic CVD has not been established and recognized there have been no prospective periodontitis intervention studies to evaluate primary CVD outcomes. The report acknowledged, however, a causal relationship is biologically plausible based on evidence that inadequately controlled moderate or severe periodontitis increases the systemic inflammatory burden and treatment of moderate to severe periodontitis, sufficient to reduce the clinical signs of the disease, also decreases the systemic inflammatory response. In providing the current clinical recommendations the panel stated periodontitis *may* independently increase the risk for CVD.

Please, note: The consensus document can be downloaded at:

<http://www.joonline.org/doi/pdfplus/10.1902/jop.2009.097001>

VIII. B. U.S. Preventive Services Task Force (USPSTF) Reports on Non-Traditional Risk Factors for CVD

The U.S. Preventive Services Task Force (USPSTF) was charged by the Agency for Healthcare Research and Quality to review current evidence for emerging, non-traditional risk factors for CHD that would have the potential to improve global risk assessment for CHD. USPSTF published three reports on October 6, 2009^{8,15,16} plus a one-page summary for patients¹⁴. One report summarized the results of the group’s systematic reviews of literature since 1996 on nine novel risk factors, one

review for each: 1) C-reactive protein (CRP), 2) coronary calcium score, 3) lipoprotein level, 4) homocysteine level, 5) leukocyte count, 6) fasting blood glucose, 7) **periodontal disease**, 8) ankle-brachial index, and 9) carotid intima-media thickness⁸. This report concluded C-reactive protein (CRP), an acute phase response inflammatory marker, was the best candidate for use in screening and the most rigorously studied. However, the report also observed evidence that changes in CRP level lead to primary prevention of CHD events is inconclusive. Overall, that report concluded current evidence does not support the routine use of any of the 9 risk factors to improve global risk assessment for CHD. The second report then focused on CRP and concluded there is strong evidence that CRP is associated with CHD events¹⁵. However, the report also concluded sufficient evidence that reducing CRP levels prevents CHD events is lacking. The third report is the USPSTF recommendation statement. This report offered the concluding recommendations that using any of the nine novel risk factors (including periodontal disease) among asymptomatic men and women with no history of CHD in order to prevent CHD is not currently warranted due to insufficient evidence to assess the balance of benefits and harms of such screening¹⁶.

The USPSTF concluded periodontal disease is an independent, though relatively weak, risk factor of coronary heart disease, but the effect of periodontal treatment on major CHD events is unclear⁸.

Further, the USPSTF acknowledged that for cardiovascular diseases in general, relative risk estimates ranged from 1.24 for periodontitis to 1.34 for individuals with zero to ten teeth, indicating people with periodontal disease and those edentulous or who have 10 or fewer teeth are one-quarter to one-third more likely to experience CVD events than those without periodontitis. However, the USPSTF did not find any direct evidence that periodontal examination would be useful for reclassifying persons already classified as intermediate-risk by the Framingham risk score⁸. It should be noted that consideration of reclassification of risk was one of the charges for the task force. This entailed evaluating the novel risk factors to identify greater risk in individuals who would ordinarily have been classified as having intermediate risk for experiencing CVD events by the Framingham risk scores. For the novel risk factors conferring sufficiently greater risk (i.e. 20 percent risk of major events within ten years), the recommendation would be more aggressive treatment to prevent such events⁸. Finally, it is important to note the six studies on which the USPSTF based its conclusions regarding the value of screening for periodontal disease were published between 1993¹⁷ and 2003.

IX. CONCLUSION

Overall, reports from published studies contribute to strengthening the concept that periodontal disease may be a previously underappreciated source of infectious and inflammatory vascular stress that may play a role in severe and often fatal cardiovascular events. Periodontitis is increasingly

regarded as a risk factor for CVD. The vast majority of this evidence comes from observational studies, which fall into the etiologic pathway in the hierarchy of evidence.

Evidence is evolving to support periodontal treatment as an intervention to aid in reducing the level of such stress on the vasculature. Eventually, good oral health, specifically good periodontal health, may in the future become accepted as an important therapeutic goal that could contribute to reducing the risk for cardiovascular events.

The encouraging recognition is that the most common forms of periodontal disease are conditions relatively easy to diagnose and treat, given individuals have access to dental care. Also, the evidence-based expectation of the outcome of periodontal treatment is improved periodontal health with negligible side effects. Until further definitive findings are reported from RCTs regarding beneficial systemic effects of periodontal treatment on decreased incidence of cardiovascular events, the strongest current evidence supports the relationship between periodontal therapy and markers or risk factors for CVD.

REFERENCES CITED IN THE TEXT IN THIS REPORT

Please, also see Appendix 3: Classification of Original Research Reports Related to Oral Health and Cardiovascular Disease Published From 2007 through October 2009 and Identified by This Report's Authors for Abstract Review and Listing in This Report.

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41. Beck JD, Pankow J, Tyroler HA, Offenbacher S. Dental infections and atherosclerosis. *Am Heart J* 1999;138(5 Pt 2):S528-33.
42. Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR, Jr., Sacco RL, et al. Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation* 2005;111(5):576-82.
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APPENDIX

- 1. Literature Search Process and MEDLINE Search Strategy**
- 2. Level of Evidence Provided by Various Types of Studies**
- 3. Classification of Original Research Reports Related to Oral Health and Cardiovascular Disease Published From 2007 through October 2009 and Identified by This Report's Authors for Abstract Review and Listing in This Report**

1. Literature Search Process and MEDLINE Search Strategy

The literature search strategy team consisted of two content expert investigators and a medical librarian expert in systematic review search methodologies. Initially, the former identified a set of sentinel articles based on their knowledge of the literature. This formed the basis of the initial search strategy, suggesting relevant Medical Subject Headings (MeSH) and text words or phrases for the search. This initial search strategy was reviewed and revised in an iterative process that was validated by testing the search results for inclusion of the sentinel articles. The process culminated in the following MEDLINE search strategy: ((exp Periodontal Diseases/ OR exp Periodontics/ OR exp Periodontitis/ OR exp Periodontium/ OR exp Gingival Crevicular Fluid/ OR Fibromatosis, Gingival/ OR exp Gingival Hemorrhage/) OR (periodont:.mp. OR gingiv:.mp. OR (gum\$1 adj3 disease\$1).mp. OR CPITN.mp.) OR (exp Dental Fistula/ OR exp Gingival Neoplasms/ OR exp Dental Health Surveys/ OR exp Oral Health/) OR ((periodontal or plaque or dental or "oral health" or schei) adj3 index).mp. OR (exp Mouth, Edentulous/ OR edentu:.mp.)) AND ((exp Cardiovascular Diseases/ OR exp Cardiology/ OR (exp Cardiovascular System/ AND (pa.fs. OR disease\$1.mp.)) / limit 1 to (English language and humans and yr="2005-Current").

MeSH terms selected included terms relevant to periodontology in various aspects of the profession and its practice, as well as anatomical terms and disease terms specific to that anatomical area. In addition, common diagnosis and oral health assessment tools and terms were included. Following the development of the filter to gather periodontics literature, a broad search on cardiovascular diseases was added into the search strategy. Limits were applied for humans, English Language results and a time span.

The two content expert authors perused a total of 659 citations resulting from the search relating to periodontitis and cardiovascular disease published in 2005 until the present. Each selected citations to further pursue, based only on the title of the publication in order to avoid any publication bias introduced by knowledge of the names of the journals and authors. After further review of the abstracts, a subset was selected for reading of the full text. Additional citations came from hand-search of relevant journal lists of contents, from references cited in relevant reports, and from the authors' weekly automated searches of by National Center for Biotechnology Information (NCBI) until and including October 26, 2009. A total of 290 articles resulted from combining the selected publications and agreeing on further pursuit, including acquiring the full-text articles. The most illustrative and recent publications were selected for this report, along with articles included to provide a historical perspective of the area of research.

2. Level of Evidence Provided by Various Types of Studies

The variation in the strength of evidence due to different study designs has led to the development of several schemes providing a hierarchy of evidence to rank studies according to the way in which their design contributes to the strength of evidence provided. The hierarchy is a way to reflect the potential of each type of study design to answer a particular type of question, based on the probability that its design has minimized the impact of bias on the results⁴⁷. The hierarchy in the following table is an ordering of the strength of the evidence each properly designed study type can yield⁴⁷.

Table 1. Evidence Hierarchy Adapted from the Australian Government’s National Health and Medical Research Council’s Designation of ‘Levels of Evidence’ According to Type of Research Question⁴⁷. (Please, see also explanatory notes below this table.)

| Level | Intervention ^a | Etiology ^b |
|----------------|--|---|
| I ^c | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomized controlled trial | A prospective cohort study |
| III-1 | A pseudorandomized controlled trial (i.e. alternate allocation or some other method) | All or none ^d |
| III-2 | A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial^e ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group | A retrospective cohort study |
| III-3 | A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study^f ▪ Interrupted time series without a parallel control group | A case-control study |
| IV | Case series with either post-test or pre-test/post-test outcomes | A cross-sectional study or case series |

Explanatory notes:

- a) Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence*⁴⁸.
- b) If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Etiology’ hierarchy of evidence should be utilized.
- c) A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall

level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

- d) All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.
- e) This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).
- f) Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

3. Classification of Original Research Reports Related to Oral Health and Cardiovascular Disease Published From 2007 through October 2009 and Identified by This Report's Authors for Abstract Review and Listing in This Report.

This table is presented to provide the reader with a comprehensive overview of the body of evidence published since January 1st, 2007. Not all of the reports listed in this table have been described in detail in the report. This table presents the full reference citation, the report's study design, and position in the hierarchy of evidence as described by Australian Government's National Health and Medical Research Council's designation of levels of evidence^{47,48}.

| 3A. Intervention Studies | Study Design | Evidence Level |
|---|--|-----------------------|
| Beck JD, Couper DJ, Falkner KL, Graham SP, Grossi SG, Gunsolley JC, et al. The Periodontitis and Vascular Events (PAVE) pilot study: adverse events.[see comment]. Journal of Periodontology 2008;79(1):90-6. | RCT | Intervention II |
| Couper DJ, Beck JD, Falkner KL, Graham SP, Grossi SG, Gunsolley JC, et al. The Periodontitis and Vascular Events (PAVE) pilot study: recruitment, retention, and community care controls. Journal of Periodontology 2008;79(1):80-9. | RCT | Intervention II |
| Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, et al. Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. Journal of Periodontology 2009;80(2):190-201. | RCT | Intervention II |
| Oz SG, Fentoglu O, Kilicarslan A, Guven GS, Tanrtover MD, Aykac Y, et al. Beneficial effects of periodontal treatment on metabolic control of hypercholesterolemia.[see comment]. Southern Medical Journal 2007;100(7):686-91. | RCT | Intervention II |
| Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function.[see comment]. New England Journal of Medicine 2007;356(9):911-20. | RCT | Intervention II |
| Tuter G, Kurtis B, Serdar M, Aykan T, Okyay K, Yucel A, et al. Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease. Journal of Clinical Periodontology 2007;34(8):673-81. | RCT | Intervention II |
| Ushida Y, Koshy G, Kawashima Y, Kiji M, Umeda M, Nitta H, et al. Changes in serum interleukin-6, C-reactive protein and thrombomodulin levels under periodontal ultrasonic debridement. Journal of Clinical Periodontology 2008;35(11):969-75. | RCT | Intervention II |
| Vidal F, Figueredo CMS, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. Journal of Periodontology 2009;80(5) | RCT | Intervention II |
| Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35(4):277-90. | Meta-analysis: a) RCT b) Non-RCT | Intervention IV |
| Ellis JS, Averley PA, Preshaw PM, Steele JG, Seymour RA, Thomason JM. Change in cardiovascular risk status after dental clearance.[see comment]. British Dental Journal 2007;202(9):543-4. | Non-RCT treatment study | Intervention IV |

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|---|-------------------------|-----------------|
| Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, et al. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. <i>Hypertension</i> 2008;51(2):446-53. | Non-RCT treatment study | Intervention IV |
| Jastrzebski M, Zaleska M, Klocek M, Stolarz K, Wojciechowska W, Olszanecka A, et al. Should dental treatment be considered for lowering inflammatory markers in hypertensive patients? <i>International Journal of Cardiology</i> 2009;132(3):439-41. | Non-RCT treatment study | Intervention IV |
| Piconi S, Trabattoni D, Luraghi C, Perilli E, Borelli M, Pacci M, et al. Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. <i>FASEB Journal</i> 2009;23(4):1196-204. | Non-RCT treatment study | Intervention IV |
| Vuletic S, Taylor BA, Tofler GH, Chait A, Marcovina SM, Schenck K, et al. SAA and PLTP activity in plasma of periodontal patients before and after full-mouth tooth extraction. <i>Oral Diseases</i> 2008;14(6):514-9. | Non-RCT treatment study | Intervention IV |

| 3B. Etiologic Observational Studies | Study Design | Evidence Level |
|---|----------------------------------|-----------------------|
| Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis.[see comment]. <i>American Heart Journal</i> 2007;154(5):830-7. | Meta-analysis: Cohort studies | Etiology I |
| Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. <i>J Gen Intern Med</i> 2008;23(12):2079-86. | Meta-analysis: Cohort studies | Etiology I |
| Janket SJ, Baird AE, Chuang SK, Jones JA. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. <i>Oral Surg Oral Med Oral Pathol Oral Radiol Endod</i> 2003;95(5):559-69. | Meta-analysis: Cohort studies | Etiology I |
| Choe H, Kim YH, Park JW, Kim SY, Lee S-Y, Jee SH. Tooth loss, hypertension and risk for stroke in a Korean population. <i>Atherosclerosis</i> 2009;203(2):550-6. | Cohort | Etiology II |
| Dietrich T, Jimenez M, Krall Kaye EA, Vokonas PS, Garcia RI. Age-dependent associations between chronic periodontitis/edentulism and risk of coronary heart disease. <i>Circulation</i> 2008;117(13):1668-74. | Cohort | Etiology II |
| Heitmann BL, Gamborg M. Remaining teeth, cardiovascular morbidity and death among adult Danes. <i>Preventive Medicine</i> 2008;47(2):156-60. | Cohort | Etiology II |
| Pussinen PJ, Tuomisto K, Jousilahti P, Havulinna AS, Sundvall J, Salomaa V. Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. <i>Arteriosclerosis, Thrombosis & Vascular Biology</i> 2007;27(6):1433-9. | Cohort | Etiology II |
| Soder B, Jin LJ, Klinge B, Soder PO. Periodontitis and premature death: a 16-year longitudinal study in a Swedish urban population. <i>Journal of Periodontal Research</i> 2007;42(4):361-6. | Cohort | Etiology II |
| Tu Y-K, Galobardes B, Smith GD, McCarron P, Jeffreys M, Gilthorpe MS. Associations between tooth loss and mortality patterns in the Glasgow Alumni Cohort.[see comment]. <i>Heart</i> 2007;93(9):1098-103. | Cohort | Etiology II |

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|--|-------------------------------------|----------------|
| Wu GH, Manzon S, Badovinac R, Woo S-B. Oral health, dental treatment, and cardiac valve surgery outcomes. <i>Special Care in Dentistry</i> 2008;28(2):65-72. | Retrospective Cohort | Etiology III-2 |
| Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis.[see comment]. <i>American Heart Journal</i> 2007;154(5):830-7. | Meta-analysis: Case-control studies | Etiology III-3 |
| Amabile N, Susini G, Pettenati-Soubayroux I, Bonello L, Gil JM, Arques S, et al. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. <i>Journal of Internal Medicine</i> 2008;263(6):644-52. | Case-control | Etiology III-3 |
| Andriankaja OM, Genco RJ, Dorn J, Dmochowski J, Hovey K, Falkner KL, et al. Periodontal disease and risk of myocardial infarction: the role of gender and smoking. <i>European Journal of Epidemiology</i> 2007;22(10):699-705. | Case-control | Etiology III-3 |
| Barak S, Oettinger-Barak O, Machtei EE, Sprecher H, Ohel G. Evidence of periopathogenic microorganisms in placentas of women with preeclampsia. <i>Journal of Periodontology</i> 2007;78(4):670-6. | Case-control | Etiology III-3 |
| Chen YW, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, et al. Periodontitis may increase the risk of peripheral arterial disease. <i>European Journal of Vascular & Endovascular Surgery</i> 2008;35(2):153-8. | Case-control | Etiology III-3 |
| Colhoun HM, Slaney JM, Rubens MB, Fuller JH, Sheiham A, Curtis MA. Antibodies to periodontal pathogens and coronary artery calcification in type 1 diabetic and nondiabetic subjects. <i>Journal of Periodontal Research</i> 2008;43(1):103-10. | Case-control | Etiology III-3 |
| Herrera JA, Parra B, Herrera E, Botero JE, Arce RM, Contreras A, et al. Periodontal disease severity is related to high levels of C-reactive protein in pre-eclampsia. <i>Journal of Hypertension</i> 2007;25(7):1459-64. | Case-control | Etiology III-3 |
| Lund Haheim L, Olsen I, Nafstad P, Schwarze P, Ronningen KS. Antibody levels to single bacteria or in combination evaluated against myocardial infarction. <i>Journal of Clinical Periodontology</i> 2008;35(6):473-8. | Case-control | Etiology III-3 |
| Oikarinen K, Zubaid M, Thalib L, Soikkonen K, Rashed W, Lie T. Infectious dental diseases in patients with coronary artery disease: an orthopantomographic case-control study. <i>J Can Dent Assoc.</i> 2009 Feb;75(1):35. | Case-control | Etiology III-3 |
| Pussinen PJ, Alftan G, Jousilahti P, Paju S, Tuomilehto J. Systemic exposure to <i>Porphyromonas gingivalis</i> predicts incident stroke. <i>Atherosclerosis</i> 2007;193(1):222-8. | Nested Case-control | Etiology III-3 |
| Siqueira FM, Cota LOM, Costa JE, Haddad JPA, Lana AMQ, Costa FO. Maternal periodontitis as a potential risk variable for preeclampsia: a case-control study. <i>Journal of Periodontology</i> 2008;79(2):207-15. | Case-control | Etiology III-3 |
| Starkhammar Johansson C, Richter A, Lundstrom A, Thorstensson H, Ravald N. Periodontal conditions in patients with coronary heart disease: a case-control study. <i>Journal of Clinical Periodontology</i> 2008;35(3):199-205. | Case-control | Etiology III-3 |

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|---|---|-------------|
| Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis.[see comment]. American Heart Journal 2007;154(5):830-7. | Meta-analysis: Cross-sectional studies | Etiology IV |
| Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. Journal of Periodontology 2007;78(12):2289-302. | Meta-analysis: a) Cohort studies b) Cross-sectional | Etiology IV |
| Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol 2008;35(4):277-90. | Meta-analysis: Cross-sectional studies | Etiology IV |
| Abou-Raya S, Abou-Raya A, Naim A, Abuelkheir H. Rheumatoid arthritis, periodontal disease and coronary artery disease.[erratum appears in Clin Rheumatol. 2008 Apr;27(4):551]. Clinical Rheumatology 2008;27(4):421-7. | Cross-sectional | Etiology IV |
| Ayo-Yusuf OA, Ayo-Yusuf IJ. Association of tooth loss with hypertension. South African Medical Journal 2008;Suid-Afrikaanse Tydskrif Vir Geneeskunde. 98(5):381-5. | Cross-sectional | Etiology IV |
| Beckstrom BW, Horsley SH, Scheetz JP, Khan Z, Silveira AM, Clark SJ, et al. Correlation between carotid area calcifications and periodontitis: a retrospective study of digital panoramic radiographic findings in pretreatment cancer patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 2007;103(3):359-66. | Cross-sectional | Etiology IV |
| Cairo F, Castellani S, Gori AM, Nieri M, Baldelli G, Abbate R, et al. Severe periodontitis in young adults is associated with sub-clinical atherosclerosis. Journal of Clinical Periodontology 2008;35(6):465-72. | Cross-sectional | Etiology IV |
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