Is Periodontal Disease a Risk Factor for Coronary Artery Disease (CAD)?

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Abstract

Coronary artery disease (CAD) remains the principal cause of death in most developed countries, despite significant preventive and therapeutic advances. Current epidemiological data imply that recent reductions in the prevalence of this disease are unlikely to be sustained until those at high risk are more precisely targeted. Although dental (especially periodontal) infections have been recently identified as independent risk factors for CAD, current evidence is insufficient to justify treatment of such infections to arrest or reverse CAD or other systemic conditions (e.g., diabetes mellitus, stroke or adverse outcomes of pregnancies).

MeSH Key Words: *coronary disease/etiology; periodontal diseases/complications; risk factors*

© J Can Dent Assoc 2002; 68(3):176-80
This article has been peer reviewed.

A high concentration of plasma cholesterol, especially low-density lipoprotein cholesterol, is the principal established risk factor for the multifactorial pathogenesis of atherosclerosis.[1] Coronary artery (ischemic) disease (CAD) is unquestionably the most important manifestation of atherosclerosis, although the pharmacologic reduction of plasma cholesterol levels and other lifestyle changes have contributed to reductions in age-adjusted mortality rates of only about 50%.[2] This implies that the pathogenesis of coronary artery atherosclerosis is linked to other risk factors, although the precise identification of these factors is hampered by complex interactions between focal lipid accumulations in arterial walls and associated host responses.[1]

More precise identification of these risk factors is further constrained by the lifelong origin of CAD. For example, CAD may initially present as "fatty streak" lesions in the arterial walls of children and adolescents, where the purely inflammatory host reactions result in focal collections of monocyte-derived macrophages and T lymphocytes.[3] Hypercholesterolemia in adults is more commonly linked to progressive extracellular deposition of amorphous and membranous lipids before the influx of inflammatory cells into these atherosclerotic lesions.[4] Significant declines in CAD mortality rates associated with these atherosclerotic lesions may be attributed to therapeutic reductions in cholesterol levels, but the recent plateau in these rates has been associated with slight resurgences in the prevalence of stroke (cerebrovascular diseases).[5] The impact of these resurgences may, in turn, exacerbate the difficulties in predicting who will experience the symptoms of CAD. For example, such symptoms tend to be prevalent in only a fraction of those with one or more established risk factors, whereas others succumb to CAD without any apparent risk factors.[2]

Current research indicates that varied clusters of interactive risk factors contribute to the onset of CAD, thereby complicating the precise assessment of high-risk individuals.[6] Recent evidence for microbial (notably herpes virus and *Chlamydia pneumoniae*) infections as independent risk factors for CAD clearly illustrates these concerns.[7] For example, administration of antibiotics significantly reduced the prevalence of ischemic attacks in a recent randomized, double-blind, placebo-controlled trial,[7] whereas interactions between infections and other, possibly more important, risk factors may predispose genetically more susceptible individuals to CAD. As a result, current evidence cannot be used to justify the routine prescription of antibiotics for prevention or treatment of CAD.[8] This review evaluates whether similar reservations apply to the treatment of oral (notably periodontal) infections for the arrest or reversal of CAD.

Is There Evidence for an Association Between Periodontitis and CAD?

Recently published studies that have purportedly designated dental infections as independent risk factors for CAD are difficult to validate. The inherent deficiencies include the following:

- difficulties in the design of studies to accommodate potential interactions between variable clusters of risk factors and other factors that are more ill defined (e.g., physical and mental stress, differential circadian periodicities);
- difficulties in the reliable acquisition of standardized data for dental (especially periodontal) infections for baseline and sequential analysis.

These deficiencies have yet to be comprehensively addressed in published studies. For example, not only do the available studies range from cross-sectional to case-control and prospective designs, but quantitative assessments of dental infections extend from periodontal probing to non-validated indices and self-reporting. Most of these studies suggest that CAD is linked to periodontal infections (Tables 1–3), although inconsistencies in design preclude rigorous assessment (e.g., through a Cochrane review).

Is the Periodontitis-Associated Risk of CAD Reversible?

If the link between periodontal infections and CAD is confirmed by subsequent studies, the question will still remain whether the benefits of treating the infections are analogous to those already proven for lifestyle changes, in terms of effects on CAD.[28] These potential benefits were tested in 4,027 people enrolled in the First National Health and Nutrition Examination Survey (NHANES I), where the prospective cohort trial comprised 2,170 people who were edentulous, with the remainder having periodontitis.[26] Over a mean follow-up period of 17 years, 1,238 CAD events (deaths or CAD-related hospital

Table 1 **Summaries of case-control studies on the relationships between periodontal infections and coronary artery disease (CAD)**

Patient numbers and characteristics	Results	Comments
100 consecutive patients ≤ 50 years of age admitted to hospital for MI and 102 ≤ 50 years without MI as controls[9]		
Series 1: 40 men with MI, 41 men without MI as controls	Significant oral health differences ($p < 0.001$) between cases and controls	Assessments of relationships between oral infections and MI compromised by unproven reliability of "total dental index" and "pantomographic index" to quantify oral health
Series 2: 44 men and 16 women with MI, 44 men and 17 women without MI as controls	Significant oral health differences ($p < 0.001$) between cases and controls	Assessments of relationships between oral infections and MI compromised by unproven reliability of "total dental index" and "Pantomographic Index" to quantify oral health
85 patients with CAD and 46 random controls without CAD[10]	No significant association between chronic CAD and severity of dental disease	Findings at variance with those reported previously,[9] possibly because of older age of patients in this study
320 veterans ≥ 60 years of age[11]	Oral health parameters more strongly associated with CAD than serum cholesterol levels, body mass index, diabetes and smoking; also, subjects with 1–14 teeth more likely to have CAD than those with 15 or more teeth	No controls included in study
60 patients with acute MI and 60 with chronic CAD[12]	Periodontal disease may have been associated with acute MI	No controls included in study
166 patients with acute cerebrovascular ischemia and 166 age- and sex-matched neurological controls without stroke who completed a standardized questionnaire; dental examination performed on 66 stroke patients and 60 controls[13]	Stroke victims tended to have more severe periodontitis than controls	Unconventional and non-validated assessments of periodontal status; cerebrovascular and cardiac ischemia may be discrete disease processes
151 subjects with either CAD or significant CAD risk factors and 943 healthy controls, 26–53 years of age[14]	CPITN scores of 4 subjects significantly related to hypercholesterolemia and possibly associated with CAD	Hypercholesterolemia was claimed to link periodontal infections with atherosclerosis, but the cross-sectional nature of this study precludes such interpretations of the data

MI = myocardial infarction, CPITN = Community Periodontal Index of Treatment Need.

Table 2 **Summaries of cross-sectional studies on the relationships between periodontal infections and coronary artery disease (CAD)**

Patient numbers and characteristics	Results	Comments
Insurance company records of 1,384 men, 45–64 years old[15]	Weak statistical association between missing teeth and history of ischemic heart disease	Uncertain reliability of missing teeth as surrogate for "sustained oral infections"
88 men referred for diagnostic coronary angiography[16]	Statistical association between severity of coronary artery stenosis and severity of radiologically evident damage from dental infections	Suggested relationships between oral infections and coronary artery stenosis compromised by unproven reliability of "total dental index" and "pantomographic index" in assessing oral health
5,564 subjects > 40 years old derived from NHANES III[17]	Significant association between clinically evident attachment loss and self-reported history of MI	Cross-sectional design hampers evidence for a relationship between attachment loss and risk of CAD
12,949 subjects ≥ 18 years old who underwent periodontal examinations and 1,817 who were edentulous (from NHANES III)[18]	Edentulism and periodontal disease associated with increased systemic inflammatory response, even with adjustment for established risk factors	Cross-sectional design hampers determination of causal relationships

NHANES = *National Health and Nutrition Examination Survey,* MI = *myocardial infarction.*

admissions) occurred among the participants. However, after adjustment for the principal risk factors (e.g., smoking, blood pressure and cholesterol level), the risks of CAD were no lower among patients without dental infections (those who were edentulous) than among those with periodontitis. These data argue against a causal relationship between these 2 variables and suggest that the limited associations reported by others may be attributable to other confounding factors, such as smoking. Inadequate prior dental histories (e.g., the prevalence and severity of previous periodontally induced bacteremia) for the patients in this and other studies further compromise more rigorous interpretation of the data. Certainly dental clearances will restore the integrity of epithelial barriers and thereby reduce the potential for recurrent oral sepsis, although CAD may be the chronic problem and may have been initiated while the patient was still dentate.

Can Treatment of Periodontal Infections Reduce the Risk of CAD?

The results of the prospective cohort study on participants in NHANES I did not confirm that treatment for periodontal infections prevents or reverses the prevalence of CAD; in other words, they failed to show that CAD risks were reduced in those with no periodontal infection (edentulous) or exacerbated in those with periodontitis.[26] These data therefore suggest that the treatment of dental (especially periodontal) infections should be based principally on dental determinants rather than CAD prevention or treatment. Alternatively, even if periodontal infections are not independent risk factors for CAD, these 2 diseases might still be associated after due consideration of confounding factors (e.g., smoking). Patients at high risk for CAD may have similar risks for periodontitis, since the diseases have some commonalities in their underlying pathophysiological processes.[29] Furthermore, patients may be genetically predisposed to both diseases, in addition to others (e.g., diabetes mellitus). If these relationships are subsequently substantiated by interventional trials, then periodontitis should not be expected to be improved by treatment for CAD, nor CAD arrested or improved after periodontal treatment. Such commonalities may, however, explain the associations between periodontitis and atherosclerosis, diabetes and adverse outcomes for pregnancy identified in animal and population-based studies.[30]

Conclusions

Current evidence is insufficient to unequivocally support the premise that dental (especially periodontal) infections constitute an independent risk factor for CAD. However, the deposition of atheromatous plaque in the coronary arteries may be associated with many other infections in addition to periodontitis (e.g., bacterial, viral and even parasitic).[29] The association between periodontitis and chronic disorders such as diabetes and CAD may also be mediated by either nonspecific (e.g., hypercoaguability, increase in C-reactive protein) or specific (e.g., induction of pathogenic anti-heat-shock protein) mechanisms, in addition to being linked to immunologic components (e.g., serum amyloid protein, fibrinogen). Therefore, evidence for potential associations between dental infections and systemic diseases must be carefully re-examined to distinguish potential confounding factors from other risk factors (e.g., smoking) before treatment with the aim of preventing or treating CAD can be justified. Alternatively, significant similarities in the etiologic and pathogenetic processes of these chronic diseases underscore the urgent need for rigorous interventional trials.

Table 3 Summaries of retrospective and prospective studies on the relationships between periodontal infections and coronary artery disease (CAD)

Patient numbers and characteristics	Results	Comments
Retrospective study		
10,368 individuals without self-reported CAD and 11,251 with cerebrovascular disease from the Nutrition Canada Survey of 1970–1972 (studied through 1993)[19]	Significant correlation between periodontal disease and risk of fatal cardiovascular disease	Cross-sectional design hampers determination of a relationship between periodontal disease and risk for CAD
Prospective studies		
214 patients studied for a median of 7.2 years[20]	Statistical evidence for association between oral infections and development of adverse cardiovascular outcomes in patients at increased risk for CAD	Suggested relationships between oral infections and risk of CAD compromised by unproven reliability of "total dental index" and "pantomographic index" to assess oral health
1,147 men 21–80 years old at baseline, derived from Normative Aging and Dental Longitudinal Studies of Boston, followed for 18 years[21]	Results support hypothesis that periodontal disease is involved in development of CAD	
22,037 male physicians 40–84 years old in the US Physicians' Health Study, followed for 12.3 years[22]	Periodontal disease was not an independent predictor of subsequent CAD	
1,372 native Americans with known high risk for diabetes mellitus, evaluated over 10 years[23]	Alveolar bone level predictive of cardiovascular disease for persons ≤ 60 years old	
22,071 US male physicians followed for a mean of 12.3 years (in randomized, double-blind placebo-controlled trial of ASA and beta-carotene)[24]	Self-reported periodontal disease not an independent predictor of cardiovascular disease in middle-aged to elderly men when adjusted for major cardiovascular risk factors	Lack of precision in self-reported assessments of periodontal disease
Prospective cohort studies		
9,769 adults from the NHANES I, followed for a median of 14 years (Russell's periodontal index used for assessment of periodontal health)[25]	Periodontal disease and tooth loss weakly associated with CAD development; stronger association for subjects ≥ 50 years old	Russell's periodontal index scores subject to considerable error
8,032 people from NHANES I Epidemiologic Follow-up Study, followed for a mean of 17 years[26]	Elimination of chronic dental infections did not lead to reductions in risk of CAD	No controlled evidence that dental treatment leads to lower incidence of CAD than among those not treated
Prospective questionnaire study		
44,119 men enrolled in Health Professionals Follow-up Study, contacted biennially by mail over 6 years for self-reported dental history[27]	No overall association between self-reported periodontal disease and CAD Weak association between tooth loss and CAD in those with history of periodontal disease	Self-assessment questionnaires for periodontal disease are imprecise

ASA = *acetylsalicylic acid*, NHANES = *National Health and Nutrition Examination Study*.

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The views expressed are those of the author and do not necessarily reflect the opinions or official policies of the Canadian Dental Association.

References

1. Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med* 1999; 340(2):115-26.

2. Pahor M, Elam MB, Garrison RJ, Kritchevsky SB, Applegate WB. Emerging noninvasive biochemical measures to predict cardiovascular risk. *Arch Intern Med* 1999; 159(3):237-45.

3. Napoli C, D'Armiento, FP, Mancini FP, Postiglione A, Witztum JL, Palumbo G, and other. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. *J Clin Invest* 1997; 100(11):2680-90.

4. Link N, Tanner M. Coronary artery disease: Part 1. Epidemiology and diagnosis. *West J Med* 2001; 174(4):257-61.

5. The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Arch Intern Med* 1997; 157(21):2413-46.

6. Genest J Jr, Cohn JS. Clustering of cardiovascular risk factors: targeting high-risk individuals. *Am J Cardiol* 1995; 76(2):8A-20A.

7. Gurfinkel E, Bozovich G, Beck E, Testa E, Livellara B, Mautner B. Treatment with antibiotic roxithromycin in patients with acute

non-Q-wave coronary syndromes. The final report of the ROXIS study. *Eur Heart J* 1999; 20(2):121-7.

8. Ngeh J, Gupta S. Inflammation, infection and antimicrobial therapy in coronary heart disease — where do we currently stand? *Fundam Clin Pharmacol* 2001; 15(2):85-93.

9. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesaniemi YA, Syrjala SL, and others. Association between dental health and acute myocardial infarction. *BMJ* 1989; 298(6676):779-81.

10. Mattila KJ, Asikainen S, Wolf J, Jousimies-Somer H, Valtonen V, Nieminen M. Age, dental infections, and coronary heart disease. *J Dent Res* 2000; 79(2):756-60.

11. Loesche WJ, Schork A, Terpenning MS, Chen YM, Dominguez BL, Grossman N. Assessing the relationship between dental disease and coronary heart disease in elderly US veterans. *J Am Dent Assoc* 1998; 129(3):301-11.

12. Emingil G, Buduneli E, Aliyev A, Akilli A, Atilla G. Association between periodontal disease and acute myocardial infarction. *J Periodontol* 2000; 71(12):1882-6.

13. Grau AJ, Buggle F, Ziegler C, Schwarz W, Meuser J, Tasman AJ, and others. Associations between cerebrovascular ischemia and chronic and recurrent infection. *Stroke* 1997; 28(9):1724-9.

14. Katz J, Chaushu G, Sharabi Y. On the association between hypercholesterolemia, cardiovascular disease and severe periodontal disease. *J Clin Periodontol* 2001; 28(9):865-8.

15. Paunio K, Impivaara O, Tiekso J, Maki J. Missing teeth and ischemic heart disease in men aged 45-64 years. *Eur Heart J* 1993; 14(Suppl K):54-6.

16. Mattila KJ. Dental infections as a risk factor for acute myocardial infarction. *Eur Heart J* 1993; 14(Suppl K):51-3.

17. Arbes SJ, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. *J Dent Res* 1999; 78(12):1777-82.

18. Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS. Acute-phase inflammatory response to periodontal disease in the US population. *J Dent Res* 2000; 79(1):49-57.

19. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk* 1999; 6(1):7-11.

20. Mattila KJ, Valtonen VV, Nieminen MS, Huttunen JK. Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. *Clin Infect Dis* 1995; 20(3):588-92.

21. Beck J, Garcia R, Heiss G, Vokonas PS, Offenbacher S. Periodontal disease and cardiovascular disease. *J Periodontol* 1996; 67(10 Suppl):1123-37.

22. Christen WG, Hennekens CH, Ajani UA, and others. Periodontal disease and risks of cardiovascular disease. *Circulation* 1998; 97:821.

23. Genco R, Chadda S, Grossi S, and others. Periodontal disease is a predictor of cardiovascular disease in a native American population (abstract). *J Dent Res* 1997; 76(Spec Iss):408.

24. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol* 2001; 37(2):445-50.

25. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ* 1993; 306(6879):688-91.

26. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *JAMA* 2000; 284(11):1406-10.

27. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. *J Dent Res* 1996; 75(9):1631-6.

28. Esselstyn CB Jr. Updating a 12-year experience with arrest and reversal therapy for coronary heart disease (an overdue requiem for palliative cardiology). *Am J Cardiol* 1999; 84(3):339-41.

29. Shoenfeld Y, Sherer Y, Harats D. Atherosclerosis as an infectious, inflammatory and autoimmune disease. *Trends Immunol* 2001; 22(6):293-5.

CDA's definition of oral health:

Oral health is a state of the oral and related tissues and structures that contributes positively to physical, mental and social well-being and the enjoyment of life's possibilities, by allowing the individual to speak, eat and socialize unhindered by pain, discomfort or embarrassment.

Approved by Resolution 2001.02
Canadian Dental Association Board of Governors
March 2001