

Periodontitis and Cardiovascular disease: Association and Risk

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Abstract:

Periodontitis has been associated with an increased risk of cardiovascular events. Two internet databases were selected in search of appropriate papers for the study purpose: i) the National Library of Medicine, Washington DC, USA (MEDLINE-PubMed) and ii) HINARI Access to Research in Health Program, World Health Organization, Geneva, Switzerland. Both databases were searched from 1985 to 2009. In the past decades, there has been renewed interest in the old hypothesis that infections increase the risk of developing cardiovascular disease. Atherosclerosis has a major inflammatory component and the main underlying pathological pathway for cardiovascular disease (CVD). Periodontal pathogens may be involved in the initiation and progression of atherosclerosis and subsequent coronary heart disease. Periodontal pathogen *Porphyromonas gingivalis* caused atherosclerosis in experimental animals and have been found in human atherosclerotic lesions. The nature of association is unclear because both periodontitis and CVD share a host of risk factors. Epidemiological studies, mainly observational studies (case-control, cross-sectional and prospective cohort studies) are usually the first to generate association data between exposure and adverse health outcomes. Clinical trials with statistically significant positive outcomes are easy to interpret and indicate that the tested intervention is effective in favorably altering the adverse health outcomes. Available evidences suggest that having periodontitis contributes to the total infection and inflammation burden and may contribute to cardiovascular events in susceptible subjects. The impact of periodontal therapy must be further investigated.

Keywords: Periodontitis, associations, cardiovascular disease (CVD).

Introduction:

Periodontitis is a progressive inflammation, leading to the destruction of the tooth supporting tissue and alveolar bone caused by a chronic, mixed infection. The infectious etiology of periodontitis is well established.¹ Cardiovascular diseases comprises a variety of heart and vascular conditions including ischemia, atherosclerosis, peripheral artery disease, infective endocarditis and acute myocardial infarction.² Coronary heart disease (CHD) refers to the failure of coronary circulation to supply adequate circulation to cardiac muscle. Atherosclerosis is the main underlying pathological pathway

for CHD. Periodontal pathogens may be involved in the initiation and progression of atherosclerosis and subsequent coronary heart disease. This was supported by epidemiological case-control studies but also by animal experiments using Apo lipoprotein E-deficient mice.³ Periodontal pathogens *Porphyromonas gingivalis* (*P. gingivalis*) cause atherosclerosis in experimental animals and have been found in human atherosclerotic lesions.⁴ *P. gingivalis* has also been recorded to give rise to inflammatory changes with high affinity to the inner lining of blood vessels.⁵

⁵Cross-sectional and longitudinal epidemiological studies have shown that cases with periodontitis were at a significantly increased risk of developing CHD.⁶ Recent systematic reviews and meta-analysis have identified that elevated antibody titers to bacteria associated with periodontitis can be linked to CHD risk.⁷ Many epidemiological studies have identified statistically significant associations provided high odds ratio (OD)s between Periodontitis and CHD.⁸ Periodontitis is a chronic inflammatory disease, that can result in increased levels of certain serological risk-markers for atherosclerosis as for example C-reactive protein (CRP), leukocytes, certain cytokines, the lipid profile and fibrinogen. This increases the risk of thrombocytes to coagulate and create atheromatous plaque. A recent systematic review concluded that there was strong evidence from cross-sectional studies that plasma CRP was elevated in periodontitis affected subjects compared with controls.⁹

Periodontitis-CVD Association Studies

The relationship between periodontitis and CVD has been summarized in two recent publications based on the principles of meta-analysis. The analysis by Behekar et al. including five prospective cohort studies (86,092 patients) indicated that individuals with periodontitis had a 1.14 times higher risk of developing coronary heart disease than subjects without periodontitis [relative risk 1.14, 95% confidence interval (CI) 1.01-1.2, p<0.001]. The case-control studies (1423 patients) showed greater odds of an association between periodontitis and coronary heart disease [odds ratio (OR) 2.2, 95% CI 1.6-3.1, p<0.001]. The prevalence of coronary heart disease in the cross-sectional studies reviewed (17,724 patients) was

greater among individuals with periodontitis than in subjects without periodontitis.¹⁰

Table-1 provides a summary based on studies on the association and risks between periodontitis and cardiovascular diseases. Meta-analysis of prospective and retrospective follow-up studies have shown that periodontal disease may only slightly increase the risk of cardiovascular disease.¹⁰ Furthermore, when adjusting for demographic factors, studies have shown that the association between periodontitis based on clinical attachment level measurements in relation to coronary artery calcification (Agatasonscore at <http://circ.ahajournals.org/content/108/8/e50>) does not demonstrate a significant association between the two conditions.¹¹ In contrast, others have found a significant relationship between periodontal status based on clinical measures of probing pocket depth/clinical attachment loss and acute myocardial infraction.¹² Most studies provide odds ratios of periodontitis (defined by clinical measures of probing pocket depth and clinical attachment levels) as a risk for cardiovascular disease at levels less than a ratio 3:1.¹³ Studies resulting in higher ORs have commonly used alveolar bone loss as the definition of periodontitis rather than measures of probing pocket depth and clinical attachment level.¹⁴ The study by Beck et al. confirmed that clinical signs (bleeding on probing, probing pocket depth, clinical attachment levels) are not representative for impact of cumulative effects of periodontitis on systemic health. Disparity in prevalence rates of periodontitis in study populations with different age groups, ethnicity, and geographic location makes it difficult to assess the likelihood of an association between periodontitis and cardiovascular diseases.¹⁵

Table-1: Studies assessing association between cardiovascular disease and periodontitis.

Briggs et al. (2006)	Case-control study	92 periodontitis cases and 79 healthy controls	Median CRP in periodontitis subjects 2.1 and 1.4 mg/l in controls. Mean age was 58 years	Periodontitis and risk for coronary heart disease OR=3.1, 95% CI: 1.0-9.2 (p<0.05) CRP (high/low): Periodontitis OR 0.1, 95% CI: 0.5-2.5 NS
Salzberg et al. (2006)	Case-control study	Serum samples were collected from 93 patients with generalized aggressive periodontitis and from 91 healthy controls	Patients with aggressive periodontitis have statistically significant elevations in serum CRP levels compared with subjects without periodontitis	Aggressive periodontitis may induce a severe host inflammatory response that can be linked to systemic disease
Gotsman et al. (2007)	Bacteria	<i>P. gingivalis</i>	201 patients with stable angina or ACS who underwent a periodontal assessment. Severity of coronary artery disease was determined by the number of obstructed coronary arteries	Patients with ACS had significantly higher plaque scores, gingival index, and <i>P. gingivalis</i> counts than stable patients
Zaremba et al. (2007)	Bacteria	<i>A. actinomycetemcomitans</i> <i>C. rectus</i> , <i>F. nucleatum</i> <i>P. gingivalis</i> , <i>P. intermedia</i> <i>T. forsythia</i> , <i>T. denticola</i>	The incidence of periodontal bacteria in atherosclerotic plaque by DNA analysis from 20 subjects was studied	<i>A. actinomycetemcomitans</i> in 1/20 <i>C. rectus</i> in 4/20 <i>F. nucleatum</i> 5/20 <i>P. intermedia</i> in 33% <i>P. gingivalis</i> in 10/20 <i>T. Denticola</i> in 6/20 <i>T. forsythia</i> in 5/20

Lessem et al. (2002)	Retrospective case series	Radiographic evidence of alveolar bone loss	Heart transplant cases were searched through medical records	76% of cases had periodontitis before heart transplantation.
Meurman et al. (2003)	Case-control study of 256 subjects with heart disease and 250 controls	Revised version of the dental index as described by Mattila et al., 1989 and based on clinical and radiological dental examinations (MDI index)	Serum samples of 256 patients with New York Heart Association class II-IV heart disease	High MDI/heart disease OR=1.3 95% CI: 1.2-1.5 Gingivitis/heart disease OR=3.4, 95% CI: 1.7-6.9
Persson et al. (2003c)	Matched case-control study based on consecutive cases of acute coronary syndrome	Alveolar bone loss X4mm at approximal sites Different proportional rates from 0% to 45% of sites with alveolar bone loss	Acute coronary syndrome consecutive cases with hospital diagnosis. Age, gender, smoking status, socio-economic matched controls through medical examination	All subjects: Bone loss >50% OR=14.1 95% CI: 5.5-28.2 Bone loss >30% of sites OR=12.95% CI: 4.7-35.3 in non-smokers: OR=5.9 95% CI: 1.4-24.4
Ravon et al. (2003)	Case-control study	Bone loss X4mm at approximal sites at 43% of sites	Positive or negative duplex ultrasonography	OR: 38.4, 95% CI: 10.6-138.7
Geerts et al. (2004)	Case-control study 108 coronary heart disease cases and 62 healthy control subjects	Periodontitis defined by probing pocket depth . One site or more X5mm New index for periodontal infection risk index (PIRI)	Hospital confirmed cases with coronary heart disease in treatment	OR: 6.5, 95% CI 1.8-23.0) A dose response curve for the PIRI index and coronary heart disease
Nakib et al. (2004)	Epidemiological study of 6931 subjects (1996-2000)	Clinical attachment level X3mm was used to define periodontitis	Coronary artery calcification (Agatston score)	OR: 1.5, 95% CI: 0.5-4.2 Not statistically significant Adjusted for demographic factors
Shimazaki et al. (2004)	Case-control study of 957 subjects	Periodontal status of 1,111 374 males and 583 female Japanese with X10 teeth was studied.	Subjects without heart disease as defined by ECG analysis were studied	PPD definition: OR:1.7 95% CI: 1.01-2.0 CAL definition OR: 1.7, 95% CI: 1.1-2.7)
Engelbreton et al. (2005)	Case-control study	Radiographic assessment of carotid calcification and alveolar bone loss	Ultrasound	OR: 3.6, 95% CI: 1.4-9.7 Association between bone loss and carotid artery plaque
Buhlin et al. (2005)	Case-control study Women only	Assessments were performed for: Number of remaining teeth and pathological periodontal pockets (X4mm), Denture/no dentures Vertical bone loss	Subjects treated for coronary heart disease (angioplasty, bypass grafting)	Periodontal pockets and coronary heart disease OR: 3.8, 95% CI: 1.68-8.74), Dentures and coronary heart disease: OR of 4.6 (0.99-21.28). No relationship to vertical bone loss
Cueto et al. (2005)	Case-control study	Percentage of sites with clinical attachment loss and probing pocket depth were dichotomized	Medically confirmed acute coronary syndrome	Adjusted OR: 3.1
Holmlund et al. (2006)	Case-control study, referred dental patients for periodontal care	Periodontal index scale 0-4 dependent on extent of bone loss (defined as 4/3 root length, bleeding on probing and teeth with furcation)	Subject self-report of a history of myocardial infarction or high blood pressure (not defined)	Periodontitis and myocardial infarction OR: 2.7, 95% CI: 1.1-6.5
Spahr et al. (2006)	Case-control study	CPITN index	Angiography confirmed coronary heart disease and controls with no medical history	OR, 1.67 95% CI, 1.08-2.58
Geismar et al. (2006)	Case-control study	Full mouth periodontal exam. Radiographic assessments	Routine serum assay. Confirmed medical conditions coronary disease (0110) or health (n5140)	OR=6.6 (95% CI: 1.9 to 25.6 Bone Loss
Rech et al. (2007)	Case-control study	Probing pocket depth 43 mm, and/or bleeding on probing, and/ or loss of clinical attachment, and /or bone loss. Diagnosis defined by clinicians unaware of medical status	ACS consecutive cases with hospital diagnosis	OR54.5 95% CI: 1.3-15.6
Seinost et al. (2005)	Case-control study:	61 subjects of 3 months duration including debridement and antibiotics in treatment group	Change in serum CRP following treatment	Healthy subjects 0.8 mg/l (SD0.8), Periodontitis subjects before treatment 1.7 mg/l (SD1.6) Periodontitis subjects after treatment 1.1 (SD10.9)
Best et al. (2005)	Case-control study:	1131 older subjects with or without periodontitis/positive bacterial enzyme test (BANA test) and serum markers of inflammation: CRP, IL-6, TNF- α	Periodontal disease and infection may be modifiable risk indicators to elevated levels of CRP in older people	Periodontitis in the presence of periodontitis (BANA test) is linked to elevated TNF- α , and IL-6 levels in older subjects. This may specifically suggest the link between periodontitis and cardiovascular diseased susceptible subjects

Authors	Study design	Periodontal diagnosis	Medical diagnosis	Association
Mattila et al. (1989)	Case-control study	Total dental index: caries, periodontitis, peri-apical lesions, abscess (14 criteria). Subjects were assigned a score from 0 to 10	ACS consecutive cases, hospital confirmed cases	ACS-cholesterol (p<0.001) ACS-dental index (p<0.01) ACS-smoking (p<0.01) Odds ratio was not calculated
DeStefano et al. (1993)	Epidemiological study based on the NHANES I and the(NHEFS) data	Russell index Gingivitis Periodontitis	Incidence of coronary heartdisease (CHD) 1974-1987	CHD-gingivitis: OR = 0.95, 95% CI: 0.5-1.8 CHD-periodontitis: OR = 1.5, 95% CI: 0.8-3.0 CHD = CHD-Russell index: OR = 1.1, 95% CI: 0.9-1.3
Beck et al. (1996)	A cohort study with combined data from (1) the Normative Aging Study, (2) the Dental Longitudinal Study (Veterans Affair)	Bone loss score based on 5 different categories was assessed. More than 20% sites with bone loss=periodontitis	Coronary heart disease including non-fatal infarction, angina pectoris, and coronary heart disease death	OR=1.5 95% CI: 1.01 to 2.1
Morrison et al. (1999)	A retrospective study 1972-1993, the Nutrition Canadian Survey	Oral health /periodontitis	Mortality experience in coronary heart disease	OR=2.2 95% CI: 1.3 to 3.7
Persson et al. (2002)	Cross-sectional study of older subjects 651	Composite of radiographic evidence and probing pocket depth	Self-reported history of cardiovascular diseases confirmed by medication lists	OR=4.3 95% CI 2.4-7.9

Discussion:

During the last two decades, there has been an increasing interest in the impact of oral health, specifically periodontitis, on cardiovascular disease. In one meta-analysis, the findings resulted in a conclusion that periodontitis and poor oral health overall indeed contribute to the pathogenesis of cardiovascular disease.¹⁶ The meta-analysis by Baheker et al. has demonstrated that having periodontitis might enhance the risk for cardiovascular disease. Some studies have provided high ORs between periodontitis and cardiovascular diseases. Some people with periodontitis developed cardiovascular disease and many did not. Also, many people who do not have periodontitis develop cardiovascular disease, because there are several different causes. Individual clinicians are rarely in a position to confirm associations between exposure and disease though they may suspect them. For accurate information, they must turn to the medical literature, particularly to studies that are carefully constructed and involve a large number of patients. Thus the strength of an association between periodontitis and cardiovascular disease based on epidemiological, and cross-sectional studies varies based on data from studies of different population and subjects. Available studies suggest that periodontitis prevalence in older subjects is high.¹⁷ The aspect of aging as a factor in link between periodontitis and cardiovascular diseases; preventive care may, in fact, be the most important effort in reducing the risk for cardiovascular disease by maintaining healthy oral conditions.

Conclusions:

Available data suggest that periodontitis may have overall health consequences. The term "cardiovascular diseases" is a broad term and efforts are needed to specifically identify which cardiovascular diseases (i.e.

stroke, acute coronary syndrome, and atherosclerosis) can be linked to periodontitis. It also raises a core question about the effect of periodontal treatment in reducing the risk of cardiovascular disease. It is likely that in future periodontal disease may be added to the list of factors, which are used to assess patients' risk profiles for cardiovascular disease should become a standard part of therapy for patients with above diseases. Finally, data suggesting an association between periodontal infections and cardiovascular diseases are strong enough to conclude that cardiologists and periodontists should vigorously pursue identification of the possible connections between these multifactorial diseases.

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