

# Periodontal and Cardiovascular Diseases: Common Inflammatory Mediators

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EXAM #11



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Evidence is mounting to suggest a link between periodontal disease and other systemic disorders with an inflammatory component and this includes cardiovascular disease. This paper critiques the studies which have explored this connection, organizing the epidemiological evidence in terms of cross-sectional and retrospective studies, and more recently prospective and interventional trials. The review also examines common inflammatory mediators, which are associated with both diseases, focusing attention in particular on C-reactive protein (CRP). The emerging hypothesis implies that the most probable mechanism for linkage is inflammation and its sequelae.

Several epidemiological studies have reported associations between periodontal disease and cardiovascular disease (**Table 1**). One of the earliest studies by Matilla et al., reported that dental health including periodontal health was significantly worse in patients with acute myocardial infarction than in controls.<sup>1</sup> DeStefano et al., analyzed data from the National Health and Nutrition Examination Study I (NHANES) and its epidemiological study.<sup>2</sup> They reported that participants in the study who had periodontitis had a twenty-five percent (25%) increased risk of coronary heart disease (CHD) relative to those with minimal periodontal disease. Beck et al.,

used combined data from the Normative Aging Study and the Dental Longitudinal Study sponsored by the United States Department of Veterans Affairs.<sup>3</sup> They concluded that the levels of bone loss and cumulative incidence of total CHD and fatal CHD indicated a biologic gradient between severity of exposure and occurrence of disease. Persson et al., studied clinical periodontal conditions, alveolar bone loss, self reported medical histories, and carotid calcifications from panoramic radiographs in older adults.<sup>4</sup> They reported an odds ratio of 2:1 for carotid calcifications and periodontitis. In another study based on a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study, Beck et al., concluded that clinical signs of periodontal disease were not associated with CHD, but systemic antibody response was associated with CHD in both smokers and non smokers.<sup>5</sup> Geismar et al., studied the association of periodontal disease and CHD and attempted to explore common risk factors.<sup>6</sup> They found a strong association between periodontal disease and CHD in subjects less than 60 years of age. They also reported that this association could be attributed to some extent to diabetes and smoking. A similar finding was reported in a recent study by Dietrich et al.<sup>7</sup> In subjects who were followed for up to thirty-five years, chronic

periodontitis was found to be associated with CHD among men less than sixty years of age, independent of established cardiovascular risk factors.

Several reports have shown increased serum C-reactive protein (CRP) levels associated with periodontal disease severity (**Table 2**). Ebersole et al., conducted the initial study measuring serum CRP and haptoglobin (Hp) levels in patients with periodontal disease.<sup>8</sup> Patients with the most severe disease demonstrated nearly a seventeen-fold increase in CRP levels compared to controls. Their results showed mechanical debridement in periodontitis patients did not lower serum CRP levels, however there was a decrease in Hp levels measured at twelve months. Patients taking 50 mg of the anti-inflammatory drug flurbiprofen displayed decreased levels of CRP over a two-year period. The first study to report a decrease in serum CRP levels following non-surgical periodontal treatment was conducted by Matilla et al.<sup>9</sup> They utilized a new assay, the high sensitivity C-reactive protein (hsCRP), to quantify serum levels. They found elevated CRP levels to be higher in individual subjects with greater disease severity than non-diseased controls. Treatment consisted of mechanical debridement and the use of an antibiotic (metronidazole) as needed for selective cases. Matilla et al., noted a

**Table 1. Epidemiological studies showing association between cardiovascular disease and periodontitis.**

	Authors	Study Design	Periodontal Status	Cardiovascular Disease	Level of Association
1.	Matilla et al. (1989) <sup>1</sup>	2 separate case-control studies	Total dental index (caries, periodontitis, PA lesions, pericoronitis)	Myocardial infection (MI)	MI- Total dental index (p<0.01)
2.	DeStefano et al. (1993) <sup>2</sup>	Prospective cohort study	Gingivitis Periodontitis	Coronary Heart Disease (CHD), Total mortality	CHD-gingivitis: Adjusted RR 1.05 CHD-periodontitis: Adjusted RR 1.25
3.	Beck et al. (1996) <sup>3</sup>	Cohort study	Mean bone loss and worst probing depth scores	Coronary heart disease (CHD), Fatal CHD	Total CHD-Bone loss OR 1.5 95% CI 1.06-2.15
4.	Persson et al. (2002) <sup>4</sup>	Cross sectional study of subjects 60-75 yrs	Radiographic bone loss, clinical periodontal status	Self-reported hx of CV diseases, radiographic evidence of carotid artery calcification	OR- 4.3 95% CI 2.4-7.9
5.	Beck et al. (2005) <sup>5</sup>	Cross-sectional study of a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study	Clinical probing depth and attachment level measurements, serum IgG levels to 17 selected periodontal organisms	Coronary Heart Disease (CHD)	Clinical signs of periodontal disease were not correlated with CHD but systemic antibody response was correlated with CHD
6.	Geismar et al. (2006) <sup>6</sup>	Case-control study	Full mouth periodontal examination, radiographic bone levels	Verified CHD or healthy subjects	OR 6.6 95% CI 1.9-25.6 for bone loss > 4 mm in subjects less than 60 years
7.	Dietrich et al. (2008) <sup>7</sup>	Long term longitudinal cohort study	Full mouth periodontal and radiographic examination conducted triennially	Myocardial infarction, angina pectoris, fatal CHD	HR 2.48 95% CI 1.49-4.12 for mean bone loss >1.5 HR 1.10, 95% CI 1.05-1.17 per 10mm increase in cumulative pocket depth

generalized decrease in CRP in the whole population, however post-treatment CRP levels did not significantly decrease in all participating subjects suggesting patient susceptibility may play a crucial role. D'Aiuto et al., treated patients with non-surgical mechanical therapy, recording serum CRP levels at baseline, two and six months post treatment.<sup>10,11</sup> They noted subjects with better clinical responses to periodontal treatment resulted in a greater decrease in CRP levels. D'Aiuto et al., also demonstrated a statistically significant decrease in serum CRP at six months but not at the two month time point. They determined patients who responded better to periodontal therapy

were four times more likely to reduce their risk category for cardiovascular disease.

Western populations, including Northern Europeans and North Americans, exhibit a higher level of serum CRP in comparison to other populations. Yamazaki et al., conducted a study with Japanese subjects who displayed baseline levels of serum CRP to be much lower than western populations with the same periodontal disease severity.<sup>12</sup> These subjects received non-surgical mechanical debridement, surgical intervention when indicated, and 4 days of non-specified antibiotics. Results showed a trend for decreased

CRP levels after treatment. Pitiphat et al., conducted a study in a Thai population that displayed lower basal levels of serum CRP compared to western populations.<sup>13</sup> Serum CRP levels correlated with periodontal disease severity. This study demonstrated that periodontal infection with *Porphyromonas gingivalis* may contribute to a systemic inflammatory burden and elevated serum CRP in otherwise healthy individuals. Tonetti et al., compared periodontal treatment outcomes and endothelial function.<sup>14</sup> Improvement of endothelial function was related to a reduction in the number of periodontal lesions. Patients underwent intensive non-surgical therapy resulting

**Table 2. Longitudinal studies evaluating effect of periodontal therapy on inflammatory markers.**

Citation	Materials and Methods	Results
Ebersole, J et al. Clin Exp Immun. 1997	Adult periodontitis, gingivitis control CRP measurements at baseline, every 2 months for 6 months. One group scaling and root planing Three groups received Flurbiprofen for 24 months.	Elevated levels CRP/Hp than controls (9.12 mg/l versus 2.17 mg/l for CRP) and (3.68 g/l versus 1.12 g/l for Hp). Most severe patient CRP levels 17-fold increase over normal Most severe groups Hp levels elevated, decreased Hp (3.68 versus 2.38 g/l; $p < 0.01$ ) after treatment. 50 mg of flurbiprofen, 40-50% decrease Hp ( $p < 0.005$ ), 35-40% for CRP over 2 yrs from baseline ( $p < 0.05$ ).
Mattila, K et al. BMC Infect. Dis. 2002	35 patients adult periodontitis Mechanical therapy, metronidazole if indicated. CRP levels measured at baseline, 6 weeks	CRP decreased from 1.05 mg/l to 0.7 mg/l ( $P = 0.05$ ) after treatment.
D'Aiuto, F et al. J. Periodontal Research 2004	94 subjects, generalized severe periodontitis. Middle age 42% current smokers, 65% European Caucasians. Examined at baseline, 2 and 6 months Non-surgical periodontal therapy	Presence of three bacteria <i>P. gingivalis</i> (77%), <i>T. Forsythensis</i> (78%), <i>A. actinomycetemcomitans</i> (45%). Severe disease increased chance of higher CRP-associated CVD risk (OR 5.6, 95% CI 1.2-27.4). Better response to therapy more decreased risk category (OR 4.8, 95% CI 1.4-15.8).
D'Aiuto, F et al. J. Dental Research 2004	94 subjects generalized severe periodontitis Non-surgical periodontal treatment Therapeutic phase completed 1-3 months from baseline Re-examination at 2 and 6 months post treatment	Differences significant between baseline, 2 and 6 months for IL-6 ( $p < 0.001$ , decrease 0.2 ng/L, 95% CI 0.1-0.4 ng/L) and baseline and 6 months for CRP ( $p < 0.0001$ , decrease 0.5 mg/L, 95% CI 0.4-0.7). 79.2% of patients responding better to treatment decrease in serum CRP
Yamazaki, K et al. J. Periodontal Research 2005	24 patients moderate to advanced periodontitis, 21 subjects without. Mechanical plaque control, scaling and root planing, unspecified antibiotics.	CRP lower than other populations (317.0 ng/ml and 261.5 ng/ml at baseline and reassessment) CRP patients showed a trend, higher levels at baseline ( $p = 0.056$ ), declining after treatment not significant ( $p = 0.138$ ).
Pitiphat, W et al. J. Clinical Periodontology 2008	21 generalized periodontitis 62 localized periodontitis 38 healthy controls. <i>P. gingivalis</i> in subgingival plaque samples analyzed.	CRP levels lower than reported in the western populations <i>P. gingivalis</i> more prevalent in both periodontitis groups than controls CRP significantly higher, generalized and localized periodontitis than controls (1.78 and 0.65 mg/l versus 0.25 mg/l, $p < 0.001$ ). Periodontitis and <i>P. gingivalis</i> associated with increased CRP levels ( $p < 0.001$ ).
Tonetti, M et al. New England Journal of Medicine 2007	120 patients, generalized severe periodontitis Intensive periodontal therapy (61) or community based care (59). Dental exams and vascular studies 1, 7, 30, 60, 180 days. Scaling and Root planing, delivery of localized minocycline (arestin)	24 hrs therapy flow mediated dilation significantly lower in the intensive group than control at 2 and 6 month (1.4%; 95% CI, 0.5 to 2.3; ( $p = 0.002$ )). 24 hours after treatment levels of IL-6 and CRP were higher in intensive group than control. 6 months after treatment benefits of oral health associated with improved endothelial function and decreased CRP levels.

at twenty-four hours in endothelial dysfunction, a decrease in endothelial flow and an increase in inflammatory markers including CRP. However, six-months post-treatment CRP levels decreased and patients showed improved endothelial function and an increase in endothelial flow rate. Thus, a majority of studies demonstrated that non-surgical periodontal therapy led to a decrease in serum hsCRP at selective time points, in conjunction with improved clinical periodontal parameters and endothelial function.

A potential link between CHD and chronic periodontitis (CP) may relate to common inflammatory mediators operable in both diseases. CP is an inflammatory disease, initiated by plaque accumulation in the gingival sulcus whose rate of progression is determined by the host response. Studies have demonstrated that there is a local response to plaque reflected by increased levels of cytokines such as IL-1, tumor necrosis factor alpha (TNF $\alpha$ ) and IL-6 in gingival crevicular fluid of CP patients.<sup>15,16</sup> In addition, cells extracted from inflamed gingival tissue produce elevated levels of these inflammatory mediators in vitro.<sup>17</sup> Moreover, heightened systemic levels of these biomarkers of inflammation have been noted in the serum of CP patients, coupled with increased numbers of leukocytes and decreased numbers of erythrocytes and hemoglobin.<sup>18</sup> Thus, CP may be viewed as a disease with both local and systemic inflammatory ramifications, which could impact distal organ systems due to “dumping” high levels of these bioactive products into the circulatory system.

Another biomarker of inflammation recently described to be elevated in CP patients is C-reactive protein. CRP is an acute phase reactant synthesized in the liver that promotes the phagocytosis of bacteria. Periodontal disease severity seems to correlate with increasing levels of serum CRP (**Table 2**). Elevated levels of CRP have been reported in conjunction with increased serum IL-6.<sup>10</sup> Mechanistically, this is important since IL-6 is not only a potent inducer of hepatic CRP synthesis, but it is also an activator of endothelial inflammation. In this manner, IL-6 induced CRP associated with periodontal disease may

contribute to the observed association of impaired endothelial function and vascular stress noted in cardiovascular patients. D’Aiuto observed the best clinical response to non-surgical periodontal therapy in patients that exhibited the greatest reduction in serum CRP and IL-6 six months post treatment.

Atherosclerosis is a complex disease associated with several well known risk factors including hyperlipidemia, hypertension, cigarette smoking, diabetes mellitus and family history of premature vascular disease. Although these risk factors are statistically associated with cardiovascular events, the precise pathophysiology and sequence of events remains elusive. Disruption of the unstable arterial plaque may be the final event initiating the cascade of arterial wall changes that culminate in myocardial infarction or stroke. Basic science studies, epidemiology and clinical trials support the hypothesis that inflammation is a critical factor in this cascade of arterial changes. Biomarkers of inflammation, such as CRP, can now be routinely measured to help identify patients at risk. High CRP levels correlate with carotid artery thickness and numerous downstream vascular events. Evidence is accumulating that CRP levels provide further predictive value for the risk of cardiovascular events for any given level of serum cholesterol.

Serum CRP levels are significantly reduced by statin therapy for hyperlipidemia and this may play a role in the reduction of cardiac events accompanying statin use. The primary objective of the *Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin* (JUPITER) trial was to investigate whether daily statin (rosuvastatin 20 mg) treatment, as compared to placebo, could regulate cardiovascular health and vascular events in subjects with normal cholesterol profiles but high levels of serum hsCRP (> 2mg/ml) over a five-year period.<sup>19</sup> The trial was halted after a median follow-up of 1.9 years. The statin group exhibited a fifty-percent (50%) reduction in LDL cholesterol levels, a thirty-seven (37%) decrease in hsCRP, and a significantly reduced incidence of major cardiovascular events compared to placebo. This study strengthens

the hypothesis that CRP plays a major role in vascular inflammation and atherosclerosis, and suggests that commonly used pharmacologic agents, such as statins, may act to attenuate these pathologic alterations. Given the results of Ridker’s JUPITER trial, it would seem logical to design an analogous study utilizing CP patients who were systemically healthy. One cohort would receive traditional periodontal therapy and a placebo while the other would receive traditional periodontal therapy and a daily statin. Following these subjects over a five-year period, it could be assessed if periodontal therapy altered the incidence of cardiovascular events, and if the combination with statins potentiated this effect. Most importantly, it could be determined if the incidence of cardiovascular events correlated with the levels of circulating markers of inflammation, endothelial function and periodontal clinical parameters.

In conclusion, epidemiological evidence supports a link between periodontal and CHD. A majority of the intervention studies demonstrated that non-surgical periodontal therapy led to a decrease in serum hsCRP at selective time points, in conjunction with improved clinical periodontal parameters and endothelial function. Some studies imply that the best clinical responses were noted in patients that exhibited the greatest reduction in IL-6 and serum CRP. These findings strengthen the hypothesis that the most likely mechanism linking periodontal and CHD are common inflammatory mediators, specifically IL-6 and CRP.

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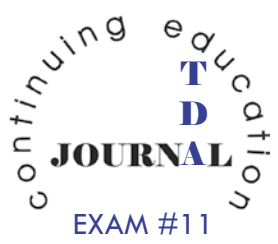
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## Questions for Continuing Education Article - CE Exam #11

- The initial study linking periodontal and coronary heart disease was published \_\_\_\_ years ago.
  - 5
  - 10
  - 15
  - 20
- Beck et al., reported a biological gradient between periodontal disease severity and coronary heart disease based upon this clinical parameter:
  - Percent attachment loss
  - Plaque index
  - Gingival index
  - Percent bone loss
- Both Giesmar et al., and Dietrich et al., found that periodontal disease was associated with coronary heart disease in patients:
  - Over sixty years of age
  - Under sixty years of age
  - Under fifty years of age
  - Under forty years of age
- The first study reporting increased levels of serum C-reactive protein were associated with periodontal disease severity was conducted by:
  - Ebersole et al.
  - Genco et al.
  - Offenbacher et al.
  - DeStefano et al.
- Western populations exhibit a(n) \_\_\_\_ basal level of serum C-reactive protein compared to other populations.
  - Higher
  - Identical
  - Lower
  - Insignificant
- Twenty four hours following intensive, non-surgical periodontal therapy, subjects exhibited \_\_\_\_ levels of serum C-reactive protein.
  - Increased
  - No change in
  - Decreased
  - Non-existent
- Chronic periodontitis patients exhibit the following:
  - Elevated numbers of erythrocytes
  - Increased serum hemoglobin
  - Elevated numbers of peripheral blood leukocytes
  - Increase basophils
- C-reactive protein is produced by the following:
  - Kidney
  - Liver
  - Macrophage
  - Neutrophil
- Which of the following is a potent inducer of C-reactive protein synthesis?
  - IL-2
  - IL-4
  - IL-6
  - IL-10
- Which of the following pharmacologic agents can reduce serum levels of C-reactive protein?
  - Antibiotics
  - Statins
  - Aspirin
  - Anti-hypertensives

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3.     a     b     c     d	8.     a     b     c     d
4.     a     b     c     d	9.     a     b     c     d
5.     a     b     c     d	10.   a     b     c     d

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