# C-reactive protein, cardiovascular disease, and periodontal disease

C-reactive protein (CRP) is an indicator of inflammation and has already been linked to an increased risk of heart attack and stroke. It is one of the acute phase proteins that increase during systemic inflammation. It has been suggested that testing CRP levels in the blood may be a new way to assess cardiovascular disease (CVD) risk. The most important role of CRP is its interaction with the complement system, which is one of the body's immunologic defence mechanisms (1).

It has been suggested that both CRP and low-density lipoprotein (LDL) cholesterol levels are elevated in persons at risk for cardiovascular events. Nevertheless, population-based information directly comparing these two biological markers was not available until recently. Data from Brigham and Women's Hospital and Harvard Medical School suggested that the CRP level is a stronger predictor of cardiovascular events than the LDL cholesterol level (2). In a study that was published in the 10 December 2003 issue of the Journal of the American Medical Association, researchers from Harvard Medical School and Harvard-affiliated Brigham and Women's Hospital found a strong link between levels of CRP in the blood and the future development of high blood pressure (3). In a more recent report that went online in the 'rapid track' portion of the website of Circulation, the journal of the American Heart Association, 26 January 2004, it was stated that when mice genetically prone to develop atherosclerosis also produced a human form of CRP, they developed larger lesions associated with the build up of fatty plaque in the arteries than did those who did not produce the protein. The study supports the use of CRP as a marker of risk for heart disease, and identifies at least one mechanism by which the protein contributes to the development of atherosclerosis. It is the first time these facts have been demonstrated in living animals (4).

A high sensitivity assay for CRP test (hs-CRP) is now widely available. While this is not a specific test, does give a general indication of acute inflammation. The CRP test might be used to check for rheumatoid arthritis or rheumatic fever flare-ups, or could be useful to monitor response to therapy. However, even in instances of inflammation in rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematous, the CRP levels may not always be elevated. The reason for this is not known at this time. Thus, a low CRP level does not always mean that there is no inflammation present.

Normally there is no CRP in the blood serum. As the CRP is a general test, a positive CRP may indicate any of a number of things:

- rheumatoid arthritis
- rheumatic fever
- cancer
- tuberculosis
- pneumococcal pneumonia
- myocardial infarction
- systemic lupus erythematosus (SLE).

Positive CRP results also occur during the last half of pregnancy or with the use of oral contraceptives (1).

C-reactive protein levels fluctuate from day to day, and levels increase with ageing, high blood pressure, alcohol use, smoking, low levels of physical activity, chronic fatigue, coffee consumption, having elevated triglycerides, insulin resistance and diabetes, taking oestrogen, eating a high-protein diet, and suffering sleep disturbances, and depression. Alcohol can cause inflammation and raise CRP. At this time, the best way we know to reduce CRP levels are exercise and a diet that includes omega-3 fatty acids. Statins appear to protect against inflammation as well as cholesterol (1).

The American Association and the Centers for Disease Control and Prevention recently published a joint scientific statement about using inflammatory markers in clinical and public health practice. This statement was developed after systematically reviewing the evidence of association between inflammatory markers (mainly CRP) and coronary heart disease and stroke. If a person's cardiovascular risk score, judged by global risk assessment, is low (the possibility of developing CVD is <10% in 10 years, no test is immediately warranted (5). The risk assessment tool uses information from the Framingham Heart Study. This tool is designed for adults who do not have heart disease or diabetes. If the risk score is in the intermediate range (10–20% in 10 years), such a test can help predict a cardiovascular and stroke event and help direct further

evaluation and therapy. However, the benefits of such therapy based on this strategy remain uncertain. A person with a high-risk score (>20% in 10 years) or established heart disease or stroke should be treated intensively regardless of hs-CRP levels (6).

What is the normal range of hs-CRP level?

- If hs-CRP level is lower than 1.0 mg $L^{-1}$, a person has a low risk of developing CVD
- If hs-CRP is between 1.0 and 3.0 mg $L^{-1}$, a person has an average risk
- If hs-CRP is higher than 3.0 mg $L^{-1}$, a person is at high risk.

There are also connections between CRP and oral health. Alveolar bone loss around posterior teeth was associated with elevated CRP in Japanese men, suggesting an association between periodontal disease and increased risk of type 2 diabetes and CVD (7). The extent of increase in CRP levels in periodontitis patients depends on the severity of the disease after adjusting for age, smoking, body mass index, triglycerides and cholesterol. In addition, there are elevated levels of CRP associated with infection with subgingival organisms often associated with periodontal disease, including *P.g.*, *P.i.*, *C.r.*, and *B.f.* As recent investigations stress the role of moderate elevated CRP plasma levels as a risk factor for CVD, the positive correlation between CRP and periodontal disease might be a possible fundamental conduit in the association between periodontal disease and the observed higher risk for CVD in these patients (8). Periodontitis results in higher systemic levels of CRP, IL-6 and neutrophils. These elevated inflammatory factors may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk for cardiac or cerebrovascular events (9). Results from a recent study suggest that destructive periodontal disease and disease progression are associated with changes in serum components consistent with an acute-phase response (10).

Elevated levels of CRP and decreased plasma adiponectin are associated with increased risk of atherosclerosis. In addition recent observations suggested that adiponectin and tumour necrosis factor-α (TNF-α) suppressed each other's production. As periodontal disease has been suggested to act as a risk factor for atherosclerosis, one study examined the effects of antimicrobial periodontal treatment on CRP, adiponectin, and TNF-α levels. Periodontal treatment is effective in reducing CRP and TNF-α, while adiponectin does not appear to be influenced by periodontal treatment. Elevated levels of CRP and TNF-α may be associated with increased risk for future development of atherosclerosis in periodontitis patients (11).

The acute-phase response involves molecules including TNF-α, interleukin-6 (IL-6), and CRP. This study aimed to determine whether subgingival scaling resulted in rapid changes in plasma concentrations of these molecules. Chronic periodontitis patients undergoing an episode of subgingival scaling show a significant elevation in circulating TNF-α and IL-6. This may account for anecdotal reports of pyrexia following treatment and may be significant in terms of the relationship between periodontal disease, bacteraemia and CVD (12).

Recent studies implicate exposure to systemic conditions involving chronic inflammation, including chronic periodontitis, in the aetiology of atherosclerosis. A systematic review of the literature was conducted to assess the association between chronic inflammatory periodontal disease and atherosclerosis. The question asked was 'Does periodontal disease influence the initiation/progression of atherosclerosis and, therefore, cardiovascular disease (CVD), stroke, and peripheral vascular disease (PVD)?' The databases searched included MEDLINE, pre-MEDLINE, MEDLINE Daily Update, and the Cochrane Controlled Trials Register to identify human studies that related variables associated with atherosclerosis to periodontal disease. Searches were conducted for papers published from 1966 to March 2002. Inclusion criteria were published randomized-controlled clinical trials (RCTs), longitudinal, cohort, and case–control studies were included. Study participants included those with atherosclerosis, myocardial infarction (MI), stroke, or PVD. Oral conditions included periodontal disease. The author concluded that periodontal disease may be modestly associated with atherosclerosis, MI and CVD. Additional large-scale longitudinal epidemiologic and intervention studies are necessary to validate this association and to determine causality (13). In the meantime, optimal professional and self-care is indicated to control the bacterial aspects of periodontal disease.

## References


1 http://www.nlm.nih.gov/medlineplus/ency/article/003356.htm.
2 Ridker PM, Nader R, Rose L et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *NEJM* 1999;**347 (20):**1557–65.
3 Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003;**290:**2945–51.
4 http://www.sciencedaily.com/releases/2004/01/040127081010.htm.
5 Pearson TA, Mensah GA, Alexander RW et al. Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107:**499–511, doi:10.1161/01.CIR.0000052939.59093.45
6 http://www.americanheart.org/presenter.jhtml?identifier = 3003500.

7 Saito T, Murakami M, Shimazaki Y et al. Association between alveolar bone loss and elevated serum C-reactive protein in Japanese men. *J Periodontol* 2003;**74:**1741–6.
8 Noack B, Genco R, Trevisan M et al. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol* 2001;**72:**1221–7.
9 Loos BG, Craandijk J, Hoek FJ et al. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000;**71:**1528–34.
10 Craig RG, Yip JK, So MK et al. Relationship of destructive periodontal disease to the acute-phase response. *J Periodontol* 2003;**74:**1007–16.
11 Iwamoto Y, Nishimura F, Soga Y et al. Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. *J Periodontol* 2003;**74:**1231–6.
12 Ide M, Jagdev D, Coward PY et al. The short-term effects of treatment of chronic periodontitis on circulating levels of endotoxin, C-reactive protein, tumor necrosis factor-α, and interleukin-6. *J Periodontol* 2004;**75:**420–8.
13 Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. *Ann Periodontol* 2003;**8:**38–53.

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