

Periodontitis and C-reactive protein as a cardiovascular risk factor—a causal relationship?

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ABSTRACT C-reactive protein is an acute-phase protein associated with systemic and local inflammation including cardiovascular disease and periodontitis. With increasing attention to this protein as a risk marker of cardiovascular disease, and the possible link between periodontal disease and systemic diseases, there is accumulating interest on the impact of periodontal disease on coronary heart disease. This paper provides an overview of the current evidence about this association of and the potential effects of periodontal treatment as a means of reducing cardiovascular risk (as measured by C-reactive protein concentration). Based on currently available information, C-reactive protein levels correlate with the severity of periodontal disease, and its treatment appears to reduce C-reactive protein levels by varying degrees. However, it is premature to confirm a causal relationship between periodontal disease and cardiovascular disease, as measured by C-reactive protein levels. Further longitudinal studies are needed before such an association can be established.

Key words: Cardiovascular diseases; C-reactive protein; Dental prophylaxis; Periodontitis

Introduction

Periodontitis is a disease of the tooth-supporting structures that usually has an infective etiology and a subclinical chronic course ¹. Unlike its name, an acute-phase reaction has chronic components, and represents the immunoinflammatory response of the body to different insults, including periodontitis ^{2,3}. C-reactive protein (CRP) has been recognized as one of the markers of acute-phase reactions and inflammation. Its utility for quantification of systemic inflammatory alterations has been boosted by recent improvements in corresponding assays ⁴, making it possible to measure very low levels of CRP (referred to as high-sensitivity CRP or hsCRP). Recently, hsCRP has been recognized as an independent predictor of chronic heart disease ⁵; increased levels also having been noted in acute ischemia and myocardial infarction ⁶. The landmark study

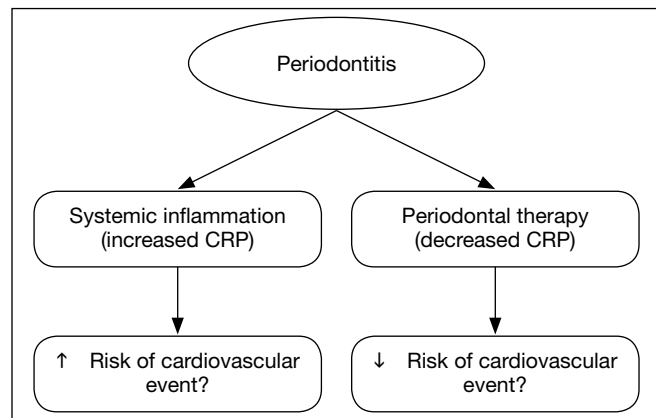


Figure 1 Possible link between periodontitis, C-reactive protein (CRP), and cardiovascular problems

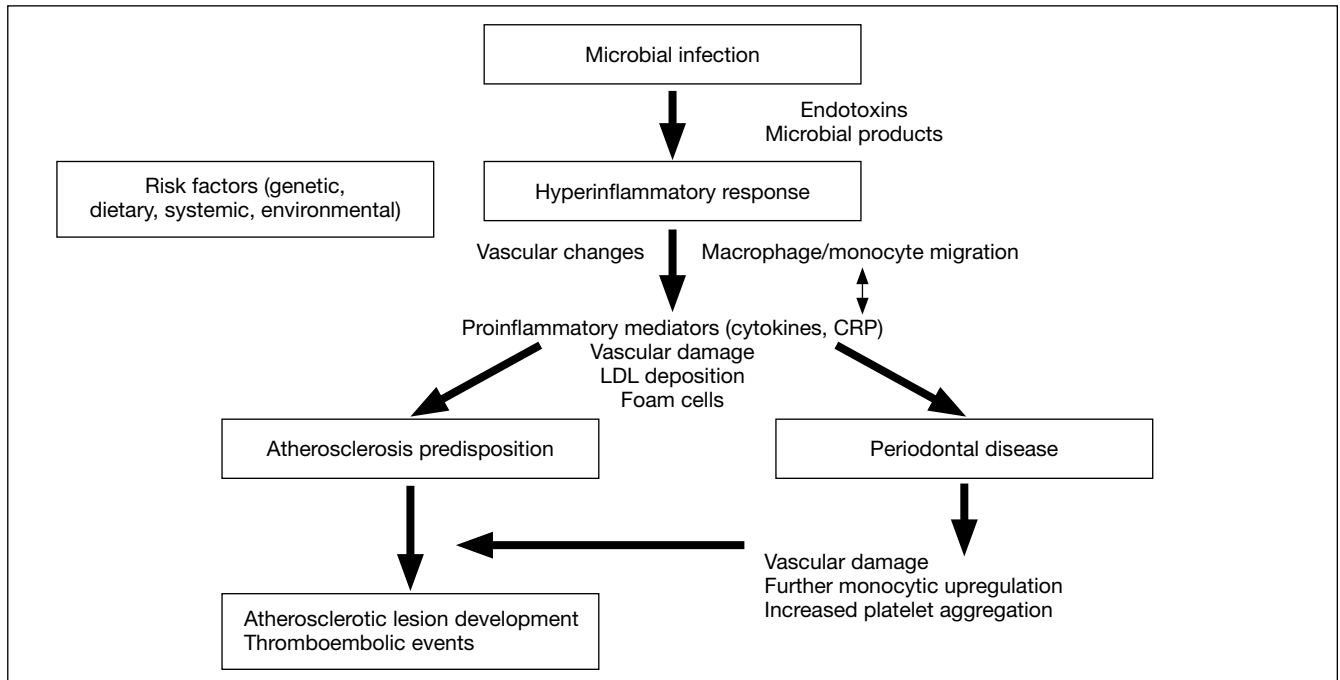
on the association between oral infections and coronary heart disease was first reported by Mattila ⁷, and led to a series of case control and cohort studies. Quantification of acute-phase reactions and their association with the extent of periodontitis has been recognized ⁸⁻¹⁰. Emerging evidence points towards a short-term reduction in CRP levels following management of periodontitis. As illustrated in Figure 1, the two main questions arising from the plausible connection between CRP with periodontitis and cardiovascular disease are therefore:

1. What is the relationship between periodontitis, CRP, and atherosclerosis?
2. Would periodontal therapy reduce cardiovascular

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* CRP denotes C-reactive protein, and LDL low-density lipoprotein

Figure 2 Proposed mechanisms of atherosclerosis and possible link with periodontal disease ¹⁶ *

risk, as measured by CRP levels?

Acute-phase reaction and C-reactive proteins

It has long been speculated that inflammation in different organ systems may have distant effects via proinflammatory mediators. The latter could be produced either at the site of initial inflammation or have a more remote origin, before causing different systemic effects. These systemic effects could be both acute and chronic in nature, but have been classically named as an ‘acute-phase response’².

It is difficult to quantify the magnitude of the widespread effects of acute-phase responses, due to the complex nature of the inflammatory and immune reactions. It is therefore also difficult to devise a reliably predictable specific marker that can adequately link local inflammation (as in the periodontium) to systemic effects (e.g. on the cardiovascular system). Thus, different markers have been used to study systemic changes related to local inflammation, of which CRP is but one.

C-reactive protein is one of the first acute-phase reactants to be recognized. It was first identified in 1930 among patients suffering from pneumococcal pneumonia. It could produce flocculation by binding with the C-polysaccharide from *Streptococcus pneumoniae*, and was

subsequently named CRP. Like most other acute-phase proteins, CRP is synthesized in the liver and its production is induced by interleukin (IL)-6¹¹.

The functions of CRP are not clearly defined, but it is reported to have opsonic and proinflammatory activities. Because of its unique pentameric structure, it can bind to negatively charged molecules on cell membranes^{12,13}. This mechanism forms the basis of its opsonization function, whereby it binds microbes that are then removed from circulation by phagocytosis. In atherogenesis, the opsonization of low-density lipoproteins appears to mediate uptake by macrophages, which in turn stimulates production of proinflammatory mediators such as IL-1, IL-6, and tumor necrosis factor- α . Moreover, CRP has also been shown to activate the classical pathway of the complement system¹⁴.

In March 2002 the Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA) convened a Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice⁵. This workshop looked into the utility of proinflammatory markers for the prediction of cardiovascular events and the assessment of prognosis. One of the markers was hsCRP. On the basis of pooled epidemiological data from about 40 000 individuals, three categories of CRP-associated risk of future cardiovascular

disease were identified: low-risk group (hsCRP, <1 mg/L), medium-risk group (hsCRP, 1-3 mg/L), and high-risk group (hsCRP, >3 mg/L). Different cut-off values have been proposed by other investigators, for example a value of 2.08 mg/L was proposed by Ridker *et al*¹⁵. It seems possible that in due course and after more studies, the cut-off value for hsCRP used to predict cardiovascular disease risk may well be lowered.

In this context, CRP and certain other inflammatory mediators have a distinct advantage in that they not only provide predictive information, but because of their role in disease pathogenesis, they may also serve as important therapeutic targets⁴.

Microbial infections, periodontal disease, and atherosclerosis

Atherosclerosis is a focal thickening of arterial intima and media of medium-to-large elastic vessels, which tends to occur at sites of turbulent blood flow. These arteries are damaged by deposition of lipid-rich materials, connective tissue elements, and smooth muscle cells. The process can be further modified by other risk factors, including infections, smoking habit, high cholesterol diets, genetic and systemic conditions such as diabetes and hypertension.

The possible mechanism of atherosclerosis and its relationship to microbial infection and periodontal disease is illustrated in Figure 2¹⁶. Microbial infections including periodontitis establish a burden of bacterial pathogens, bacterial antigens, and endotoxins which trigger the inflammatory response. They include the release of inflammatory cells, cell adhesion molecules, CRP, prostaglandins and ILs that lead to a cascade of events, such as deposition of lipoproteins to form foam cells. The host response can also result in production of antibodies including those to bacterial heat-shock proteins of the heart and vasculature, thus contributing to atherogenesis and thromboembolic events. The resulting plaques may reduce vascular patency and atheroma formation in the wall can eventually occlude the lumen. The process of periodontal destruction also causes vascular damage, up-regulates monocytes, and increases platelet aggregation, all of which could further enhance atherosclerosis.

C-reactive protein and periodontitis

Periodontal disease in its less intense forms (gingivitis) affects almost every individual, while more advanced

forms (chronic and aggressive periodontitis) affect about 10 to 15% of adults^{17,18}. Periodontitis is caused by subgingival microbes, the most important being *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia* (previously known as *Bacteroides forsythus*), and *Treponema denticola*. Most such infections follow a subclinical, chronic course resulting in inflammatory changes and periodontal destruction¹. Not surprisingly, CRP levels may be elevated in patients suffering from periodontitis^{9,10}.

Relationship of C-reactive protein with periodontitis

The relationship of periodontal disease to CRP has been shown in cross-sectional studies (Table 1)¹⁹⁻²⁸. Earlier studies utilized the latex agglutination assay available at that time, the presence or absence of CRP being reported. One of the first¹⁹ showed that 20 out of 40 cases with periodontitis (including periodontal abscess) were CRP-positive. A subsequent study by Boucher *et al.*²⁰ assessed 59 systemically healthy subjects with varying degrees of periodontal disease, ranging from acute periodontal abscesses to chronic gingivitis. Of 10 patients, nine with an acute periodontal abscess were CRP-positive, as opposed to none of the controls with chronic gingivitis. It was therefore inferred that periodontal infection contributes to presence of CRP in serum; the limit for detection being about 10 mg/L.

Recent studies have involved more sensitive assays, with detection limits as low as 0.21 mg/L. One such study from Denmark by Loos *et al.*²¹ investigated systemic levels of inflammatory markers of cardiovascular disease (hsCRP, IL-6, total leukocyte and differential leukocyte count) in an unselected population with and without periodontitis. The patients were divided into three groups based on radiographic evidence of bone loss. While 90% of all the patients had detectable hsCRP, there was a significant difference in median values between the three groups; those with more advanced bone loss exhibited higher hsCRP levels. Similar findings were reported by others²²⁻²⁴. Craig *et al.*²⁵ estimated an odds ratio of 14.1 for having 'high normal' hsCRP in patients exhibiting disease progression. A trend towards increased hsCRP levels and progression of periodontal disease was evident in this study, leading the authors to suggest that periodontitis may be a modifiable risk marker of increased CRP and subsequent cardiovascular events. Salzberg *et al.*²⁹ and Cairo *et al.*²⁶ also found higher hsCRP in patients with aggressive periodontitis. In Asia, a recent study in Thailand reported

Table 1 Summary of reports of the relationship between C-reactive protein (CRP) and periodontal status^{19-28 *}

Study	Subjects	Assay	Periodontitis	Systemic	Confounders	Results
Adam and Christidis (1962) ¹⁹	40	Non-hsCRP	All periodontal patients (including periodontal abscess)	Not available	Not available	Of 40 patients, 20 were positive for CRP
Boucher <i>et al.</i> (1967) ²⁰	59 periodontal, 7 control	Non-hsCRP	59 Patients	H	Not available	Positive CRP in 90% of abscess patients; negative in chronic gingivitis and controls
Loos <i>et al.</i> (2000) ²¹	150	hsCRP	107 With periodontitis and 43 controls	H	Body mass index	CRP in generalized periodontitis, 1.45 mg/L CRP in controls, 0.90 mg/L
Noack <i>et al.</i> (2001) ²²	174	hsCRP	High AL Mild AL Low AL	H	Not available	CRP in those with high AL, 3.79±0.86 mg/L CRP in those with mild AL, 2.39±0.29 mg/L CRP in those with low AL, 1.74±0.18 mg/L
Saito <i>et al.</i> (2003) ²³	179	hsCRP	High bone loss Mid bone loss Low bone loss	H	80% Patients were ex- or current smokers	CRP in those with low bone loss, 0.43 mg/L CRP in those with mid bone loss, 1.88 mg/L Odds ratio=8.2 for high bone loss patients to have CRP ≥1.3 mg/L
Craig <i>et al.</i> (2003) ²⁵	69	hsCRP	44 With periodontitis and 25 controls	H	Asian/hispanic decent; high antibodies to <i>Porphyromonas gingivalis</i>	No significant difference in CRP between periodontally healthy and the diseased Odds ratio=14.1 for patients with periodontal disease progression to have CRP >2.08 mg/L
Slade <i>et al.</i> (2003) ²⁴	5,552	CRP	ARIC participants	Mixed	White and African Americans' body mass index, age	Mean CRP of 7.6 mg/L; those with more extensive periodontal disease had significantly higher CRP; positive relationship between body mass index and CRP
Lim <i>et al.</i> (2007) ²⁸	171	hsCRP	Acceptable and unacceptable glycemic controls	Diabetic	Asians	Patients with more advanced periodontal disease had higher hsCRP; glycemic controls did not have high impact on CRP values
Pitiphat <i>et al.</i> (2008) ²⁷	121	hsCRP	100 With periodontitis and 21 controls	H	Patients attending treatment at three dental centers	Patients with periodontitis had higher median CRP levels than controls
Cairo <i>et al.</i> (2008) ²⁶	90	hsCRP	45 With periodontitis and 45 controls	H	Referral periodontal patients	Patients with periodontitis had higher hsCRP, total serum cholesterol, and low-density cholesterol; no association between hsCRP and carotid intima thickness

* AL denotes attachment loss, ARIC Atherosclerosis Risk in Communities study, H hypertension, Mixed diabetes and other medical conditions, and hsCRP high-sensitivity CRP

a higher median hsCRP in patients with periodontitis as compared to controls²⁷. Studies in patients with diabetes also confirmed that hsCRP levels were higher in those having more sites with probing depths of ≥5 mm²⁸.

Effects of periodontal therapy on C-reactive protein

The impact of periodontal therapy on CRP levels has

Table 2 Summary of reports on the effects of periodontal therapy on C-reactive protein (CRP) levels^{30-40 *}

Study	Subjects	Assay	Periodontitis	Systemic
Shklair <i>et al.</i> (1968) ³⁰	129	Non-hsCRP	43 With NUG, 18 with periodontitis, 21 with gingivitis, 14 with miscellaneous periodontal problems, and 33 controls	Not available
Ebersole <i>et al.</i> (1997) ³¹	75	hsCRP	40 With chronic periodontitis, 35 controls	H
Mattila <i>et al.</i> (2002) ³²	35	hsCRP	28 With severe periodontitis, 7 with moderate periodontitis	H
Ide <i>et al.</i> (2004) ³³	39 (treatment and non-treatment groups)	hsCRP	Moderate-to-advanced periodontitis	H
D'Aiuto <i>et al.</i> (2004) ³⁴	94	hsCRP	High AL Mild AL Low AL	H
Christgau <i>et al.</i> (1998) ³⁵	40	Non-hsCRP	Moderate-to-severe periodontitis	20 Diabetic and 20 non-diabetic
Iwamoto <i>et al.</i> (2003) ³⁶	15	hsCRP	Severe chronic periodontitis	Nine had diabetes
Yamazaki <i>et al.</i> (2005) ³⁷	47	hsCRP	Periodontitis and controls	Not available
D'Aiuto <i>et al.</i> (2006) ³⁸	40 (conventional and intensive treatment group)	hsCRP, cholesterol	Severe periodontitis	H
Elter <i>et al.</i> (2006) ³⁹	22	hsCRP, IL-6, cholesterol	Moderate-to-severe periodontitis	H
Jastrzebski <i>et al.</i> (2007) ⁴⁰	50	hsCRP, fibrinogen, cholesterol		

* hsCRP denotes high-sensitivity CRP, NUG necrotizing ulcerative gingivitis, NSAIDs nonsteroidal anti-inflammatory drugs, AL attachment loss, BOP bleeding on probing, IL-6 interleukin 6, and H hypertension

been investigated in a number of studies in recent years (Table 2)³⁰⁻⁴⁰.

One of the earliest³⁰ reported data from 96 patients, of whom 43 had necrotizing ulcerative gingivitis (NUG), 18 had (including 10 with severe) periodontitis, and 21 had gingivitis. A high percentage of individuals with more severe forms of disease were CRP-positive, the highest being in the NUG group (67% positive), followed by the severe periodontitis group (50% positive), and least in the moderate gingivitis group (14% positive). Moreover, in most instances CRP was not detectable by 3 to 7 days after treatment.

The effects of periodontal treatment on acute-phase reactants in a group of adult periodontitis (chronic

periodontitis group) and periodontally healthy controls were reported by Ebersole *et al.*³¹ in a study carried out in three phases. Phase I was a cross-sectional analysis, whereby serum samples were drawn from 40 patients with chronic periodontitis and 35 controls. After excluding patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) and those with metabolic diseases, in phase II, the remaining 38 with chronic periodontitis were divided into groups based on the number of sites with ≥ 2 mm loss of attachment. This was followed by a double-blind phase III study, in which all the patients underwent nonsurgical periodontal instrumentation and were randomly assigned to receive placebo, 5, 15, or 50 mg of flubriprofen twice daily for 24 months. In phase I, baseline levels of CRP in periodontitis patients were about 9 mg/L, while in the controls they were close to 2 mg/L. The group with

Confounders	Treatment	Follow-up	Results
Not available	Periodontal treatment only	Not available	>50% in NUG; those with advanced periodontitis had positive CRP; negative CRP found in most cases after treatment
Not available	Nonsurgical periodontal treatment with NSAIDs	30 Months	CRP of those with chronic periodontitis, 9 mg/L CRP of those without periodontitis, 2 mg/L 40-50% Reduction in CRP in patients who had less residual periodontal disease
Not available	Nonsurgical periodontal treatment with Flayl	6 Weeks	Mean reduction in CRP, 0.34 mg/L; higher reduction in patients with higher baseline CRP; reduction was independent of severity of periodontal disease
Not available	Nonsurgical periodontal treatment	6 Weeks	Significant improvement after periodontal treatment but no significant changes in CRP levels
42% Smokers; age, body mass index, and average AL	Nonsurgical periodontal treatment with complex dental treatment	6 Months	79.2% Reduction in CRP in patients who showed good response to periodontal treatment; effect present after adjusting for covariates. Periodontal treatment reduces risk of cardiovascular disease based on reduced CRP-related risk
Not available	Nonsurgical periodontal treatment	4 Months	No significant differences in treatment outcome. At all times CRP was ≥ 2.8 mg/L in diabetic group and for non-diabetic group it was < 2.8 mg/L (not significant)
Not available	Local drug Minocyclin	4 Weeks	Significant improvement in periodontal status and reduction in CRP
All non-smokers	Nonsurgical and surgical treatment	Not available	Some reduction in CRP following treatment (from 317 ng/mL to 261.5 ng/mL) but difference was not significant
-	Nonsurgical with local drug in 1 group	1, 2, and 6 Months	Significant improvement in intensive treatment group (with local drug) in CRP, total cholesterol, low-density cholesterol, and IL-6. Some improvement in conventional treatment but less than that in intensive group
Healthy	Nonsurgical	1 Month	Significant improvement in flow-mediated dilation and IL-6 but non-significant in CRP and cholesterol
	Nonsurgical, antibiotics	6 Months	Improvement in BOP but not CRP and fibrinogen

highest numbers of attachment loss had nearly 17-fold higher CRP levels than the healthy group. Similar results were noted for haptoglobin levels. In the group receiving 50 mg NSAID doses there was a 40 to 50% reduction in CRP level. The additional benefit of 50 mg flubriprofen was clearly evident, but long-term usage of such doses is a major concern due to side-effects.

In a pilot intervention on 35 patients, 28 of whom had severe periodontitis; Mattila *et al.*³² assessed the changes in circulating CRP levels after 6 weeks of nonsurgical periodontal treatment. A statistically significant mean reduction of 0.34 mg/L from baseline values (baseline median value, 1.05 mg/L; baseline range, 0.2-5.4 mg/L) was noted. In the study carried out in a Japanese population, Iwamoto *et al.*³⁶ also found significant reductions in CRP

levels after treating patients with severe periodontitis. In both studies, antibiotics were administered as an adjunct to periodontal therapy.

A series of reports from D'Aiuto *et al.*^{9,34,41} also highlighted the promising effects of nonsurgical periodontal treatment, in terms of reducing cardiovascular risk factors. There was a significant improvement in oral hygiene and all periodontal parameters; the mean number of pockets with probing depths of >4 mm decreased from 77 at baseline to 28 at 2 months and 23 at 6 months. A significant interaction was noted between treatment outcomes and overall CRP levels at all three examinations. The decrease in CRP was significant in subjects who had shown the best response to treatment (after adjusting for age, body mass index [BMI] and smoking habit) indicating

that residual pockets may have actually hindered a more favorable reduction in CRP levels. The authors concluded a causal relationship between periodontitis and systemic inflammatory status. They also performed further bivariate and multivariate logistic regression analyses to compare the CRP-associated risk of cardiovascular disease before and after treatment. Based on AHA and CDC recommendations, at baseline patients were divided into the three CRP-associated risk categories; 12 were at low risk (CRP, <1 mg/L), 47 at medium risk (CRP, 1-3 mg/L), and 35 at high risk. After the institution of periodontal treatment, 50 patients remained in the same risk category, 13 moved from the high- to medium-risk category, 25 moved from medium- to the low-risk group, while 2 moved from high-risk to the low-risk group. Four subjects however, moved from the medium- to the high-risk group. A binary logistic regression analysis controlling for potential confounders, namely age, gender, ethnicity, smoking habit, and BMI described the effect of nonsurgical periodontal treatment on CRP-associated risk of cardiovascular disease. The dependent variables were 'reduced CRP-associated risk' and 'no change or increase in CRP-associated risk' of cardiovascular disease. It was found that patients with good responses to periodontal treatment had 4 (95% confidence interval, 1.4-15.8) times the chance of being in the low-risk category compared to patients with suboptimal responses. In a subsequent randomized controlled trial conducted by the same investigators³⁸, among inpatients with severe periodontitis, intensive periodontal treatment (topical antibiotics) resulted in an overall improvement in systemic inflammatory markers and cardiovascular risk scores as compared to conventional periodontal treatment. However, a similar study by Tonetti *et al.*⁴² with a larger sample size of 120 patients yielded somewhat different results. They employed the same protocol but with the addition of flow-mediated dilation for diagnosis of endothelial dysfunction and more frequent follow-ups. The authors reported a drastic (8-fold) increase in CRP and IL-6 levels 24 hours after intensive periodontal therapy, which decreased by week 1 and remained low after 6 months. The sharp rise in CRP may reflect an acute inflammatory response immediately following treatment.

Ide *et al.*³³ evaluated the effect of nonsurgical periodontal treatment in patients with moderate-to-advanced periodontal disease on circulating serum levels of acute-phase proteins. While a significant improvement in periodontal status was evident, there was no significant change in serum hsCRP levels and other inflammatory markers at the end of the trial. The authors concluded

that the periodontal infection and periodontal treatment may not contribute significantly to serum CRP levels.

Yamazaki *et al.*³⁷ in their study of a cohort of Japanese patients with and without periodontitis found a trend towards reduced CRP levels following periodontal therapy, although the differences did not reach statistical significance. Notably, patients in this group tended to have lower CRP levels than other groups and only non-smokers were included. The results also pointed to possible racial and genetic differences in CRP levels, a factor that should be taken into consideration in future clinical studies.

An earlier interventional study carried out by Christgau *et al.*³⁵ in patients with reasonably well-controlled diabetes noted an improvement in periodontal status of diabetics and healthy controls after periodontal treatment; in the former there were no marked changes in metabolic serum markers. Thus, in well-controlled diabetes, the impact of periodontal therapy on CRP levels and hence cardiovascular risk may be minimal. Jastrzebski *et al.*⁴⁰ also did not find a significant impact of dental treatment on CRP or fibrinogen levels in a group of patients with hypertension, and concluded that in the presence of other cardiovascular risk factors, the impact of dental infection on the total inflammatory burden may be masked. Elter *et al.*³⁹ found a significant improvement in periodontal status following periodontal treatment, with some changes in systemic inflammatory markers. However, the reduction in CRP did not reach statistical significance, possibly due to the small sample size.

Two systematic reviews published to date revealed no consistent agreement regarding the effects of periodontal intervention on CRP levels^{43,44}. In their review, Ioannidou *et al.*⁴³ concluded that there was inadequate evidence that periodontal treatment reduces CRP levels. The very recent meta-analysis of 10 cross-sectional studies carried out by Paraskevas *et al.*⁴⁴ found a weighted mean difference of 1.56 mg/L in CRP levels between treated patients and controls. In the same report, an analysis of six interventional studies revealed the weighted mean difference in CRP level reductions to be 0.50 mg/L following therapy. The differing conclusions from these studies could be due to the methodology used to analyze the results. Both studies acknowledged the inadequate numbers of clinical studies (especially randomized controlled trials) and lack of adjustment for potential confounders as limiting meaningful, collective interpretation.

Discussion

In summary, studies reported so far demonstrate the following trends:

1. Patients with more advanced periodontal disease display higher CRP levels.
2. There is a trend towards improvement of CRP levels following periodontal therapy, though not consistently (due in part to variations in study design).

The effect of periodontal disease progression on the risk of having higher levels of CRP appears to predict cardiovascular disease and has been well documented in the current literature²¹⁻²⁵. Setting optimal cut-off levels to predict cardiovascular disease risk remains problematic, as does the possible role of CRP in cardiovascular disease.

The consensus conference of the AHA⁵ advised that in a metabolically healthy individual (i.e. with no active infection), CRP should be measured by a high-sensitivity assay, in a fasting or non-fasting state. Preferably there should be two determinations spaced 15 days apart to ensure a stable estimate. The conference also inferred that hsCRP is an independent predictor of increased cardiovascular risk. The risk prediction based on CRP as proposed by AHA/CDC categorizes patients with 1 to 3 mg/L as being at moderate risk. Ridker *et al.*¹⁵ recommended a cut-off level of CRP >2 mg/L as a level that predicts cardiovascular risk. In their study, Craig *et al.*²⁵ reported this value to be associated with more advanced periodontitis. An increased risk of cardiovascular disease in a Japanese population has been reported with CRP levels above 1.3 mg/L. Since minor changes in CRP levels are critical for such predictions, it seems that there is still lack of consensus and a precise numerical value is not yet agreed^{45,46}. Furthermore, while the compelling evidence regarding the clinical importance of hsCRP in cardiovascular risk assessment is widely accepted, not all experts in the cardiovascular community share this view. The causal role of CRP in the development of cardiovascular disease therefore needs further validation.

That periodontal disorder which can result in increased CRP level elevations could be explained by the inflammatory/infective nature of the disease. The presence of periodontal pathogens could stimulate the inflammatory response sharing a common pathogenic pathway to that in atherosclerosis. This might result in elevated levels of inflammatory markers like tumor necrosis factor- α , IL-6, IL-1, which trigger the

inflammatory cascade. These proinflammatory effects have been found to have profound effects on endothelial cells, causing upregulation of vascular adhesion molecule 1, intracellular adhesion molecule 2, and E-selectin. All of these modulate monocyte recruitment in the presence of fatty streaks form foam cells, which results in atheroma⁴⁷. In their study, Haraszthy *et al.*⁴⁸ found that periodontal pathogens like *P. gingivalis* have also been isolated in the atheroma of patients with atherosclerosis, which points to a possible infective nature of this disease. Since both periodontitis and cardiovascular events may share a common pathogenic pathway and common risk factors, it is difficult to confirm a cause-and-effect relationship. Interventional studies are therefore needed. Glurich *et al.*⁴⁹ found elevated levels of CRP in patients with periodontal and cardiovascular diseases. However, the levels increased 3-fold when both conditions were present, suggesting that inflammation-associated molecules may contribute to an additional burden in the infectious and inflammatory processes in both conditions.

Based on the AHA/CDC guidelines, an improvement in CRP-associated cardiovascular risk has been inferred following periodontal treatment³⁴. The variable results reported could be due to the presence of other confounding factors for CRP levels, namely age, ethnicity, smoking history, systolic blood pressure, BMI, triglyceride and high-density lipoprotein cholesterol levels, IL-6, intake of statins, antibiotics, and medical status⁵⁰⁻⁵². In several studies demonstrating a positive outcome in terms of reduction in CRP levels, antimicrobials and NSAIDs have been included in the relevant treatment regimens, which itself would have contributed to a reduction in the inflammatory load^{31,32,36}. In their studies involving smokers and non-smokers, Tonetti *et al.*⁴² found a modest improvement in CRP levels following treatment; among smokers the reduction was only detected in the intensive therapy group. Evidently a significant proportion of older adults may be taking statins to control cholesterol levels, which could also explain the reduced CRP levels¹⁵. All these confounders make a definite conclusion on the effects of periodontal therapy per se difficult. Due consideration should therefore be given to a possible bi-directional causal relationship between periodontal disease and CRP levels. There is also a need for more randomized clinical trials and the use of other criteria to identify cardiovascular dysfunction.

Future implications and directions

Periodontal disease and periodontal therapy may have

an impact on cardiovascular risk and have practical implications for the management of patients at risk. The latter include those with hyperlipidemia, diabetes, hypertension, metabolic syndrome, and renal disease. While statins reduce cardiovascular risk and CRP levels, it is less certain whether periodontal therapy can influence cholesterol levels, though there is limited evidence to support such an effect⁵²⁻⁵⁵. Also, diabetes is a significant risk factor for periodontal disease and coronary heart disease, more interventional clinical trials should therefore be conducted to further explore the impact of periodontal therapy in this patient category. Improving glycemic control as well as reduction of cardiovascular risk should both be addressed. Emerging evidence also points to a link between periodontal and renal disease. As renal disease patients are at greater cardiovascular risk and have elevated CRP levels, this too requires further investigation^{56,57}. Finally, long-term studies on the effects of CRP antagonists and CRP-lowering strategies on periodontal health and coronary heart disease are needed.

Conclusions

The link between systemic and oral conditions is still not clearly defined, one of the major reasons being the use of inappropriate surrogate markers. In this context, CRP measured by a high-sensitivity assay may be a useful tool. The studies presented and discussed in the present paper demonstrate an association between raised CRP level and periodontal disease, and a trend towards an improvement in levels following periodontal therapy. While the majority of the studies show a positive relationship, there are some inconsistencies; the strength of evidence is not strong enough to confirm a causal relationship. Further studies based on CRP are needed to establish a link between systemic and oral conditions as are other methods of investigating endothelial dysfunction⁵⁸. Furthermore, variations do exist among different racial/ethnic groups^{37,59}. Focus should perhaps be directed at patients at risk to cardiovascular problems, metabolic syndrome and those having aggressive periodontitis. If indeed this periodontal systemic link is proven to be true, a new holistic approach to controlling periodontal disease and reducing cardiovascular risks might become available.

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