

Persistently raised C-reactive protein levels are associated with advanced periodontal disease

Gerard J. Linden¹, Kathy McClean²,
Ian Young², Alun Evans² and Frank
Kee²

¹Oral Science Research Centre, Queen's University, Belfast, UK; ²Department of Epidemiology and Public Health, Queen's University, Belfast, UK

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Abstract

Objective: The aim was to investigate whether there was an association between periodontitis or tooth loss in a homogeneous group of 60–70-year-old Western European men and either a sustained high or low level of C-reactive protein (CRP).

Material and Methods: Men enrolled in a cohort study of cardiovascular disease in Northern Ireland were screened in 1990–1994 and rescreened in 2001–2004, when a periodontal examination was completed. High-sensitivity CRP was measured from fasting blood samples. There were 806 men with six or more teeth who had either a high level (> 3 mg/l) or a lower level of CRP at both time points. Multivariate analysis was carried out using logistic regression with adjustment for possible confounders. Models were constructed with the CRP level as the outcome variable and various measures of periodontal status (low and high threshold periodontitis) or tooth loss as predictor variables. Confounders included in the analysis were known cardiovascular risk factors of age, smoking, diabetes, BMI and socioeconomic status.

Results: There were 67 men who had a high value of CRP (> 3 mg/l) and 739 men who had a CRP value ≤ 3 mg/l at both time points. The unadjusted odds ratio (OR) for advanced periodontitis to be associated with high CRP was 3.62, $p = 0.0003$. The association was somewhat attenuated but remained significant (OR = 2.49, $p = 0.02$) after adjustment for confounders. A high level of tooth loss was also associated with high CRP with an adjusted OR of 2.17, $p = 0.008$. Low threshold periodontitis was not associated with the level of CRP.

Conclusion: There was an association between advanced periodontitis and elevated CRP levels as measured at two time points at a 10-year interval in the 60–70-year-old European males investigated. This association was adjusted for various cardiovascular risk factors. There was also an association between high levels of tooth loss and high CRP in the men studied.

Key words: BMI; CRP; periodontitis; smoking; tooth loss

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C-reactive protein (CRP) production is part of the non-specific acute-phase response to most forms of inflammation, infection and tissue damage (Pepys &

Hirschfield 2003). Prospective epidemiological studies have demonstrated that CRP levels independently predict the risk of first coronary events (Ridker et al. 2000, Danesh et al. 2004). In this context, the clinical relevance of moderate increases in CRP, smaller than those associated with systemic infection, has been highlighted (Ridker et al. 2000, Pearson et al. 2003). Experimental studies have shown that CRP binds to ligands exposed in damaged tissue and then activates complement,

which may lead to complement-mediated exacerbation of tissue injury (Pepys et al. 2006). Nevertheless, there is still no consensus whether high levels of CRP are part of the mechanism through which inflammation contributes to atherogenesis or are merely a marker of atherosclerosis or other vascular damage. Cardiovascular disease (CVD) and a heightened acute phase response with increased levels of CRP share many common risk factors including smoking, high BMI and older age

Conflict of interest and source of funding statement

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(Visser et al. 1999, Pepys & Hirschfield 2003).

Periodontal diseases are infections characterized by inflammation and destruction of the supporting tissues of the affected teeth. Gram-negative anaerobes are present in large numbers in subgingival dental plaque in periodontal pockets. Endotoxin derived from Gram-negative microorganisms interacts with toll-like receptors (TLR) expressed on the surface of neutrophils and monocytes, which are abundant in periodontal inflammation. TLR-ligand complexes activate signal transduction pathways in both the innate and adaptive immune systems leading to the production of cytokines, which coordinate the local and systemic inflammatory response (Akira & Takeda 2004). Pro-inflammatory cytokines, originating at the site of local pathology, activate hepatocytes to produce acute phase proteins including CRP (Medzhitov 2007) and this forms part of the non-specific response. Epidemiological studies have shown that levels of acute phase proteins including CRP are increased in otherwise healthy adults with poor periodontal status (Loos et al. 2000, Slade et al. 2000). 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 (Paraskevas et al. 2008). It has been hypothesized that any association between periodontitis and CVD could be due to the moderate increases in CRP reported in subjects with poor periodontal health (D'Aiuto et al. 2004).

Most studies of the association between CRP and periodontal status have been cross-sectional in nature and involved a one off measurement of CRP. Various factors such as intercurrent illness can result in transient increases in CRP and therefore a single measurement may not represent the true basal level of CRP (Ledue & Rifai 2003). The design of the current cohort study enabled CRP levels to be recorded at two time points separated by 10 years. The aim is to investigate the association between periodontal status and tooth loss in a homogenous group of 60–70-year-old Western European men and either a sustained high or low level of CRP.

Material and Methods

The study subjects were participants in Prospective Epidemiological Study of

Myocardial Infarction (PRIME), which is a cohort study of CVD in men in Northern Ireland. The sampling frame was based on industry, the civil service and general medical practices. Between 1991 and 1994 a sample of 2745 50–60-year-old men, representing approximately 5% of the respective greater Belfast population, were recruited to match broadly the social class structure of the population in Northern Ireland (Yarnell 1998). Between 2001 and 2003, the surviving men were contacted by post and invited to attend for re-screening as part of their continuing involvement in the PRIME study. A total of 2010 men were reviewed and a clinical periodontal examination was completed for 1400 (69.7%) of the men. The remainder of the sample was made up of 363 (18.1%) men who did not have a dental examination because a specialist dental examiner was not available during their visit, 158 (7.9%) who were edentulous and 89 (4.4%) who refused or had a medical condition that precluded periodontal probing.

The inclusion criteria for the current study were a valid measurement of CRP at both time points combined with a clinical periodontal examination and six or more teeth at the re-screening visit. In the sample of 1400 men, who had a periodontal examination there were 38 (2.7%) men who had <6 teeth and 357 (25.5%) who did not have a measurement of CRP at both the time points and they were excluded. The high number of exclusions due to no CRP measurement was principally related to limited availability of blood from the first time point due to previous investigations completed on these participants in the PRIME cohort study. Each subject who met the inclusion criteria completed a questionnaire, which gathered information on their demographic and socioeconomic background and tobacco consumption. Measurements of weight and height were also recorded. Approval for the project was obtained from the Research Ethics Committee of the Faculty of Medicine, Queen's University, Belfast. The aims of the investigation and the nature of the study were fully explained to the subjects, who gave their informed written consent before participation.

All the periodontal examinations were completed by one of four dental hygienists who were calibrated to a "gold standard" senior clinical researcher before the study. There were regular

monthly meetings to ensure inter- and intra-examiner consistency and reproducibility throughout the study period. In the periodontal examination, clinical measurements were made at the mesial, distal, buccal and palatal/lingual aspects of all teeth excluding third molars. Probing pocket depths were measured from the gingival margin to the base of the clinical pocket with the probe tip parallel to the long axis of the tooth and positioned interproximally as close as possible to the contact point. Measurements were made to the nearest millimetre and when any doubt existed the lower value was scored. Clinical attachment level was recorded as the distance from the cement–enamel junction (CEJ) to the base of the clinical pocket. This was calculated by measuring the distance from the CEJ to the gingival margin and subtracting this value from the probing depth measurement (recession was recorded as a negative value). All clinical measurements were recorded using Michigan O periodontal probes with Williams markings from a batch of probes purchased for the study.

Periodontal status and tooth loss

Low threshold periodontitis was identified by the presence of at least two teeth with non-contiguous inter-proximal sites with ≥ 6 mm loss of attachment and at least one pocket of ≥ 5 mm. High threshold advanced periodontitis was identified when >15% of all sites measured had loss of attachment ≥ 6 mm and there was at least one site with deep pocketing (≥ 6 mm).

Third molars were excluded from periodontal assessment and were not included when the number of teeth was recorded. High tooth loss equated with the loss of 14 or more teeth.

CRP

Venous blood samples were collected after a 12 h fast and centrifuged within 4 h. The aliquots were then frozen at -80°C . The plasma samples were defrosted in 2006/2007 and Ultra sensitive CRP was measured using Quantex Biokit Reagents and the Instrumentation Laboratory (ILab 600) (Lexington, MA, USA) automated random access Clinical Chemistry Analyser. This test is standardized on the International Reference Material CRM470 (International Federation of Clinical Chemistry and Laboratory Medicine, Milan, Italy)

using the recommended test parameters. The baseline samples had been in storage for an average of 15 years before being defrosted and analysed. The follow-up samples had been in storage for 3 years. The same kit was used for both sets of samples and they were standardized on the same reference material and measured within a year of each other.

Potential predictors of CRP

BMI was calculated as the body weight/height² (kg/m²) and categorized using the World Health Organization (2000) classification: normal weight equated to BMI < 25 kg/m², overweight \geq 25 to \leq 30 kg/m² and obese > 30 kg/m². Smokers were divided into current, past or never. Diabetes was categorized by self-report of the condition. Socioeconomic status was categorized as using a composite measure of material conditions into high, middle and low. The material conditions variable was based on the type of living accommodation (rented or owned/mortgage), number of cars/vans/motorcycles in the household and the number of baths and/or showers and toilets in the home (Wagner et al. 2003).

Statistical analysis

Mann-Whitney, Wilcoxon's matched pairs or χ^2 analysis were used to compare the subgroups of the men with the level of significance set at $p < 0.05$. Multivariate analysis was carried out using logistic regression to obtain odds ratios (ORs) adjusted for possible confounders. Models were constructed with the levels of CRP as the outcome variable and periodontal disease status or tooth loss as a categorical predictor variable. Confounders included in the analysis were the known cardiovascular risk factors of age, smoking, diabetes, socioeconomic status and BMI. To check for possible effect modification interactions were incorporated into the fully adjusted models and assessed for significance using likelihood ratio tests. All confounding variables were checked for effect modification.

Results

In total, 1005 men with six or more teeth had a serum estimate of CRP at both the time of recruitment to the cohort study (1991-1994) and at the second time point (2001-2004) when they had a clinical periodontal examination. There

was no difference in the age, smoking status or BMI of those included in this analysis and those without paired measurements of CRP (data not shown). The subjects were divided into groups according to the CRP value recorded at each visit with > 3 mg/l taken as a high value (Pearson et al. 2003). There were 739 (73.5%) men who had a CRP value \leq 3 mg/l at both time points and 67 (6.7%) who had a high value of CRP at both time points. There were 129 men (12.8%) who had CRP \leq 3 mg/l at the first time point and > 3 mg/l at the second and 70 (7%) who had CRP > 3 mg/l at baseline followed by \leq 3 mg/l at re-screening. These men were not studied further.

The 806 men who had either a high level or a low level of CRP at both time points formed the basis for further study. Over the period CRP (mg/l) increased within both groups. In the low group, the change in CRP from 0.98 (median; interquartile range [IQR] 0.70) at baseline to 1.22; IQR 0.81 at re-screening was highly significant ($p < 0.0001$). In the high group the increase from 4.30; IQR 0.70 at baseline to 5.24; IQR 3.25 at re-screening was not significant ($p = 0.72$). The clinical characteristics of the study participants according to their CRP level at both

time points are shown in Table 1. Those who were in the high CRP group had fewer teeth, higher levels of low and high threshold periodontitis, a higher proportion of pockets \geq 5 mm, a higher BMI, were more likely to have smoked and to suffer from diabetes than those with low CRP levels (Table 1).

Periodontitis and CRP

Within the low CRP group men who had the lowest level of CRP (< 1 mg/l) at both time points had a lower prevalence of both low threshold (15.1%) and high threshold periodontitis (3.2%) compared with the remaining members of the low CRP group (low threshold periodontitis 25.5%, high threshold periodontitis 6.4%). A much higher proportion (18%) of the men in the high CRP group had advanced high threshold periodontitis compared with only 6% of those in the low CRP group, $p = 0.0001$ (Table 1). The unadjusted OR for advanced periodontitis to be associated with high CRP was 3.62, 95% confidence intervals (CI) 1.80-7.27, $p = 0.0003$. The association, although somewhat attenuated, remained significant (OR = 2.49, $p = 0.02$) after adjustment for age, smoking, BMI, socioeconomic status and diabetes (Table 2).

Table 1. Baseline characteristics among men in PRIME according to CRP as measured at baseline in 1990-93 and repeated at re-screening in 2001-2003

	High CRP <i>n</i> = 67	Low CRP <i>n</i> = 739	<i>p</i>
Age (years), mean (SD)	63.6 (2.9)	63.9 (2.9)	0.57
Number of teeth, mean (SD)	17.8 (6.9)	20.4 (5.3)	0.0003
Periodontitis: low threshold, <i>n</i> (%)	22 (32.8)	169 (22.9)	0.066
Periodontitis: high threshold, <i>n</i> (%)	12 (17.9)	42 (5.7)	0.0001
% pockets \geq 5 mm, mean (SD)	6.9 (12.5)	3.1 (6.7)	<0.0001
BMI, <i>n</i> (%)			
Normal	9 (13.4)	209 (28.3)	
Overweight	27 (40.3)	404 (54.7)	<0.0001
Obese	31 (46.3)	126 (17.1)	
BMI at baseline, mean (SD)	27.8 (3.2)	25.8 (3.0)	<0.0001
BMI at re-screening, mean (SD)	29.4 (3.7)	27.0 (3.4)	<0.0001
Smoking, <i>n</i> (%)			
Never	14 (20.9)	316 (42.8)	
Past	36 (53.7)	309 (41.8)	0.0015
Current	17 (25.4)	114 (15.4)	
Smoking: pack years at baseline, mean (SD)	35.9 (37.1)	16.2 (22.2)	<0.0001
Smoking: pack years at re-screening, mean (SD)	40.2 (38.5)	18.0 (24.6)	<0.0001
Diabetes, <i>n</i> (%)	6 (9.0)	37 (5.0)	0.17
Material conditions, <i>n</i> (%)			
High	341 (46.1)	22 (32.8)	
Medium	171 (23.1)	18 (26.9)	0.10
Low	227 (30.7)	27 (40.3)	

High CRP, men with CRP > 3 mg/l at both time points; Low CRP, men with CRP \leq 3 mg/l at both time points.

BMI, body mass index; CRP, C-reactive protein.

Table 2. Multivariable analysis

High threshold periodontitis OR 95% CI	Low threshold periodontitis OR 95% CI	Tooth loss (Lost \geq 14 teeth) OR 95% CI
2.49* 1.16–5.35	1.09 0.61–1.95	2.17** 1.22–3.84

Predictors of high CRP values (>3 gl) at time points 10 years apart. Adjusted for age, smoking, diabetes, BMI and socioeconomic status. * $p < 0.05$. ** $p < 0.01$.

In the final model, the other factors which were significantly associated with high CRP were current smoking ($p = 0.008$), past smoking ($p = 0.02$) and BMI ($p < 0.0001$). There were no significant interactions in the fully adjusted analysis.

Low threshold periodontitis was present in a higher proportion of the group with high levels of CRP than the group with low CRP but this was not significant (Table 1). In the final multivariate model, only current and past smoking and BMI were significantly associated with high CRP.

Tooth loss and CRP

Men in the high CRP group had fewer remaining teeth than those in the low CRP group (Table 1). A higher proportion (34%) the group with high CRP had lost 14 or more teeth compared with only 16% of those with low CRP, $p = 0.0001$. The unadjusted OR for a high level of tooth loss to be associated with high CRP was 2.84, $p = 0.0002$. The association remained significant (OR = 2.17, $p = 0.008$) after adjusting for age, smoking, BMI, socioeconomic status and diabetes (Table 2). In the final model factors which were significantly associated with high CRP were current smoking ($p = 0.008$), past smoking ($p = 0.025$) and BMI ($p < 0.0001$). There were no significant interactions in the fully adjusted analysis.

Discussion

The main finding of this population-based study was that in a homogenous group of 60–70-year-old men, advanced periodontitis was associated with a significantly increased risk of a sustained high (>3 mg/l) CRP level. The men with two independent readings of CRP of >3 mg/l would have been in a high risk category for incident coronary

disease (Pearson et al. 2003). The case definition of periodontitis was relevant because when periodontitis was assessed at two levels, as suggested by Tonetti & Claffey (2005), low threshold periodontitis was not significantly associated with high CRP. A high level of tooth loss was also associated with a significantly increased risk of a sustained high CRP level.

Atherosclerosis is multifactorial, however, in recent years it has become increasingly evident that inflammation plays an important role in its pathogenesis (Libby 2002). CRP is a sensitive circulating marker of inflammation and prospective epidemiological studies have consistently demonstrated that CRP levels independently predict the risk of first coronary events and have prognostic value in acute coronary syndromes (Ridker et al. 2005). The results of both case control and epidemiological investigations have identified an association between periodontitis and elevated levels of CRP (see review Loos 2005). It has been postulated that increased CRP as a result of periodontal inflammation could provide an explanation of the reported relationship between periodontitis and coronary heart disease (D'Aiuto et al. 2004).

CRP is a sensitive marker of inflammation and single measurements may be misleading because intercurrent infections and other factors can affect its level. To allow for within subject variability in CRP concentration, it has been suggested that two independent measurements are appropriate for clinical use (Pearson et al. 2003). Danesh et al. (2004) also found relatively high stability in CRP levels from paired samples obtained on average 12 years apart with a within person correlation coefficient of 0.59. The in depth study of possible associations between periodontitis and CRP was limited to those who had a high or a low CRP level at two time points to exclude factors which may have resulted in significant increases or decreases in CRP. There was a general small increase in CRP in the men over the 10-year period which is likely due to ageing and increased BMI (Pepys & Hirschfield 2003).

The study was performed on a representative sample of 60–70-year-old males in Northern Ireland who were almost exclusively of Western European origin. In general they were older than those examined in most other studies of CRP and periodontitis. Each subject had

a careful periodontal examination under ideal conditions and while it is possible that there was some misclassification due to inaccuracies in the clinical examination this was unlikely to have been a major factor in the identification of those with the poorest periodontal condition. Low threshold periodontitis was relatively common affecting 24% of the men which is broadly similar to previous work on the population of Northern Ireland (Mullally & Linden 1992). A limitation of the study is that the assessment of periodontal status was only made at the re-screening visit. The pivotal study of Loe et al. (1986) provided evidence that only a small susceptible subfraction of the population experience advanced periodontitis. Longitudinal studies in different population groups with advanced periodontitis have shown that the condition is slowly progressive (Lindhe et al. 1983, 1989). Therefore, the small proportion (7%) who presented with advanced periodontitis at 60–70 years of age were likely to have suffered from this condition for many years and to have exhibited signs of severe disease 10 years previously. Further support is provided by studies which have shown that past periodontal disease has a significant and direct correlation with future periodontal disease (Machtei et al. 1997, 1999).

Clinical measurement error could have been a factor affecting the categorisation of periodontitis and therefore the analyses were repeated with tooth loss as an independent variable. It has been shown that the number of remaining teeth is an independent predictor of severe periodontal disease (Locker & Leake 1993). High levels of tooth loss ($\geq 50\%$) had an association with high CRP after adjustment for confounders.

The pro-inflammatory cytokine interleukin-6 (IL-6) acts as a major regulator of the acute phase response by controlling the synthesis of CRP (Yudkin et al. 2000). The systemic concentration of IL-6 is increased in periodontitis (Loos et al. 2000) and this may affect CRP production. However, as much as one-third of circulating IL-6 originates from adipose tissue (Yudkin et al. 2000) and this explains the association between obesity and increased CRP concentration. Obesity may be associated with periodontitis (Linden et al. 2007) and thus may prove to be a major confounder of any putative association between periodontitis and CRP. Smoking is also

a potential confounder because it is responsible for increases in CRP levels and is the principal environmental risk factor for periodontitis (Tomar & Asma 2000). Nevertheless, in the current study severe periodontitis, with evidence of generalized advanced loss of periodontal attachment, was associated with sustained high CRP after adjustment for BMI and smoking as well as other potential confounders. This agrees with the findings of Slade et al. (2003) who reported elevated CRP in individuals with extensive periodontal disease (>30% sites with pockets \geq 4 mm). In the current study, the association between lower levels of periodontal disease and high CRP was not statistically significant ($p = 0.07$). It could be that substantial peripheral inflammation is necessary to trigger increases in CRP. A large epidemiological study in Finland reported that CRP levels were only weakly associated with self-reported gingivitis in young adults (Ylostalo et al. 2008). Craig et al. (2003) suggested that sites of active periodontal breakdown potentiated the acute-phase response. In the older group (60–70 years of age) studied there may be reduced disease activity except in those with the most advanced levels of periodontitis. This may explain the association with advanced but not low level periodontitis in the current study.

It has been shown that both confounding and effect modification should be taken into account when considering possible relationships between periodontitis and systemic diseases or conditions (Hyman et al. 2002, Ylostalo & Knuutila 2006). In line with suggestions made by Hyman (2006) checks for effect modification were made in the logistic regression analysis through the incorporation of interactions. There were no significant interactions and it was concluded that the data set supplied no evidence of effect modification between periodontal status and socio-demographic factors in the identification of subjects with high CRP values.

The findings of the current study support previous work which identified increased levels of serum CRP in subjects with chronic periodontitis (Slade et al. 2000, 2003, Noack et al. 2001, Pitiphat et al. 2008) including a study in Northern Ireland (Briggs et al. 2006). There were differences between the CRP levels reported in the current study and those reported in other epidemiological studies of periodontitis and CRP

completed in the United States. In the current study, high CRP (>3 mg/l) was present in 14% of the men at baseline and this increased to almost one in five (19.5%) of the men at the re-screening visit. This can be compared with 28% in the NHANES III study which had subjects with a much wider age range starting from 18 years of age (Slade et al. 2000). In the current study, only 2.9% had a very high CRP (>10 mg/l) compared with 7.3% in NHANES III (Slade et al. 2000) and 16.6% in the ARIC study which had subjects aged 52–75 years (Slade et al. 2003). Overall there is support for the view that the Northern Ireland cohort had lower CRP levels than those reported in epidemiological studies carried out in the United States. It is unclear whether this was due to differences in the higher sensitivity of the assay used in the present study or due to factors which have an effect on CRP such as the very high levels of obesity in the United States (Olshansky et al. 2005). It has been argued that highly elevated CRP (>10 mg/l) may reflect acute inflammation and that in clinical practice any such value should be discarded and the level re-measured after the acute inflammation has subsided (Pearson et al. 2003). In the current study, the analyses were repeated after excluding men who had CRP > 10 mg/l. This resulted in a reduction in the number of men in the high CRP group but did not change the outcome of the analyses. The subjects who changed CRP from a high to a low level or vice versa had prevalences of both low- and high-threshold periodontitis, which were intermediate between the values found in the low and high CRP groups (data not shown). Furthermore, a dose–response was supported by the finding of the lowest prevalence of periodontitis in the men who had the lowest levels of CRP (<1 mg/l) at both time points.

It is important to understand the inter-relationship between periodontal disease, CRP and atherosclerosis to be in a position to give more rational advice to ‘at-risk’ patients with chronic periodontitis, particularly in relation to possible prevention of CVD. In recent years there has been a major focus on interventions aimed at the prevention of coronary events. Large prospective studies have shown that patients who have low CRP levels after statin therapy have better clinical outcomes irrespective of resultant level of LDL cholesterol

(Ridker et al. 2005). In studies completed on subjects with widespread severe periodontitis it has been shown that the periodontal treatment results in a significant decrease in serum CRP (D’Aiuto et al. 2005) and an improvement in endothelial function (Tonetti et al. 2007). While it was made clear that no extrapolation could be made to those affected by less severe forms of periodontitis (Tonetti et al. 2007), nevertheless, there is a need for further studies of the effects of periodontal treatment on cardiovascular risk.

It is concluded that there was an association between advanced periodontitis and elevated CRP levels as measured at two time points at a 10-year interval in the 60–70-year old European males investigated. This association was adjusted for various cardiovascular risk factors. There was also an association between tooth loss and elevated CRP levels. The results extend the findings of previous investigations, which have reported cross-sectional associations between periodontitis and CRP. Advanced periodontitis is rare, therefore only a low proportion of the population will be at risk if the mechanism for the linkage between periodontitis and CVD in this age group is through increased CRP levels. It remains important to clarify whether chronic periodontitis is a true risk factor for CVD and to determine the mechanism underpinning any such relationship.

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Address:
Gerard Linden
Oral Science Research Centre
School of Dentistry
Queen’s University
Grosvenor Road, Belfast BT12 6BP
Northern Ireland, UK
E-mail: g.linden@qub.ac.uk

Clinical Relevance

Scientific rationale for the study : An association between chronic periodontitis and the acute phase protein CRP has been identified in cross sectional studies. It is not clear whether periodontitis is associated with a sustained increase in CRP.

Principal findings: After adjustment for possible confounders there was

an association between advanced periodontitis and a sustained high level of CRP (>3 mg/l) in the 60–70-year-old European men studied. There was also an association between high levels of tooth loss and high CRP.

Practical implications: Dentists should be aware that advanced periodontitis is associated with high levels

of CRP. Sustained levels of CRP which are >3 mg/l place individuals into a high-risk category in relation to the occurrence of cardiovascular events. An increased focus on lowering CRP, which may include treatment aimed at improving the periodontal condition, may benefit cardiovascular health.