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A systematic review and meta-analyses on C-reactive protein in relation to periodontitis

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Abstract

Aim: Elevated plasma C-reactive protein (CRP) is regarded as a risk predictor for cardiovascular diseases. This systematic review explored the robustness of observations that CRP is elevated in periodontitis. Similarly, the effect of periodontal therapy on CRP levels was investigated.

Material and Methods: Selection of publications was based on: (1) cross-sectional (case–control) studies; (2) longitudinal (treatment) studies; (3) high-sensitivity CRP measurement; (4) median and/or mean (± SD) values presented; and (5) subjects with no systemic disorders.

Results: Screening of the initially 448 identified studies and reference checking resulted in 18 suitable papers. The majority of the studies showed that CRP levels are higher in patients than in controls. Often, studies showed that patients had CRP levels >2.1 mg/l. A meta-analysis of 10 cross-sectional studies showed that the weighted mean difference (WMD) of CRP between patients and controls was 1.56 mg/l ($p<0.00001$). Evidence from available treatment studies ($n=6$) showed lower levels of CRP after periodontal therapy. Eligible treatment studies in a meta-analysis demonstrated a WMD of reductions of CRP after therapy of 0.50 mg/L (95% CI 0.08–0.93) ($p=0.02$).

Conclusions: There is strong evidence from cross-sectional studies that plasma CRP in periodontitis is elevated compared with controls. There is modest evidence on the effect of periodontal therapy in lowering the levels of CRP.

Key words: cardiovascular diseases; C-reactive protein (CRP); meta-analysis; periodontitis; systematic review

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Periodontitis is a destructive inflammatory disease of the supporting tissues of the teeth (Pihlstrom et al. 2005). This condition is caused by a chronic, mixed infection of Gram-negative bacteria, such as *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythensis* and *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*, and Gram-positive bacteria, such as *Peptostreptococcus micros* and *Streptococcus intermedius* (Socransky et al. 1998). Epidemiological studies have shown that about 10% of the adult population and about 30% of individuals over the age of 50 years suffer from severe periodontitis (Brown et al. 1990, Gjermo 1998), although a more recent epidemiological study indicates that the prevalence in the USA may have decreased to 4.2–7.3% (Borrell et al. 2005).

The host responds to the periodontal infections with an array of events involving both innate and adaptive immunity. Although periodontitis is chronic in nature, acute-phase elements are also part of the innate immunity in periodontitis and confirm that in periodontitis a systemic inflammation is present (Ebersole & Cappelli 2000, Loos 2005). The acute-phase reactants have pro-inflammatory properties; they activate complement factors, neutralize invasive pathogens and stimulate repair and regeneration of a variety of tissues. The acute-phase reactants receiving the most attention are C-reactive protein (CRP), plasminogen-activator 1 (PAI-1), and fibrinogen (Blake & Ridker 2002). CRP in particular has been the focus of attention as a key marker of atherosclerosis and elevated levels (e.g. $\geqslant 2.1$ mg/l) constitute a risk predictor for cardiovascular disease (CVD) (Ridker et al. 1997, 2004, Danesh et al.

Conflict of interest and source of funding statement

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1998, Blake & Ridker 2001, 2002, 2003, Blake et al. 2003). Importantly, CRP is currently regarded as a biomarker of systemic inflammation.

Several studies have examined the relationship between periodontitis and CRP using various designs including observational cross-sectional (case–control) and longitudinal studies. The reason for the interest in plasma levels of CRP in periodontitis lies in the fact that epidemiological research indicates that periodontitis is associated with CVD. A number of studies have demonstrated an association between periodontal disease and the risk of myocardial infarction and stroke as well as the underlying condition atherosclerosis (Janket et al. 2003, Meurman et al. 2004, Desvarieux et al. 2005, Leivadaros et al. 2005, Söder et al. 2005). However, the identified relationship between periodontal disease and CVD has not yet indicated a causal association. It is conceivable that elevated levels of CRP in periodontitis can explain at least in part the association between periodontitis and CVD.

The purpose of the present review was to investigate the robustness of observations that plasma/serum levels of CRP are elevated in patients with destructive periodontal disease in comparison with subjects without periodontitis. Two hypotheses were formulated: (1) CRP levels in periodontitis patients are significantly higher than in subjects who are not suffering from periodontitis and (2) periodontal treatment can reduce CRP levels in periodontal patients.

Material and Methods

Literature search

Two internet databases were selected in search of appropriate papers for the study purpose: the National Library of Medicine, Washington DC, USA (MEDLINE-PubMed), and the Cochrane Central Register of Controlled Trials (CENTRAL) (both databases were searched from 1965 up to 1 June 2007).

Eligibility criteria were:

(a) (Observational) cross-sectional (case–control) studies in humans (plasma/serum CRP levels in periodontitis patients and control subjects);
(b) Longitudinal (treatment) studies: randomized-controlled trials (RCT's) and controlled clinical trials (CCT's) (CRP levels before and after periodontal therapy); >1-month follow-up;
(c) High sensitivity-CRP (hs-CRP) measurement; and
(d) Subjects with no systemic disorders, including no history of CVD and/or atherosclerosis and/or diabetes.

Only articles in English were included (Moher et al. 2000). Papers without abstracts whose title suggested that they were related to the objectives of this review were also selected so that the full text could be screened. Data that were published twice or more often were selected only once. Reviews on CRP levels were excluded after screening for unpublished data. The search was supplemented by reference checking.

Search strategy

We performed the electronic search according to the most recent recommendations (Midgette et al. 1993, Deville et al. 2002, Cochrane Collaboration-Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests Recommended methods www.cochrane.org/docs/sadt.htm). The primary outcome variable was CRP plasma/serum levels in periodontitis patients. The databases were searched using the following strategy and keywords:

(Disease or parameter of disease) Periodontitis [MeSH] in all trees/subheadings OR Periodontal Attachment Loss [MeSH] in all trees/subheadings OR Periodontal Diseases [MeSH] in all trees/subheadings OR Periodontitis [Text Words] OR Periodontal Attachment Loss [Text Words] OR Periodontal Disease(s) [Text Words] OR Periodontal Pocket [Text Words]

AND

(Outcome) C-Reactive Protein(s) [MeSH] in all trees/subheadings OR CRP [MeSH] in all trees/subheadings OR Acute Phase Protein(s) [MeSH] in all trees/subheadings in OR C-Reactive Protein(s) [Text Words] OR CRP [Text Words] OR Acute Phase Protein(s) [Text Words]

Screening and selection of papers

We evaluated independently papers derived from the literature searches by title and abstract. As a second step, full-text papers were obtained when they fulfilled the criteria of the study aim. Any disagreement between the reviewers was resolved after additional discussion.

Factors that were evaluated to be able to investigate the heterogeneity of the primary outcome across studies:

(a) Definition of periodontitis (case status) and definition of control by the various research groups;
(b) History of systemic medications including antibiotics and non-steroidal anti-inflammatory drugs within the last 6 months;
(c) Number of subjects;
(d) Mean age and age range of subjects;
(e) Gender;
(f) Social Economic Status (SES); and
(g) Methodological study quality assessment.

Methodological study quality assessment:

For cross-sectional (observational) studies, the quality assessment was based on the use of checklists (Centre for Reviews and Dissemination, University of York, York, UK, YO10 5DD, http://www.york.ac.uk/inst/crd/; http://www.york.ac.uk/inst/crd/pdf/crd4_ph0.pdf) evaluating the following parameters:

(a) adequacy of definition of patients *versus* controls;
(b) adequacy of definition of and the method used to measure the exposure;
(c) exclusion of possible selection bias;
(d) control of possible confounders; and
(e) comparability of cases and controls with respect to potential confounding factors.

For RCTs or CCTs, the following parameters were investigated (Cochrane Handbook of Systematic reviews, http://www.cochrane.dk/cochrane/handbook/hbook.htm):

(a) allocation concealment;
(b) randomization;
(c) blindness of examiner or patients; and
(d) loss to follow-up.

Data extraction and statistical analysis

We included all appropriate studies reporting medians (and range if reported)

and/or means [± standard deviation(SD)] for hsCRP. When periodontitis patients were stratified by severity categories, data from all severity groups were entered separately and used in the analyses. Some studies reported only median values (and range) due to the non-normal data distribution. Because meta-analysis of median values was not possible, as a second step, studies reporting means (± SD) were processed for data extraction and meta-analyses. When not reported, or where it was not clear whether data normalization had taken place it was assumed that the means (± SD) in a given study were rightfully used. All suitable data were entered and analysed with RevMan 4.2. (http://www.cc-ims.net/RevMan). Meta-analyses were conducted separately for cross-sectional studies and longitudinal (treatment) studies. For the latter, the difference (Δ) baseline-end was calculated by means of the formula:

$$\Delta\text{CRPti} = \text{CRPti1} - \text{CRPti2},$$

where CRPti1 is the mean CRP value before treatment and CRPti2 is the mean CRP value after treatment. For each study, the variance (and consequently the SD) of ΔCRPti was estimated as follows (Rosner 2000):

$$\text{Sti}^2 = \text{Sti1}^2 + \text{Sti2}^2 - 2r \cdot \text{Sti1} \cdot \text{Sti2},$$

where Sti^2 is the variance of difference in CRP levels, Sti1^2 is the variance of the mean baseline CRP value, Sti2^2 is the variance of the mean end CRP value, r is the correlation between the baseline and end values and Sti1 and Sti2 are the SDs of the baseline and end values, respectively. We assumed a correlation r of 0.5 as was described before (Ioannidou et al. 2006).

For each meta-analysis, the weighted mean difference (WMD) nested in a random effect model, with corresponding Z-statistics, p-values and 95% confidence intervals (CI), was calculated. Also, a test for heterogeneity for each meta-analysis was performed; for this test, the I^2-statistic describes the proportion of total variation due to heterogeneity, where 0% indicates no heterogeneity and 100% indicates maximal heterogeneity among studies included in the meta-analysis (Higgins & Thompson 2002). Further analysis of heterogeneity included controlling for gender and socioeconomic level because it is often reported that these factors can independently have a major impact on the CRP values (Jousilahti et al. 2003, Lakoski et al. 2006, Pollitt et al. 2007); if possible, during this investigation we strived for meta-analyses with an I^2 of 0%, to secure maximal robustness of any result that appeared.

The forest plots for each meta-analysis present:

(a) The raw data (means, SDs and sample sizes) for each arm per included study;
(b) Point estimates and CIs for the chosen effect measure, as blocks and lines, respectively;
(c) Heterogeneity statistic (I^2);
(d) The total number of participants per group;
(e) The overall average effect (WMD and Z-statistics) in the random effect model; and
(f) Percent weight given to each study.

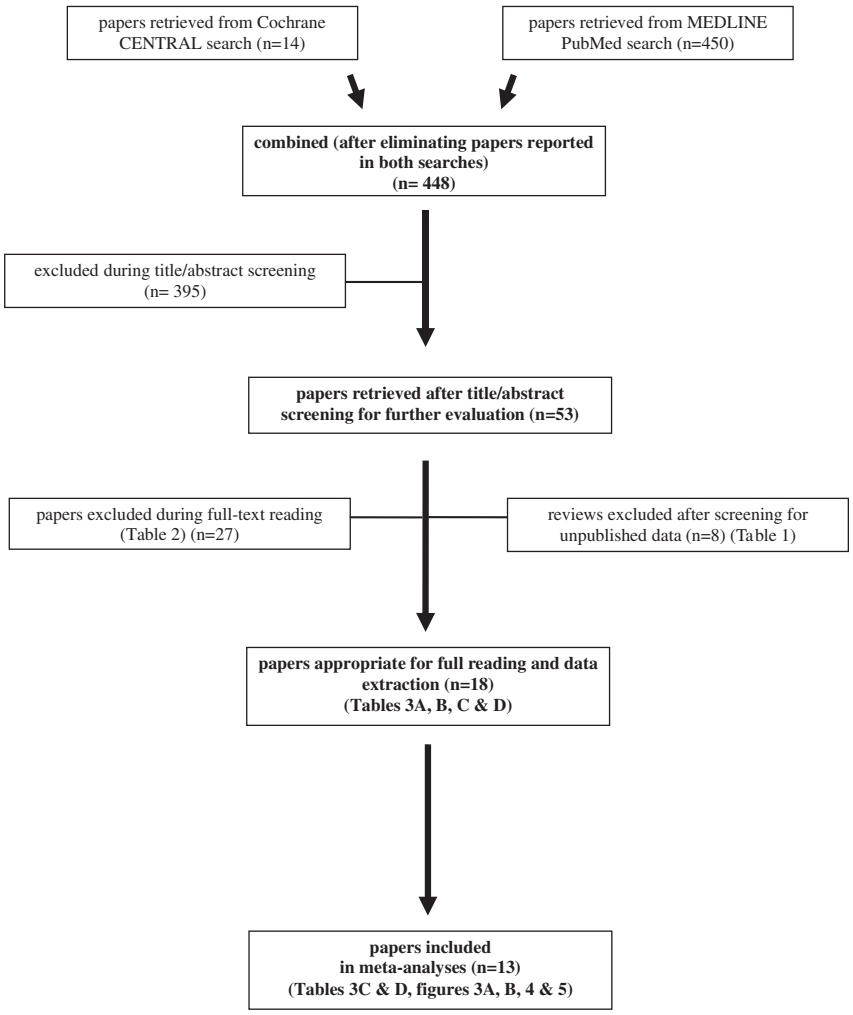

Fig. 1. Flow-chart outlining the search strategy and results along the various steps.

Results

The combined MEDLINE PubMed and Cochrane CENTRAL search resulted in 448 potentially eligible articles (Fig. 1). These articles were screened by title and abstract for eligibility. The screening resulted in 53 articles, that qualified for full-text reading. Screening of reviews ($n = 8$) (Table 1) for unpublished data did not give any additional paper. One review, however, (Loos 2005) provided additional information on means (± SD) of an already published paper (Loos et al. 2000). After full-text reading, 27 papers were considered to be unsuitable and were therefore excluded; Table 2 presents the excluded studies and the main reason(s) for exclusion. Eighteen articles fulfilled the inclusion criteria and were processed for data extraction (Tables 3A–D) (Fredriksson et al. 1998, 1999, 2003, Loos et al. 2000, Noack et al. 2001,

Table 1. Reviews used for screening of unpublished data and reference checking, in reversed chronological order

Author(s)	Type of review	Results
Ioannidou et al. (2006)	Systematic	No further new data retrieved
Loos (2005)	Traditional	Provided means (± SD) for Loos et al. (2000)
Ebersole et al. (2002)	Traditional	No further new data retrieved
Beck & Offenbacher (2002)	Traditional	No further new data retrieved
Ebersole & Cappelli (2000)	Traditional	No further new data retrieved
Beck et al. (2000)	Traditional	No further new data retrieved
Greenwell (2000)	Traditional	No further new data retrieved
McCarty (1999)	Traditional	No further new data retrieved

Table 2. Studies ($n = 27$) which were excluded from the review in reversed chronological order and main reason(s) for rejection

Author(s)	Main reason for exclusion
Taylor et al. (2006)	No control group, no periodontal therapy, only extractions
Elter et al. (2006)	Short-term (<1 month), no control group
D'Aiuto et al. (2005a)	Short-term (1 month), means (± SD) reported on graphs
Bretz et al. (2005)	No case–control, no treatment
Persson et al. (2005)	No distinction between periodontitis and non-periodontitis individuals in the non-acute myocardial infarction (AMI) group
Leivadaros et al. (2005)	Mean (± SD) reported on graphs
Rahman et al. (2005)	No high sensitivity C-reactive protein (CRP) measurement used, no periodontal therapy, only extractions
Dye et al. (2005)	Detection limit for the CRP measurement was 3 mg/l
D'Aiuto et al. (2004a)	1 month, no control group
D'Aiuto et al. (2004b)	No control group
Ide et al. (2004)	< 1 month follow-up
D'Aiuto et al. (2004c)	Additional analysis of already reported study D'Aiuto et al. (2004b)
Saito et al. (2003)	Sensitivity of the method for the CRP measurement not reported, detection limit for the CRP measurement not reported, no quantitative data could be extracted
Furuichi et al. (2003)	CRP determination method is not reported, periodontal status determined by means of CPITN
Iwamoto et al. (2003)	Systemically not healthy patients, no control group, no quantitative data could be extracted
Ajwani et al. (2003)	No quantitative data could be extracted, detection limit for the CRP measurement was 3 mg/l
Slade et al. (2003)	No high sensitivity CRP measurement used; no case–control, no means (± SD) or medians reported
Mattila et al. (2002)	No quantitative data could be extracted after intervention; unclear whether high sensitivity CRP method was used
Bloemenkamp et al. (2002)	Only women, cases were unhealthy (peripheral arterial disease), only odds ratios, no means (± SD) or medians reported
Glurich et al. (2002)	No high sensitivity CRP measurement used
Fredriksson et al. (2002)	Treated patients, no high sensitivity CRP measurement used
Wu et al. (2000)	No quantitative data could be extracted
Slade et al. (2000)	Detection limit for the CRP measurement was 3 mg/l
Wakai et al. (1999)	No quantitative data could be extracted, periodontal status determined by means of CPITN
Ebersole et al. (1997)	No high sensitivity CRP measurement used
Shklair et al. (1968)	No high sensitivity CRP measurement used
Boucher et al. (1967)	No high sensitivity CRP measurement used

Amar et al. 2003, Buhlin et al. 2003, Craig et al. 2003, Ide et al. 2003, Joshipura et al. 2004, D'Aiuto et al. 2005a, 2006, Seinost et al. 2005, Yamazaki et al. 2005, Havemose-Poulsen et al. 2006, Salzberg et al. 2006, Bizzarro et al. 2007, Tonetti et al. 2007).

Tables 3A and B present the median values (and range, if available) for patients and controls from the cross-sectional and interventional studies, respectively. Tables 3C and D display the included papers for the cross-sectional and interventional studies, respectively, reporting on mean values (± SD).

Quality assessment

The various aspects of the quality assessment of the included studies are presented in Tables 3A–D.

Quantitative data analysis

Evaluation of studies reporting median values (and ranges)

Cross-sectional studies. From the studies appearing in Table 3A (representing in total 421 patients and 240 controls), five studies (Fredriksson et al. 1999, Loos et al. 2000, Yamazaki et al. 2005, Havemose-Poulsen et al. 2006, Salzberg et al. 2006) reported higher median values of CRP for periodontal patients (range 0–14.4 mg/l) in relation to the controls (range 0–12 mg/l), whereas only one paper (Fredriksson et al. 2003) reported equal median values between cases and controls. Figure 2 displays the distribution of the median values for the periodontitis patients and controls of the studies reporting medians. Out of nine median CRP values presented for patients, four were > 2.1 mg/l. Reported statistical analysis yielded the following: two studies (Fredriksson et al. 1999, Salzberg et al. 2006) revealed statistically significant differences between patients and controls, whereas two other studies (Loos et al. 2000, Havemose-Poulsen et al. 2006) demonstrated significant differences only at the subgroup level (i.e. only subjects with generalized disease showed significantly higher CRP plasma levels in comparison with the controls). Finally, two studies (Fredriksson et al. 1999, Yamazaki et al. 2005) showed no statistical differences between periodontal patients and their healthy counterparts for CRP levels.

Longitudinal (treatment) studies (Table 3B). Two studies (in total 48 patients and 38 controls) (Ide et al. 2003, Yamazaki et al. 2005) reported lower median CRP values after treatment compared with baseline levels; however, the treatment effect was not statistically significant.

Table 3A. Included cross-sectional studies using median values (and range), in reversed chronological order, and study characteristics

Author(s)	Study design	Diagnostic criteria*/examiner	Method†	*n* (P/C)	CRP median (mg/l) (range) (P/C)	Medical condition	Age (mean) (P/C)	Controlling for potential confounding factors for CRP levels
Havemose-Poulsen et al. (2006)	Case–control	Subgroup GaP: interproximal attachment loss on at ⩾3 permanent teeth other than first molars and incisors and ⩾10 of the sites showing bleeding/suppuration on probing Periodontist	4	27/25	5 (NR)/3 (NR)	Given	32/25	NR
Havemose-Poulsen et al. (2006)	Case–control	Subgroup LaP : interproximal AL⩾2 permanent teeth, one of which was a first molar, and involving no more than two teeth other than first molars and incisors; confirmed circumpubertal disease onset and at least one of the sites showing bleeding/suppuration on probing Periodontist	4	18/25	3 (NR)/3 (NR)	Given	20/25	NR
Salzberg et al. (2006)	Case–control	Subgroup GaP: ⩾5 mm on ⩾8 teeth, ⩾3 of which are not first molars and incisors; age of onset was under 35 years Unknown examiner	2	93/91	2.732 (0.073–14.04)/0.816 (0.033–10.07)	Given	31/31	Age, gender, race, smoking
Salzberg et al. (2006)	Case–control	Subgroup LaP: localized pattern of clinical AL limited to first molar or incisor teeth and up to two additional teeth; age of onset was under 30 years Unknown examiner	2	97/91	1.115(0.024–14.13)/0.816 (0.033–10.07)	Given	23/31	Age, gender, race, smoking
Yamazaki et al. (2005)	Case–control	Pocket depth, attachment loss, radiographs, moderate to advanced periodontitis patients, non-smokers Unknown examiner	1	24/23	0.317‡/0.195	Given	41/44	NR
Fredriksson et al. (2003)	Case–control (matched) Cases: treated periodontal patients with healthy gingiva	At least six sites with AL > 5 mm Unknown examiner		15/15	1 (0.45–2.4)/0.6 (0.3–1.5)	Given	51/53	Matched for age gender and smoking (non-smokers); other factors are not reported
Loos et al. (2000)	Case–control	Subgroup GP: ⩾8 teeth with bone loss extending to the middle 1/3 RL Periodontist	1	54/43	1.45/0.90	Given	42/42	Educational level, age, gender, ethnicity, BMI, smoking, high blood pressure, cholesterol. Seropositivity for CMV, *Chlamydia pneumoniae* and *H. pylori*
Loos et al. (2000)	Case–control	Subgroup LP: <8 teeth with bone loss extending to the middle 1/3 RL periodontist	1	53/43	1.30/0.90	Given	42/42	Educational level, age, gender, ethnicity, BMI, smoking, high blood pressure, cholesterol. Seropositivity for CMV, *C. pneumoniae* and *H. pylori*
Fredriksson et al. (1999)	Case–control	At least six sites with AL⩾5 mm Unknown examiner	4	40/43	2 (0–13)/0 (0–12)		52/51	NR

P, periodontitis; C, control; NR, not reported; LaP, localized aggressive periodontitis; GaP, generalized aggressive periodontitis; LP, localized periodontitis; GP, generalized periodontitis.

*Diagnostics: PD, probing depth; RL, root length; AL, attachment loss.

†Method: 1 = nephelometric, 2 = ELISA, 3 = radial immunodiffusion assay, 4 = immunoturbidimetric.

‡C-reactive protein (CRP) value for the P (periodontitis) group before periodontal treatment.

Table 3B. Included treatment studies using median values and range in the presentation of results in reversed chronological order and study characteristics

Author(s)	Study design	Intervention	Diagnostics criteria*/examiner	Method†	*n* (P/C)	CRP median (range) (mg/l) before/after treatment	Baseline CRP median (mg/l) P/C	Medical condition	Age (mean) P/C
Yamazaki et al. (2005)	Case–control	Non-surgical periodontal therapy, periodontal surgery (antibiotics for 4 days)	Pocket depth, attachment loss, radiographs, moderate to advanced periodontitis patients non-smokers unknown examiner	1	24/23	0.317/0.261 (periodontitis patients) (NR)	0.397/0.195 (NR)	Given	41/44
Ide et al. (2003)	Prospective RCT 2 groups of periodontitis patients Immediate *versus* delayed treatment	Non-surgical periodontal therapy	At least five sites with PPD > 5 mm and radiographic evidence of AL unknown examiner	1	24/15	1.42 (IQR: 0.63–2.53)/1.28 (IQR: 0.39–2.45)‡	1.42 (IQR: 0.63–2.53)/2.19 (IQR: 0.26–2.91)‡	Given	48/46 range 30–60

*Diagnostics: PD, probing depth; RL, root length; AL, attachment loss.
†Method: 1 = nephelometric, 2 = ELISA, 3 = radial immunodiffusion assay, 4 = immunoturbidimetric.
‡Values referring to the delayed treatment group.
For abbreviations see Table 3A.
IQR, inter-quartile range.

Evaluation of studies reporting means (± SD)

Cross-sectional studies (Table 3C). Ten studies (Fredriksson et al. 1998, Loos et al. 2000, Noack et al. 2001, Amar et al. 2003, Buhlin et al. 2003, Craig et al. 2003, Joshipura et al. 2004, Havemose-Poulsen et al. 2006, Salzberg et al. 2006, Bizzarro et al. 2007) totalled 702 patients with periodontitis and 902 control subjects. The majority of the studies (Fredriksson et al. 1998, Loos et al. 2000, Noack et al. 2001, Amar et al. 2003, Joshipura et al. 2004, Bizzarro et al. 2007) showed statistically significant differences between patients and controls for CRP levels. Two studies (Buhlin et al. 2003, Havemose-Poulsen et al. 2006) showed significant differences at the subgroup level, namely the subgroup of male smoking patients (Buhlin et al. 2003) and the generalized aggressive periodontitis subgroup (Havemose-Poulsen et al. 2006) showed statistically significant higher CRP levels when compared with controls. Lastly, only one study (Craig et al. 2003) reported no significant differences between groups although the absolute values of CRP plasma levels were higher in the patient groups. All studies reported mean CRP values >2.1 mg/l for patients and eight out of 10 papers reported values $\leqslant 2.1$ mg/l for controls.

Longitudinal (treatment) studies (Table 3D). The total number of treated patients and controls (non-treated individuals) from the four interventional studies was 152 and 134, respectively. One study (Seinost et al. 2005) included healthy controls. Two studies included untreated periodontitis as controls (D'Aiuto et al. 2005b, Tonetti et al. 2007). In the studies by D'Aiuto et al. (2005b) and Seinost et al. (2005), intensive periodontal treatment (including the use of systemic or local antibiotics) resulted in a statistically significant decrease of the CRP plasma levels after 2 and 3 months, respectively. In the Tonetti et al. (2007) study, the difference between the intensive periodontal treatment group and the control group receiving supragingival scaling/polishing was 1.4 mg/l at 2 and 6 months post-treatment, but failed to reach statistical significance. Two studies (D'Aiuto et al. 2005b, 2006) used a similar protocol and compared the standard treatment with the intensive

Table 3C. Included cross-sectional studies reporting means (± SD), study characteristics and quality assessment, in reversed chronological order

Author(s)	Study design	Diagnostics*/examiner, criteria	Method†	*n* (P/C)	CRP (mg/l) levels P/C	Medical condition	Age (mean) (P/C)	Controlling for potential confounding factors for CRP levels
Bizzarro et al. (2007)	Case–control	Subgroup severe periodontitis radiographs Severe Periodontitis (SeP): Patients with ⩾7 teeth with ⩾50% bone loss Periodontist	1	38/39	3.10 (4.40)/1.9 (2.00)	Given	46/40	NR
Bizzarro et al. (2007)	Case–control	Subgroup moderate periodontitis radiographs Moderate periodontitis (MoP): patients with <7 teeth with <50% bone loss Periodontist	1	53/39	3.10 (3.30)/1.90 (2.00)	Given	44/40	NR
Havemose-Poulsen et al. (2006)	Case–control	GaP: interproximal attachment loss on at ⩾3 permanent teeth other than first molars and incisors and ⩾10 of the sites showing bleeding/suppuration on probing Periodontist	4	27/25	5.00 (2.70)/3.00 (2.00)	Given	32/25	NR
Havemose-Poulsen et al. (2006)		LaP: interproximal AL⩾2 permanent teeth, one of which was a first molar, and involving no more than two teeth other than first molars and incisors; confirmed circumpubertal disease onset and at least one of the sites showing bleeding/suppuration on probing Periodontist	4	18/25	5.00 (5.40)/3.00 (2.00)	Given	20/25	NR
Salzberg et al. (2006)	Case–control	Subgroup GaP: ⩾5 mm on ⩾8 teeth, ⩾3 of which are not first molars and Incisors; age of onset was under 35 years Unknown examiner	2	93/91	3.72 (2.88)/1.54 (2.95)	Given	31/31	Age, gender, race, smoking
Salzberg et al. (2006)	Case–control	Subgroup LaP: localized pattern of clinical AL limited to first molar or incisor teeth and up to two additional teeth; age of onset was under 30 years Unknown examiner	2	97/91	2.57 (2.95)/1.54 (2.95)	Given	23/31	Age, gender, race, smoking
Joshipura et al. (2004)	Case–control	Self-report	1	91/377 all men	2.20 (2.25)/1.80 (3.00)	Given	All 47–80	Age, alcohol, cigarette smoking, BMI, physical activity and regular aspirin intake
Buhlin et al. (2003)	Case–control	At least seven sites with >6 mm AL Dentist	1	50/46	3.28 (4.64)/1.74 (1.68)	Given	50/52	NR
Amar et al. (2003)	Case–control	Radiographs at least six teeth with pocket depth >5 mm and loss of attachment of ⩾3 mm in three aspects of each involved tooth Periodontist	1	26/29	2.30 (2.30) ($n = 17$)/1.00 (1.00) ($n = 21$)	Given	42/41	NR
Craig et al. (2003)	Case–control	⩾20 teeth with ⩾4 sites with PD >3 mm and ⩾4 sites with AL>3 mm Unknown examiner	2	44/25	5.78 (1.07)/2.46 (1.44)	Given	39/30	Age, gender and percentage current smokers
Noack et al. (2001)	Case–control	>3 mm AL Calibrated examiner	3	50/65	4.06 (5.55)/1.70 (1.91)	Given	68/54	Age, gender, origin, Smoking, Cholesterol, BMI, LDL, HDL, TG
Loos et al. (2000)	Case–control	Pooled sample of: GP ($n = 54$): ⩾8 teeth with bone loss extending to the middle 1/3 RL LP ($n = 53$): <8 teeth with bone loss extending to the middle 1/3 RL Periodontist	1	107/43	2.64 (3.48)/1.21 (1.34)‡	Given	41/42	Educational level, age, gender, ethnicity, BMI, smoking, high blood pressure, cholesterol. Seropositivity for CMV, *Chlamydia pneumoniae* and *Helicobacter pylori*

Table 3C. (Contd.)

Author(s)	Study design	Diagnostics*/examiner, criteria	Method†	*n* (P/C)	CRP (mg/l) levels P/C	Medical condition	Age (mean) (P/C)	Controlling for potential confounding factors for CRP levels
Fredriksson et al. (1998)	Case–control (matched)	At least six sites with marked attachment loss (clinical attachment level >5 mm) Unknown examiner	1	17/17	2.62 (2.90)/0.87 (1.73)	Given	53/52	NR

*Diagnostics: PD, probing depth; RL, root length; AL, attachment loss.
†Method: 1 = nephelometric, 2 = ELISA, 3 = radial immunodiffusion assay, 4 = immunoturbidimetric.
‡Data reported by Loos (2005).
For abbreviations see Table 3A.
BMI, body mass index, HDL, high-density lipoproteins; LDL, low-density liporoteins; TG, triglycerides.

Table 3D. Included treatment studies reporting means (± SD), study characteristics and quality assessment, in reversed chronological order

Author(s)	Study design/ duration.	Diagnostics*/examiner, criteria	*n* (P/C)	CRP (mg/l) levels before/after treatment	Medical condition	Age (mean) (P/C)	Method†	Treatment‡	Quality assessment§			
									RAND	ALLOC	BLIND	FOL
Tonetti et al. (2007)	Longitudinal RCT¶ 6 months	PD >6 mm and marginal alveolar bone loss of >30% with ⩾50% of teeth Well trained dental examiner	61/59	3.8 (5.3‖)/NR (data presented in graphs)	Given	48/48	4	1, 2	1	1	1	1, 2
D'Aiuto et al. (2006)	Longitudinal RCT** 6 months	>4 mm PD radiographic Unknown examiner	20/20	1.80/1.10	Given	48	4	1, 2	1	1	1	1, 2
Seinost et al. (2005)	Longitudinal CCT†† 3 months	>5 mm AL radiographic Periodontists	30/31	1.70/1.10	Given	40/41	1	1, 2	1	1	3	1, 2
D'Aiuto et al. (2005b)	Longitudinal RCT‡‡ 2 months	>6 mm PD Unknown examiner	20/24	2.00/1.60	Given	51/48	4	1, 2	1	1	1	1, 2, 3

*Diagnostics: PD, probing depth; RL, root length; AL, Attachment loss.
†Method: 1 = nephelometric, 2 = RID/ELISA, 3 = radial immunodiffusion assay, 4 = immunoturbidimetric.
‡Treatment: 1 = root planning, 2 = antibiotics.
§Quality assessment: RAND: randomization ALLOC, allocation concealment; BLIND, blindness; FOL, Follow-up.
Randomization: 1 = adequate, 2 = inadequate, 3 = unclear;
Allocation: 1 = adequate, 2 = inadequate, 3 = unclear;
Blindness: 1 = single blind, 2 = double blind, 3 = not blind/unclear;
Follow-up: 1 = The number of patients at baseline and at completion of the follow-up interval reported, 2 = all the patients who entered the trial properly accounted for at completion, 3 = The analysis take into account the drop-outs/losses to follow-up or the excluded patients.
¶PICO; P, periodontal patients; I, intensive (with local antibiotics) periodontal Tx and supragingival scaling/polishing; C, supragingival scaling/polishing *versus* standard periodontal Tx; O, levels of biomarkers (CRP).
‖Standard error of the mean.
**PICO: P, periodontal patients; I, intensive (with local antibiotics) periodontal Tx and standard periodontal Tx; C, intensive *versus* standard periodontal Tx; O, levels of biomarkers such as CRP.
††PICO: P, periodontal patients; I, periodontal Tx (with syst. antibiotics) and standard periodontal Tx; C, intensive *versus* standard periodontal Tx or Control; O, levels of biomarkers such as CRP.
‡‡PICO: P, periodontal patients, I, intensive periodontal Tx (with local antibiotic), C: diameter brachial artery before and after periodontal Tx *versus* control subjects; O, levels of biomarkers and diameter of brachial artery.
For abbreviations see Table 3A.

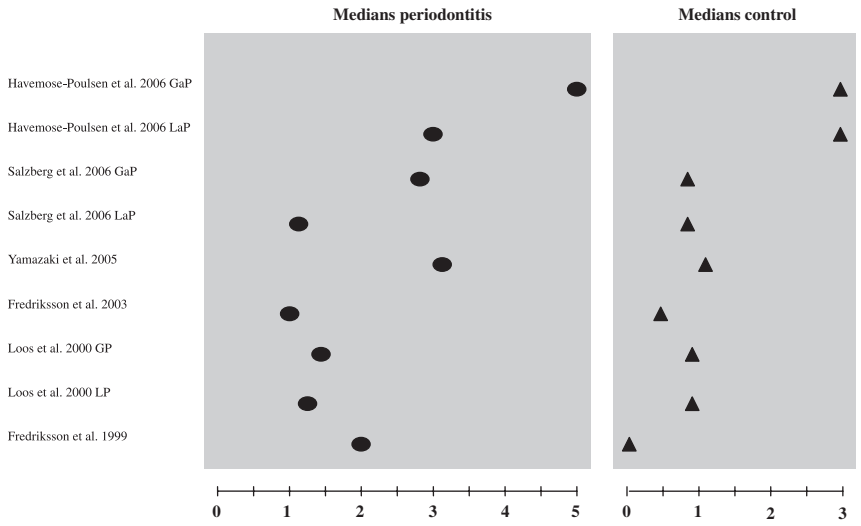

Fig. 2. Distribution of median values in case-control studies.

periodontal treatment. In those studies, the intensive periodontal treatment was found to be more effective than the standard periodontal treatment in reducing the plasma CRP levels.

Meta-analyses

The main outcome measure was the WMD of plasma/serum CRP levels in the cross-sectional studies for periodontitis patients and controls, and in longitudinal treatment studies (RCTs and CCTs) the WMD of the differences in CRP levels between before and after treatment for patients and untreated subjects (controls).

In the first meta-analysis, only the cross-sectional studies were included (Fig. 3a) (Fredriksson et al. 1998, Loos et al. 2000, Noack et al. 2001, Amar et al. 2003, Buhlin et al. 2003, Craig et al. 2003, Joshipura et al. 2004, Havemose-Poulsen et al. 2006, Salzberg et al. 2006, Bizzarro et al. 2007). The mean (± SD) levels for CRP in the Loos et al. (2000) study were provided in the Loos (2005) paper. Consistently, all studies showed higher CRP levels in periodontitis patients than in controls. There was a statistically significant WMD (1.65 mg/l; 95% CI 1.05–2.24; $p<0.00001$) in CRP levels between the periodontitis patients and controls. However, there was considerable heterogeneity among the studies ($I^2 = 76.7\%$, Fig. 3a). Further investigation of heterogeneity (controlling for gender and SES as the most important factors) revealed two studies that contributed considerably to heterogeneity: the Craig et al. (2003) study, where there was a remarkable contribution of subjects with low SES, which is a known confounder in the outcome of CRP levels, and the Joshipura study (Joshipura et al. 2004), which not only showed a high SES, but additionally, only male subjects were included. Again, consistently all studies showed higher CRP levels in patients than in controls. The difference between patients and controls was highly significant ($p<0.00001$), and the estimated WMD was 1.56 mg/l (95% CI 1.21–1.90) (Fig. 3b) (Fredriksson et al. 1998, Loos et al. 2000, Noack et al. 2001, Amar et al. 2003, Buhlin et al. 2003, Havemose-Poulsen et al. 2006, Salzberg et al. 2006, Bizzarro et al. 2007).

The effect of periodontal treatment on CRP levels was also analysed from the available treatment studies. The Tonetti et al. (2007) study was not included in this analysis because no end-of-trial means (± SD) were reported. Figure 4 presents the results of the meta-analysis of the remaining studies comparing the groups receiving periodontal treatment with controls (Seinost et al. 2005, D'Aiuto et al. 2005b). It should be noted that a subgroup of the D'Aiuto et al. (2005b) and the study group of Seinost et al. (2005) received either local (D'Aiuto et al. 2005b) or systemic (Seinost et al. 2005) antibiotics (intensive treatment). The range of mean differences between baseline and end for the treatment groups was 0.00–0.60 mg/l, while untreated individuals showed a corresponding range of −0.10 to 0.00 mg/l. The WMD for the means of CRP differences baseline-end between treatment groups and control groups was 0.50 mg/L (95% CI 0.08 to 0.93) (test of the overall effect $p = 0.02$, $I^2 = 0\%$).

Finally, a meta-analysis was performed (Fig. 5) for two studies where we could compare the intensive and standard periodontal treatment protocols (D'Aiuto et al. 2005a, 2006). The mean differences between baseline and end for the intensive treatment groups were 0.40 and 0.60 mg/l, while standard treatment groups showed corresponding mean differences of −0.30 and 0.00 mg/l. The WMD for the means of CRP differences baseline-end between intensive treatment groups and standard treatment groups was 0.67 mg/L (95% CI −0.07 to 1.40); however, no statistically significant difference between the different protocols was found (test of the overall effect $p = 0.08$, $I^2 = 0\%$).

Discussion

There are now several reports indicating that bacteraemia may occur frequently in the periodontitis patient (Geerts et al. 2002, Kinane et al. 2005, Forner et al. 2006). The host responds to short-lived bacteraemia and systemic cytokine dumping from smouldering periodontitis lesions in a similar manner as would be the case with other chronic infections or inflammatory processes. For example, elevated levels of interleukin-6 (IL-6), known to induce hepatocytes to produce CRP and other acute-phase proteins and pro-coagulant mediators have also been reported in periodontitis patients (Loos 2005). Thus, it is not surprising that in periodontitis changes in cellular and molecular components of peripheral blood have been observed. The changes in blood parameters in periodontitis, however, are modest and, when they exist, often do not exceed the clinical ''normal'' values. The current study evaluated in a systematic manner the robustness of the observations that CRP levels are elevated in periodontitis patients and reviewed the effect of periodontal therapy on CRP levels.

Systematic reviews and meta-analyses are very useful tools for summarizing various findings. In the meta-analyses, only studies that reported mean values and SDs were included. However, often, investigators report only median values for CRP because plasma levels of CRP appear to have a statistically non-normal distribution. For this reason, separate tables and Fig. 2 were created for the studies reporting on medians (and ranges).

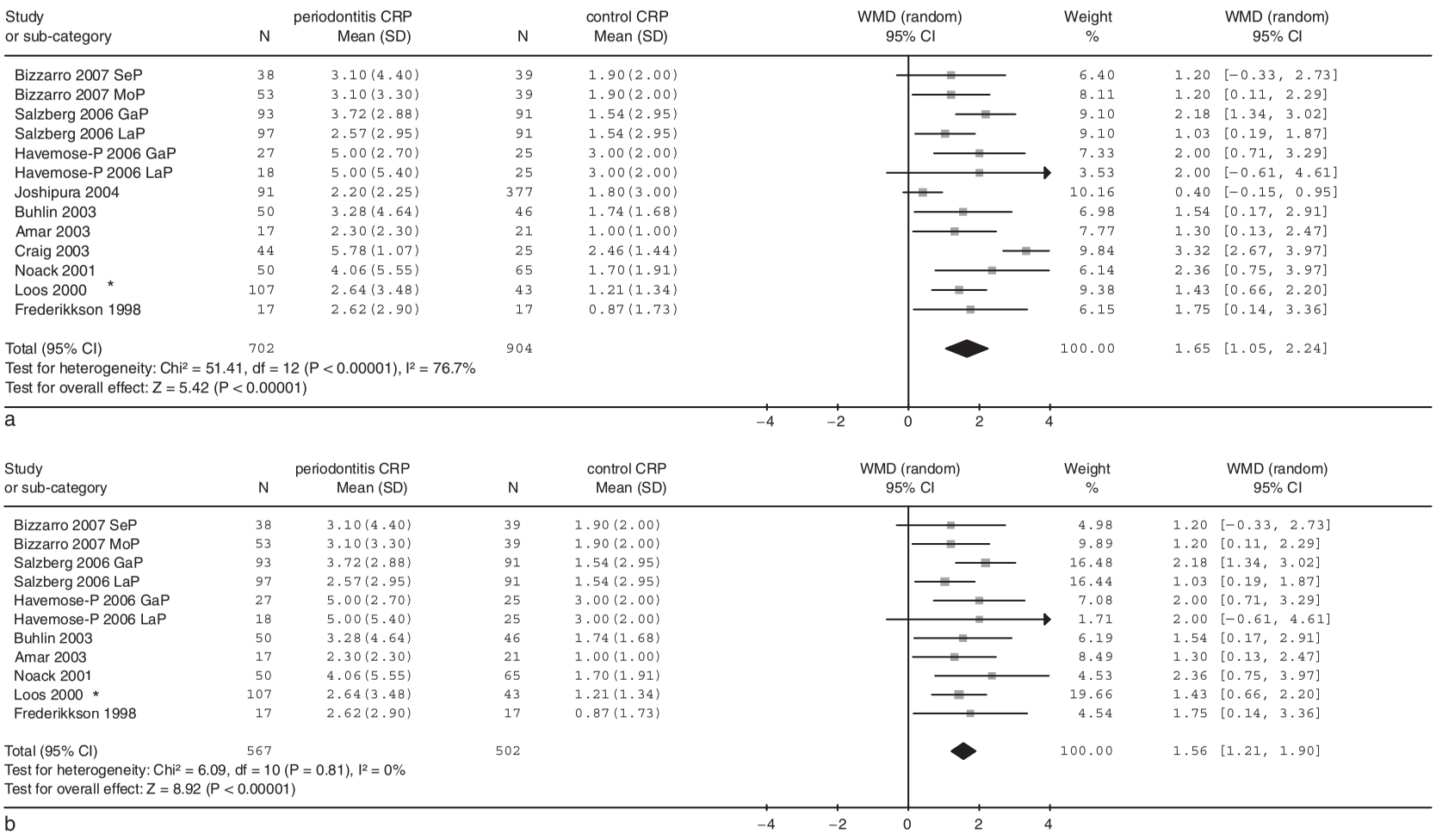

Fig. 3. Forest plots presenting the weighted mean difference (WMD) of CRP levels in mg/l between periodontitis patients and control subjects in cross-sectional studies, heterogeneity and overall effect for the initial analysis (a) and after controlling for heterogeneity (b). The studies are displayed in reverse chronological order. *Means and standard deviations were published in a review by Loos (2005). CRP, C-reactive protein.

Fig. 4. Forest plots presenting the weighted mean difference (WMD) of Δbaseline–end CRP levels in mg/l between the treatment groups and control groups, heterogeneity and overall effect for treatment studies. diff, difference; B, baseline; E, end; C, control (group); Tx, treatment (group); STx, standard treatment; ITx, intensive treatment; CRP, C-reactive protein.

Fig. 5. Forest plots presenting the weighted mean difference (WMD) of Δbaseline – end CRP levels in mg/l between intensive and standard periodontal treatment in periodontitis patients, heterogeneity and overall effect for treatment studies. diff, difference; B, baseline; E, end; ITx, intensive treatment; STx, standard treatment.

In the current systematic review, an important reason for study exclusion was related to the methodology of the CRP measurement; only high-sensitivity CRP measurements were accepted and therefore several studies were also excluded (Boucher et al. 1967, Shklair et al. 1968, Ebersole et al. 1997, Fredriksson et al. 2002, Glurich et al. 2002, Slade et al. 2003, Rahman et al. 2005). Similarly, when it was not clear or not stated whether the method used was of high sensitivity, studies had to be excluded (Mattila et al. 2002, Furuichi et al. 2003, Saito et al. 2003). Although the Dye et al. (2005) and Slade et al. (2000) studies used measurement by nephelometry with a latex particle-enhanced immunoassay, they could not detect CRP levels below 3 mg/l. Because the range 1–3 mg/l contains the critical values pertaining to CRP as a risk predictor, those studies were also excluded from the meta-analyses. Another study (Leivadaros et al. 2005) was excluded, because the means and SD could not be read reliably from the presented figure in the paper. A number of studies did not satisfy the criterion of >1-month follow-up results and therefore had to be excluded after full-paper reading (Ide et al. 2004, D'Aiuto et al. 2005a, Elter et al. 2006). Nevertheless, regardless of the reasons for exclusion, most of the excluded studies (Table 2) (Ebersole et al. 1997, Slade et al. 2000, Fredriksson et al. 2002, Glurich et al. 2002, Furuichi et al. 2003, Slade et al. 2003, Ide et al. 2004, Bretz et al. 2005, Dye et al. 2005, Leivadaros et al. 2005, Rahman et al. 2005, Elter et al. 2006) also reported CRP levels >2.1 mg/l in subjects with periodontitis.

In the present study, we show convincing evidence that CRP is consistently elevated in periodontitis patients compared with healthy controls. Analogous to the hypothesis that some infectious and inflammatory diseases may be associated with CVD, it is conceivable that the chronically elevated CRP levels in periodontitis patients exacerbate ongoing inflammatory processes in atherosclerotic lesions, thereby increasing the risk for cardiovascular and cerebrovascular events (Lusis 2000, Libby et al. 2002, Haynes & Stanford 2003, Tousoulis et al. 2003). Elevated levels of CRP (>2.1 mg/l) are associated with a higher incidence of acute thrombotic events including stroke and myocardial infarction (Ridker et al. 1997, 2002). CRP levels >2.1 mg/l in healthy

individuals may be associated with a chronic pro-coagulant state and they may serve as markers for an increased long-term risk of CVD (Blake & Ridker 2002, 2003).

Long-term treatment studies evaluating the effect of periodontal treatment on CRP values in relation to healthy controls are scarce. All treatment studies show an effect on CRP levels in favour of periodontal treatment (Tables 3B and D). The available studies included in the meta-analysis (Fig. 4) again showed a benefit of periodontal treatment for patients compared with untreated subjects. In two studies from D'Aiuto et al. (2005b, 2006), a standard periodontal treatment was also given to a second treatment group; the meta-analysis comparing the two treatment protocols (standard *versus* intensive treatment) (Fig. 5) failed to show a significant benefit of the intensive treatment although a trend ($p = 0.08$) towards intensive treatment was noted. Similar to another review on CRP levels before and after treatment (Ioannidou et al. 2006), we conclude that there are currently no large-scale and conclusive intervention trials investigating the effect of periodontal therapy on CRP levels.

It needs to be stressed that CRP is a non-specific marker of the acute-phase response. That is, many potential stimuli, including (unknown) chronic infections and or inflammatory conditions, smoking, obesity and trauma, may also account for mild increases in CRP (Blake & Ridker 2001, Blake et al. 2003, Florez et al. 2006). In the current meta-analyses, we could not adjust for these potential confounders although all studies were screened for these variables. Only a few studies (see Tables 3A and C) have controlled for potential confounding factors when analysing differences between patients and controls. It is therefore fair to speculate that periodontitis, in addition to other factors and infections reported in the literature, will result in moderately elevated levels of CRP and perhaps in part via this acute-phase response reactant may contribute to a higher risk for CVD.

In conclusion, this systematic review provides evidence that periodontitis elicits a mild acute-phase response with elevation of CRP levels compared with healthy controls. Periodontal treatment results in lowered CRP levels; however, the treatment studies available are scarce. Further research should investigate whether the changes in cellular and molecular markers in peripheral blood in periodontitis are indeed causally related to cardiovascular events and whether periodontal therapy and maintenance of periodontal health will reduce the risk for such events.

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References

Ajwani, S., Mattila, K. J., Narhi, T. O., Tilvis, R. S. & Ainamo, A. (2003) Oral health status, C-reactive protein and mortality – a 10 year follow-up study. *Gerodontology* **20**, 32–40.

Amar, S., Gokce, N., Morgan, S., Loukideli, M., Van Dyke, T. E. & Vita, J. A. (2003) Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, 1245–1249.

Beck, J. D. & Offenbacher, S. (2002) Relationships among clinical measures of periodontal disease and their associations with systemic markers. *Annals of Periodontology* **7**, 79–89.

Beck, J. D., Slade, G. & Offenbacher, S. (2000) Oral disease, cardiovascular disease and systemic inflammation. *Periodontology 2000* **23**, 110–120.

Bizzarro, S., van der Velden, U., Ten Heggeler, J. M., Leivadaros, E., Hoek, F. J., Gerdes, V. E., Bakker, S. J., Gans, R. O., Ten Cate, H. & Loos, B. G. (2007) Periodontitis is characterized by elevated PAI-1 activity. *Journal of Clinical Periodontology* **34**, 574–580.

Blake, G. J. & Ridker, P. M. (2001) High sensitivity C-reactive protein for predicting cardiovascular disease: an inflammatory hypothesis. *European Heart Journal* **22**, 349–352.

Blake, G. J. & Ridker, P. M. (2002) Inflammatory bio-markers and cardiovascular risk prediction. *Journal of Internal Medicine* **252**, 283–294.

Blake, G. J. & Ridker, P. M. (2003) C-reactive protein: a surrogate risk marker or mediator of atherothrombosis? *American Journal of Physiology – Regulatory Integrative and Comparitive Physiology* **285**, R1250–R1252.

Blake, G. J., Rifai, N., Buring, J. E. & Ridker, P. M. (2003) Blood pressure, C-reactive protein, and risk of future cardiovascular events. *Circulation* **108**, 2993–2999.

Bloemenkamp, D. G., van den Bosch, M. A., Mali, W. P., Tanis, B. C., Rosendaal, F. R., Kemmeren, J. M., Algra, A., Visseren, F. L. & van der Graaf, Y. (2002) Novel risk factors for peripheral arterial disease in young women. *American Journal of Medicine* **113**, 462–467.

Borrell, L. N., Burt, B. A. & Taylor, G. W. (2005) Prevalence and trends in periodontitis in the USA: the [corrected] NHANES, 1988 to 2000. *Journal of Dental Research* **84**, 924–930.

Boucher, N. E. Jr., Hanrahan, J. J. & Kihara, F. Y. (1967) Occurrence of C-reactive protein in oral disease. *Journal of Dental Research* **46**, 624.

Bretz, W. A., Weyant, R. J., Corby, P. M., Ren, D., Weissfeld, L., Kritchevsky, S. B., Harris, T., Kurella, M., Satterfield, S., Visser, M. & Newman, A. B. (2005) Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. *Journal of the American Geriatrics Society* **53**, 1532–1537.

Brown, L. J., Oliver, R. C. & Loe, H. (1990) Evaluating periodontal status of US employed adults. *Journal of the American Dental Association* **121**, 226–232.

Buhlin, K., Gustafsson, A., Pockley, A. G., Frostegard, J. & Klinge, B. (2003) Risk factors for cardiovascular disease in patients with periodontitis. *European Heart Journal* **24**, 2099–2107.

Cochrane. (2005) Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests Recommended methods, updated 6 June 1996. www.cochrane.org/docs/sadt.htm

Craig, R. G., Yip, J. K., So, M. K., Boylan, R. J., Socransky, S. S. & Haffajee, A. D. (2003) Relationship of destructive periodontal disease to the acute-phase response. *Journal of Periodontology* **74**, 1007–1016.

D'Aiuto, F., Nibali, L., Mohamed-Ali, V., Vallance, P. & Tonetti, M. S. (2004a) Periodontal therapy: a novel non-drug-induced experimental model to study human inflammation. *Journal of Periodontal Research* **39**, 294–299.

D'Aiuto, F., Nibali, L., Parkar, M., Suvan, J. & Tonetti, M. S. (2005a) Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. *Journal of Dental Research* **84**, 269–273.

D'Aiuto, F., Parkar, M., Andreou, G., Suvan, J., Brett, P. M., Ready, D. & Tonetti, M. S. (2004b) Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *Journal of Dental Research* **83**, 156–160.

D'Aiuto, F., Parkar, M., Nibali, L., Suvan, J., Lessem, J. & Tonetti, M. S. (2006) Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results

from a randomized controlled clinical trial. *American Heart Journal* **151**, 977–984.

D'Aiuto, F., Parkar, M. & Tonetti, M. S. (2005b) Periodontal therapy: a novel acute inflammatory model. *Inflammation Research* **54**, 412–414.

D'Aiuto, F., Ready, D. & Tonetti, M. S. (2004c) Periodontal disease and C-reactive protein-associated cardiovascular risk. *Journal of Periodontal Research* **39**, 236–241.

Danesh, J., Collins, R., Appleby, P. & Peto, R. (1998) Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *Journal of the American Medical Association* **279**, 1477–1482.

Desvarieux, M., Demmer, R. T., Rundek, T., Boden-Albala, B., Jacobs, D. R. Jr., Sacco, R. L. & Papapanou, P. N. (2005) Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation* **111**, 576–582.

Deville, W. L., Buntinx, F., Bouter, L. M., Montori, V. M., de Vet, H. C., van der Windt, D. A. & Bezemer, P. D. (2002) Conducting systematic reviews of diagnostic studies: didactic guidelines. *BioMed Central – Medical Research Methodology* **2**, 9.

Dye, B. A., Choudhary, K., Shea, S. & Papapanou, P. N. (2005) Serum antibodies to periodontal pathogens and markers of systemic inflammation. *Journal of Clinical Periodontology* **32**, 1189–1199.

Ebersole, J., Machen, R. L., Steffen, M. & Willman, D. (1997) Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. *Clinical and Experimental Immunology* **107**, 347–352.

Ebersole, J. L. & Cappelli, D. (2000) Acute-phase reactants in infections and inflammatory diseases. *Periodontology 2000* **23**, 19–49.

Ebersole, J. L., Cappelli, D., Mathys, E. C., Steffen, M. J., Singer, R. E., Montgomery, M., Mott, G. E. & Novak, M. J. (2002) Periodontitis in humans and non-human primates: oral-systemic linkage inducing acute phase proteins. *Annals of Periodontology* **7**, 102–111.

Elter, J. R., Hinderliter, A. L., Offenbacher, S., Beck, J. D., Caughey, M., Brodala, N. & Madianos, P. N. (2006) The effects of periodontal therapy on vascular endothelial function: a pilot trial. *American Heart Journal* **151**, 47.

Florez, H., Castillo-Florez, S., Mendez, A., Casanova-Romero, P., Larreal-Urdaneta, C., Lee, D. & Goldberg, R. (2006) C-reactive protein is elevated in obese patients with the metabolic syndrome. *Diabetes Research and Clinical Practice* **71**, 92–100.

Forner, L., Larsen, T., Kilian, M. & Holmstrup, P. (2006) Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. *Journal of Clinical Periodontology* **33**, 401–407.

Fredriksson, M., Bergstrom, K. & Asman, B. (2002) IL-8 and TNF-alpha from peripheral neutrophils and acute-phase proteins in periodontitis. *Journal of Clinical Periodontology* **29**, 123–128.

Fredriksson, M., Gustafsson, A., Asman, B. & Bergstrom, K. (1998) Hyper-reactive peripheral neutrophils in adult periodontitis: generation of chemiluminescence and intracellular hydrogen peroxide after in vitro priming and FcgammaR-stimulation. *Journal of Clinical Periodontology* **25**, 394–398.

Fredriksson, M. I., Figueredo, C. M., Gustafsson, A., Bergstrom, K. G. & Asman, B. E. (1999) Effect of periodontitis and smoking on blood leukocytes and acute-phase proteins. *Journal of Periodontology* **70**, 1355–1360.

Fredriksson, M. I., Gustafsson, A. K., Bergstrom, K. G. & Asman, B. E. (2003) Constitutionally hyperreactive neutrophils in periodontitis. *Journal of Periodontology* **74**, 219–224.

Furuichi, Y., Shimotsu, A., Ito, H., Namariyama, Y., Yotsumoto, Y., Hino, Y., Mishige, Y., Inoue, M. & Izumi, Y. (2003) Associations of periodontal status with general health conditions and serum antibody titers for *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. *Journal of Periodontology* **74**, 1491–1497.

Geerts, S. O., Nys, M., De, M. P., Charpentier, J., Albert, A., Legrand, V. & Rompen, E. H. (2002) Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. *Journal of Periodontology* **73**, 73–78.

Gjermo, P. (1998) Epidemiology of periodontal diseases in Europe. *Journal de Parodontologie et d'Implantologie Orale* **17**, 111–121.

Glurich, I., Grossi, S., Albini, B., Ho, A., Shah, R., Zeid, M., Baumann, H., Genco, R. J. & De Nardin, E. (2002) Systemic inflammation in cardiovascular and periodontal disease: comparative study. *Clinical and Diagnostic Laboratory Immunology* **9**, 425–432.

Greenwell, H. (2000) Periodontitis as a risk factor for cardiovascular disease. *Journal of Contempary Dental Practice* **1**, 106.

Havemose-Poulsen, A., Westergaard, J., Stoltze, K., Skjodt, H., Danneskiold-Samsoe, B., Locht, H., Bendtzen, K. & Holmstrup, P. (2006) Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. *Journal of Periodontology* **77**, 280–288.

Haynes, W. G. & Stanford, C. (2003) Periodontal disease and atherosclerosis: from dental to arterial plaque. *Arteriosclerosis, Thrombosis, and Vascular Biology* **23**, 1309–1311.

Higgins, J. P. & Thompson, S. G. (2002) Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* **21**, 1539–1558.

Ide, M., Jagdev, D., Coward, P. Y., Crook, M., Barclay, G. R. & Wilson, R. F. (2004) The short-term effects of treatment of chronic periodontitis on circulating levels of endotoxin, C-reactive protein, tumor necrosis factor-alpha, and interleukin-6. *Journal of Periodontology* **75**, 420–428.

Ide, M., McPartlin, D., Coward, P. Y., Crook, M., Lumb, P. & Wilson, R. F. (2003) Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses. *Journal of Clinical Periodontology* **30**, 334–340.

Ioannidou, E., Kao, D., Chang, N., Burleson, J. & Dongari-Bagtzoglou, A. (2006) Elevated serum interleukin-6 (IL-6) in solid-organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium. *Journal of Periodontology* **77**, 1871–1878.

Iwamoto, Y., Nishimura, F., Soga, Y., Takeuchi, K., Kurihara, M., Takashiba, S. & Murayama, Y. (2003) Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. *Journal of Periodontology* **74**, 1231–1236.

Janket, S. J., Baird, A. E., Chuang, S. K. & Jones, J. A. (2003) Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* **95**, 559–569.

Joshipura, K. J., Wand, H. C., Merchant, A. T. & Rimm, E. B. (2004) Periodontal disease and biomarkers related to cardiovascular disease. *Journal of Dental Research* **83**, 151–155.

Jousilahti, P., Salomaa, V., Rasi, V., Vahtera, E. & Palosuo, T. (2003) Association of markers of systemic inflammation, C reactive protein, serum amyloid A, and fibrinogen, with socioeconomic status. *Journal of Epidemiology Community Health.* **57**, 730–733.

Kinane, D. F., Riggio, M. P., Walker, K. F., MacKenzie, D. & Shearer, B. (2005) Bacteraemia following periodontal procedures. *Journal of Clinical Periodontology* **32**, 708–713.

Lakoski, S. G., Cushman, M., Criqui, M., Rundek, T., Blumenthal, R. S., D'Agostino, R. B. & Herrington, D. M. (2006) Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis(MESA) cohort. *American Heart Journal* **152**, 593–598.

Leivadaros, E., van der Velden, U., Bizzarro, S., ten Heggeler, J. M., Gerdes, V. E., Hoek, F. J., Nagy, T. O., Scholma, J., Bakker, S. J., Gans, R. O., ten Cate, H. & Loos, B. G. (2005) A pilot study into measurements of markers of atherosclerosis in periodontitis. *Journal of Periodontology* **76**, 121–128.

Libby, P., Ridker, P. M. & Maseri, A. (2002) Inflammation and atherosclerosis. *Circulation* **105**, 1135–1143.

Loos, B. G. (2005) Systemic markers of inflammation in periodontitis. *Journal of Periodontology* **76**, 2106–2115.

Loos, B. G., Craandijk, J., Hoek, F. J., Wertheim-van Dillen, P. M. & van der Velden, U. (2000) Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of Periodontology* **71**, 1528–1534.

Lusis, A. J. (2000) Atherosclerosis. *Nature* **407**, 233–241.

Mattila, K., Vesanen, M., Valtonen, V., Nieminen, M., Palosuo, T., Rasi, V. & Asikainen, S.

(2002) Effect of treating periodontitis on C-reactive protein levels: a pilot study. *BioMed Central – Infectious Diseases* **2**, 30.

McCarty, M. F. (1999) Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: downregulation with essential fatty acids, ethanol and pentoxifylline. *Medical Hypotheses* **52**, 465–477.

Meurman, J. H., Sanz, M. & Janket, S. J. (2004) Oral health, atherosclerosis, and cardiovascular disease. *Critical Reviews in Oral Biology and Medicine* **15**, 403–413.

Midgette, A. S., Stukel, T. A. & Littenberg, B. (1993) A meta-analytic method for summarizing diagnostic test performances: receiver-operating-characteristic-summary point estimates. *Medical Decision Making* **13**, 253–257.

Moher, D., Pham, B., Klassen, T. P., Schulz, K. F., Berlin, J. A., Jadad, A. R. & Liberati, A. (2000) What contributions do languages other than English make on the results of meta-analyses? *Journal of Clinical Epidemiology* **53**, 964–972.

Noack, B., Genco, R. J., Trevisan, M., Grossi, S., Zambon, J. J. & De Nardin, E. (2001) Periodontal infections contribute to elevated systemic C-reactive protein level. *Journal of Periodontology* **72**, 1221–1227.

Persson, G. R., Pettersson, T., Ohlsson, O. & Renvert, S. (2005) High-sensitivity serum C-reactive protein levels in subjects with or without myocardial infarction or periodontitis. *Journal of Clinical Periodontology* **32**, 219–224.

Pihlstrom, B. L., Michalowicz, B. S. & Johnson, N. W. (2005) Periodontal diseases. *Lancet* **366**, 1809–1820.

Pollitt, R. A., Kaufman, J. S., Rose, K. M., Diez-Roux, A. V., Zeng, D. & Heiss, G. (2007) Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. *European Journal of Epidemiology* **22**, 55–66.

Rahman, A. U., Rashid, S., Noon, R., Samuel, Z. S., Lu, B., Borgnakke, W. S. & Williams, R. C. (2005) Prospective evaluation of the systemic inflammatory marker C-reactive protein in patients with end-stage periodontitis getting teeth replaced with dental implants: a pilot investigation. *Clinical Oral Implants Research* **16**, 128–131.

RevMan. *http://www.cc-ims.net/RevMan*

Ridker, P. M., Brown, N. J., Vaughan, D. E., Harrison, D. G. & Mehta, J. L. (2004) Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation* **109**, IV6–IV19.

Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P. & Hennekens, C. H. (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New England Journal of Medicine* **336**, 973–979.

Ridker, P. M., Rifai, N., Rose, L., Buring, J. E. & Cook, N. R. (2002) Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events. *New England Journal of Medicine* **347**, 1557–1565.

Rosner, B. (2000) *Fundamentals of Biostatistics*, 5th edition, pp. 135–138. Pacific Grove, CA: Duxbury Press.

Saito, T., Murakami, M., Shimazaki, Y., Oobayashi, K., Matsumoto, S. & Koga, T. (2003) Association between alveolar bone loss and elevated serum C-reactive protein in Japanese men. *Journal of Periodontology* **74**, 1741–1746.

Salzberg, T. N., Overstreet, B. T., Rogers, J. D., Califano, J. V., Best, A. M. & Schenkein, H. A. (2006) C-reactive protein levels in patients with aggressive periodontitis. *Journal of Periodontology* **77**, 933–939.

Seinost, G., Wimmer, G., Skerget, M., Thaller, E., Brodmann, M., Gasser, R., Bratschko, R. O. & Pilger, E. (2005) Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *American Heart Journal* **149**, 1050–1054.

Shklair, I. L., Loving, R. H., Leberman, O. F. & Rau, C. F. (1968) C-Reactive protein and periodontal disease. *Journal of Periodontology* **39**, 93–95.

Slade, G. D., Ghezzi, E. M., Heiss, G., Beck, J. D., Riche, E. & Offenbacher, S. (2003) Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. *Archives of Internal Medicine* **163**, 1172–1179.

Slade, G. D., Offenbacher, S., Beck, J. D., Heiss, G. & Pankow, J. S. (2000) Acute-phase inflammatory response to periodontal disease in the US population. *Journal of Dental Research* **79**, 49–57.

Socransky, S. S., Haffajee, A. D., Cugini, M. A., Smith, C. & Kent, R. L. Jr. (1998) Microbial complexes in subgingival plaque. *Journal of Clinical Periodontology* **25**, 134–144.

Söder, P. O., Söder, B., Nowak, J. & Jogestrand, T. (2005) Early carotid atherosclerosis in subjects with periodontal diseases. *Stroke* **36**, 1195–1200.

Taylor, B. A., Tofler, G. H., Carey, H. M. R., Morel-Kopp, M. C., Philcox, S., Carter, T. R., Elliott, M. J., Kull, A. D., Ward, C. & Schenck, K. (2006) Full-mouth tooth extraction lowers systemic inflammatory and thrombotic markers of cardiovascular risk. *Journal of Dental Research* **85**, 74–78.

Tonetti, M. S., D'Aiuto, F., Nibali, L., Donald, A., Storry, C., Parkar, M., Suvan, J., Hingorani, A. D., Vallance, P. & Deanfield, J. (2007) Treatment of periodontitis and endothelial function. *The New England Journal of Medicine* **356**, 911–920.

Tousoulis, D., Davies, G., Stefanadis, C., Toutouzas, P. & Ambrose, J. A. (2003) Inflammatory and thrombotic mechanisms in coronary atherosclerosis. *Heart* **89**, 993–997.

Wakai, K., Kawamura, T., Umemura, O., Hara, Y., Machida, J., Anno, T., Ichihara, Y., Mizuno, Y., Tamakoshi, A., lin, Y., Nakayama, T. & Ohno, Y. (1999) Associations of medical status and physical fitness with periodontal disease. *Journal of Clinical Periodontology* **26**, 664–672.

Wu, T., Trevisan, M., Genco, R. J., Falkner, K. L., Dorn, J. P. & Sempos, C. T. (2000) Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *American Journal of Epidemiology* **151**, 273–282.

Yamazaki, K., Honda, T., Oda, T., Ueki-Maruyama, K., Nakajima, T., Yoshie, H. & Seymour, G. J. (2005) Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. *Journal of Periodontal Research* **40**, 53–58.

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Clinical Relevance

Scientific rationale for the study: Elevated plasma CRP is a risk predictor for CVD. A systematic review was performed to examine the robustness of observations of elevated plasma CRP in periodontitis and to review periodontal therapy on CRP levels.

Principle findings: The review and meta-analyses show that in periodontitis patients, CRP is elevated in comparison with control subjects and frequently CRP levels are >2.1 mg/l. It seems that periodontal therapy is able to reduce the CRP levels in patients although few studies are available.

Practical implications: Periodontitis is another condition to be considered when evaluating CRP levels in relation to cardiovascular diseases. Given the relatively high prevalence of periodontitis in the population, health care professionals should be aware that this condition results in an increased systemic inflammatory burden. Periodontal treatment seems to be an effective way to lower plasma CRP.