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Periodontal disease and C-reactive protein-associated cardiovascular risk

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Background: Periodontitis has been associated with a moderate systemic inflammatory response. Successful periodontal therapy could decrease serum inflammatory parameters. The aim of this report was to explore the outcomes of periodontal therapy in terms of changes in C-reactive protein (CRP)-associated cardiovascular disease (CVD) risk as defined in a recent American Heart Association (AHA) consensus conference.

Methods: Ninety-four systemically healthy subjects suffering from severe generalized periodontitis received standard non-surgical periodontal therapy. Periodontal parameters and serum inflammatory responses [interleukin-6 (IL-6) and CRP] were monitored 2 and 6 months after therapy.

Results: At baseline, subjects with more severe and widespread periodontitis had a higher chance of having high CRP-associated CVD risk (OR 5.6, 95% CI 1.2–27.4). Age and body mass index were also significant in the analysis. After therapy, a significant decrease in number of subjects associated with a medium and high CRP-associated risk was observed ($p < 0.001$ χ^2), with 40 of 94 subjects displaying a decrease in their class of risk. Patients who had a better oral response to periodontal therapy were also more likely to have decreased their inflammatory risk category (OR 4.8, 95% CI 1.4–15.8) after correcting for age, gender, ethnicity and cigarette smoking.

Conclusions: This study indicated that periodontitis may add to the inflammatory burden of the individual and may result in increased levels of cardiovascular risk based on serum CRP concentrations. These observations will need to be confirmed in a definitive trial. Given the high prevalence of periodontitis in the population, these data would caution physicians to be aware of the possible oral source of an increased inflammatory burden.

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The systemic implications of chronic and acute infections have attracted increasing attention in the past decade. Common pathogens (e.g. *Chlamydia pneumoniae*, *Helicobacter pylori*, *Escherichia coli*, cytomegalovirus) have been associated with atherosclerosis and cardiovascular events (1, 2). Reports from preliminary intervention trials assessing the impact of antimicrobial therapy on cardiovascular disease have supported the hypothesis that the observed association may be causal in nature. Some of these pilot studies (ACADEMIC, ROXIS, and STAMINA) showed a significant effect of antibiotic therapy on the occurrence of clinical events (cardiovascular complications) but the matter has not been fully resolved (3–5). Furthermore, insufficient evidence has been produced on the potential mechanisms. An intriguing but hypothetical model is based on the systemic

inflammatory response subsequent to chronic low-grade infections (6). Within this context great interest has risen from the discovery that even minimally raised concentrations of inflammatory markers may accurately predict future cardiovascular (CVD) events. Interleukin-6 (IL-6) and C-Reactive protein (CRP) represent the most sensitive makers used to evaluate the inflammatory status of an individual. Also of significance are the results of prospective longitudinal trials that indicate that these markers appear to be useful predictors for future cardiovascular events in a variety of populations (7, 8). Preliminary intervention trials showed a significant effect of systemic antibiotic therapy in reducing systemic inflammatory markers (4, 5).

A recent joint consensus conference of the American Heart Association (AHA) and the Center for Diseases Control (CDC) has focused on the clinical utility of these markers in the management of CVD risk (9). In addition to the classical risk estimation based on well-defined markers (such as smoking, obesity, hyperlipidaemia, hypertension, diabetes, age, gender), and due to the available evidence on the role of inflammation in the pathogenesis of atherosclerosis, the consensus conference identified three different risk categories based on serum CRP levels. Pooled epidemiological data from 40,000 subjects have shown that different levels of serum CRP predict future cardiovascular events in otherwise healthy individuals. Based on these observations, subjects with CRP concentrations less than 1 mg/l are considered to be at low risk, whereas those with concentrations in the 1–3 mg/l range are assigned a medium risk level and those with more than 3 mg/l in serum CRP are considered to be at high risk for future cardiovascular disease and events.

Periodontitis is a prototype of low grade local infection associated with a moderate systemic inflammatory response. Patients suffering from severe forms of this disease seem to have a perturbation of their systemic homeostasis (10). Not all periodontitis patients manifest with the same systemic response. It is reasonable to believe that the individual systemic response to periodontitis may be modulated by different genetic (polymorphisms) and environmental (e.g. cigarette smoking or obesity) factors. Periodontitis has been repeatedly associated with increased odds of atherosclerotic events (11). Systemic inflammation may represent the underlying mechanism that links these two common chronic diseases. Successful control of the local infection has been preliminary associated with a significant reduction of the inflammatory markers (IL-6, CRP) but not without a significant variability among subjects (12, 13).

This study reports an additional analysis of a previously reported trial (12) focusing on the effects of periodontal therapy on changes in the recently defined CRP-associated CVD risk in a group of otherwise healthy individuals. Results indicated that 6 months following completion of non-surgical periodontal therapy a significant decrease in CVD risk was observed.

Methods

Systemically healthy subjects referred to the department of Periodontology of the Eastman Dental Hospital and Institute and presenting with severe generalized periodontitis (probing pocket depths greater than 6 mm and marginal alveolar bone loss greater than 30% affecting at least 50% of the dentition) were invited to participate in this study. Patients taking any medication, those who had antimicrobial therapy in the previous 3 months, and pregnant females were excluded. A single blind intervention design was chosen to preliminary explore the association between periodontitis and systemic inflammation. Due to the extent and severity of periodontitis, an untreated control group was not included for ethical considerations. Details of the design and analysis have been reported in the principal report of this study (12).

In brief, all participants were examined prior and 6 months after delivery of standard non-surgical periodontal therapy by a single calibrated examiner. The tested intervention was a standard phase of non-surgical, cause-related periodontal therapy consisting of oral hygiene instructions, extraction of hopeless teeth and mechanical debridement with a piezoceramic device (Electro Medical Systems, Nyon, Switzerland) performed by a periodontist, under local anaesthesia and without time limitation. Subjects were examined at baseline and at 2 and 6 months following completion of periodontal therapy. A set of standard periodontal (probing pocket depths, recession of the gingival margin, and clinical attachment level) and medical parameters were recorded at all visits for all participants. A blood sample was also drawn at all visits and immediately stored in a −70 freezer after serum separation. Serum quantification of IL-6 was performed by high sensitivity ELISA (HS600 Quantikine, R & D Inc., Minneapolis, USA, detection limit of 0.04 ng/l), and CRP determination was performed with a high sensitivity immunoturbidimetric assay (Cobas Integra 700, Roche, Mannheim, Germany, detection limit of 0.25 mg/l). All analyses were performed at the end of the study and in a blind fashion. The four deepest subgingival sites (one for each quadrant) were sampled at all visits for microbial analysis. Presence of three common periodontal pathogens (*Porphyromonas gingivalis*, *Tannerella forsythensis*, *Actinobacillus actinomycetemcomitans*) was determined by multiplex polymerase chain reaction as previously described (14).

Sample size was not based on formal power calculations due to the absence of available data at the time the study commenced. Continuous variables are presented as mean and standard deviation or as median and interquartile range if data were not normally distributed. A logarithmic transformation was necessary to normalize IL-6 and CRP serum concentrations prior to any parametric analysis. The Shapiro–Wilk test was used to validate the normality assumptions of both log(IL-6) and log(CRP) concentrations. Differences in periodontal and inflammatory marker levels among various subgroups and between visits were analysed by

t-test or Wilcoxon rank-signed test as appropriate. Chi-squared test was utilized to determine significant association among categorical variables. Differences of binomial variables between visits were tested by means of McNemar paired bivariate analysis. Significant correlations among inflammatory markers were tested by non-parametric analysis (Spearman's rank analysis). Bivariate and multivariate logistic regression analyses were also used to compare different CRP-associated risk categories before and after periodontal treatment. Odds ratios (95% CI) were calculated after correcting for potential confounders such as age, gender, ethnicity, body mass index and cigarette smoking. The SPSS statistical software package (version 11) was used. Significance was set at $p < 0.05$.

Results

A total of 94 subjects were included in the six months intervention trial. On average participants were middle aged (46 ± 9 years of age), equally distributed in terms of gender (54% females), normo-weighted (body mass index of 25.3 ± 3.8 kg/m^2) with a relevant number of current smokers (42%) and European Caucasians (65%).

All included individuals had severe generalized periodontitis as indicated by mean full mouth clinical attachment level of 4.9 ± 1.1 mm, probing pocket depths of 4.4 ± 0.6 mm, the presence of an average of 77 ± 23 periodontal pockets 5 mm or deeper, and a full mouth bleeding and plaque scores of 63.5 ± 16.4% and 58 ± 20.7%. Local infection was confirmed by detection of periodontal pathogens in subgingival plaque. Seventy-seven percent of subjects tested positive for *P. gingivalis*, 78% for *T. forsythensis* and 45% for *A. actinomycetemcomitans*. None of the patients reported any significant change in their medical history throughout the trial. Serum concentrations of the tested inflammatory markers, IL-6 and CRP, were significantly correlated with the extent and severity of periodontitis (data not shown).

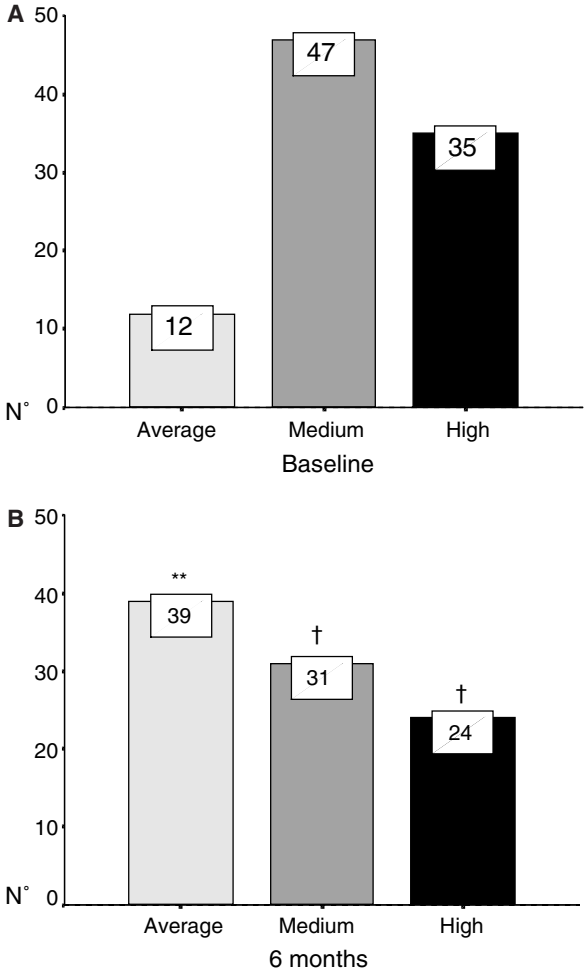

Fig. 1. Bar chart showing baseline (A) and 6 months (B) frequency of individuals in each C-reactive protein (CRP)-associated cardiovascular disease (CVD) risk category. $^{**}p < 0.0001$, $\dagger p < 0.05$ McNemar bivariate paired test used to compare each frequency between baseline and 6 months.

Categorizing the population according to the AHA/CDC guidelines at baseline, 12 patients were in the low, 47 in the medium and 35 in the high risk group. (Fig. 1A). A logistic regression model with the AHA/CDC three categories as dependent variable was performed to ascertain the probability of individuals falling in a different category of risk. Estimates and odds ratios (95% CI) were calculated (Table 1). Patients presenting with more widespread periodontitis (expressed by the presence of greater than median number of periodontal pockets 5 mm or deeper) had an OR of 5.6 (95% CI 1.2–27.4, $p < 0.04$) and an OR of 3.5 (95% CI 1.2–10.1, $p < 0.02$) of being in the highest category of risk compared to the lowest and medium, respectively. Age and body mass index were the only other significant factors in the model. The analysis accounted for other common confounders such as gender and cigarette smoking.

Non-surgical periodontal therapy resulted in a significant improvement of all clinical periodontal parameters after 6 months. A mean reduction of 57 ± 24 in the number of periodontal pockets greater than 4 mm ($p < 0.0001$ *t*-test) was obtained together with a significant reduction in full mouth bleeding (45 ± 17%, $p < 0.0001$ *t*-test) and plaque scores (38 ± 18%, $p < 0.0001$ *t*-test). Six months after therapy a significant reduction in the number of plaque samples positive for periodontal pathogens ($p < 0.001$ McNemar test) was observed.

Table 1. Logistic multinomial regression analysis of C-reactive protein-associated cardiovascular disease risk categories in patients suffering from severe periodontitis (n = 94)

	Average (CRP < 1 mg/l) vs. high (CRP > 3 mg/l)				Medium (1 mg/l < CRP < 3 mg/l) vs. high (CRP > 3 mg/l)			
	β ± SE	*p*	OR	95% CI	β ± SE	*p*	OR	95% CI
Constant	3.911 ± 2.574	0.129			1.879 ± 1.586	0.236		
Age	−0.153 ± 0.053	**0.004**	**0.858**	**0.774–0.953**	−0.057 ± 0.030	0.060	0.945	0.891–1.003
Gender[a]	0.953 ± 0.811	0.240	2.593	0.529–12.71	0.654 ± 0.520	0.208	1.923	0.695–5.326
Smoking[b]	−0.939 ± 0.806	0.244	0.391	0.081–1.898	−0.619 ± 0.536	0.248	0.538	0.188–1.540
Ethnicity[c]	−0.083 ± 0.840	0.921	0.921	0.178–4.772	0.229 ± 0.548	0.676	1.257	0.430–3.678
BMI-1[d]	2.163 ± 1.072	**0.044**	**8.696**	**1.064–71.10**	1.692 ± 0.670	**0.012**	**5.431**	**1.460–20.20**
BMI-2[e]	1.306 ± 1.016	0.199	3.692	0.504–27.06	0.385 ± 0.583	0.509	1.470	0.469–4.609
Periodontal pockets[f]	1.724 ± 0.810	**0.033**	**5.605**	**1.146–27.41**	1.262 ± 0.535	**0.018**	**3.533**	**1.238–10.08**

Model $p < 0.01$, −2 log likelihood = 147.590, chi-square 31.325, pseudo R-square 0.331.
[a]Male vs. female.
[b]Smoker vs. non-smoker.
[c]Caucasian vs. non-Caucasian.
[d]Body Mass Index-1: 3rd tertile (> 26.3 kg/m^2) vs. 1st (< 23.4 kg/m^2).
[e]Body Mass Index-2: 3rd tertile (> 26.3 kg/m^2) vs. 2nd (> 23.4 kg/m^2).
[f]Patients who presented with a baseline number of periodontal pockets 5 mm or deeper greater than median (79).
CRP, C-reactive protein.

Table 2. Logistic regression analysis of the C-reactive protein-associated risk reduction after periodontal therapy (n = 94)

	β ± SE	*p*	OR	95% CI
Constant	−0.705 ± 2.355	0.764	0.494	
Age	0.008 ± 0.030	0.777	1.008	0.951–1.069
Gender[a]	−0.931 ± 0.563	0.098	0.394	0.131–1.188
Ethnicity[b]	−0.104 ± 0.256	0.686	0.813	0.298–2.220
Smoking[c]	1.080 ± 0.603	0.073	2.944	0.903–9.596
BMI[d]	−0.085 ± 0.076	0.260	0.918	0.791–1.065
Extracted teeth (*n*)[e]	0.333 ± 0.140	**0.017**	**1.395**	**1.060–1.834**
ΔFMPS[f]	0.029 ± 0.018	0.103	1.030	0.994–1.067
ΔFMBS[g]	−0.011 ± 0.018	0.540	0.989	0.954–1.025
PPK-effect[h]	1.557 ± 0.613	**0.011**	**4.746**	**1.428–15.773**
P. gingivalis change[i]	0.139 ± 0.536	0.796	1.149	0.402–3.286
T. forsythensis change[j]	−0.604 ± 0.619	0.329	0.546	0.163–1.837
A. actinomycetemcomitans change[k]	0.363 ± 0.578	0.530	1.438	0.463–4.463

Model $p = 0.01$, −2 log likelihood 94.938, chi-square 24.819, pseudo R-square 0.337.
[a]Male vs. female.
[b]Caucasian vs. non-Caucasian.
[c]Smoker vs. non-smoker.
[d]Body Mass Index (kg/m^2).
[e]Number of hopeless teeth extracted during treatment.
[f]Difference in Full Mouth Plaque Scores between 0 and 6 months.
[g]Difference in Full Mouth Bleeding Scores between 0 and 6 months.
[h]Patients who presented with a reduction in number of periodontal pockets (5 mm or deeper) greater than the median(56 pockets) 6 months after therapy.
[i]Patients with undetectable *P. gingivalis* at 6 months.
[j]Patients with undetectable *T. forsythensis* at 6 months.
[k]Patients with undetectable *A. actinomycetemcomitans* at 6 months.

Serum concentrations of inflammatory markers were also significantly reduced after 6 months for both CRP (median decrease 31%, 54 IQ, $p < 0.0001$ Wilcoxon test) and IL-6 (median decrease 12%, 50 IQ, $p < 0.0001$ Wilcoxon test). A significant correlation was observed between the difference in IL-6 and the difference in CRP ($r = 0.38$, p = 0.001 Spearman's rank test).

At 6 months a significant reduction in number of subjects in the high and medium CRP-associated CVD risk classes was observed ($p < 0.0001$ chi-squared test). 13 subjects moved from the high to the medium category, 25 from the medium to the low, two from the high to the low, four from the medium to the high and 50 individuals remained in the same category (12 in the low, and 19 each in the medium and high categories). Differences in the number of observations before and 6 months after therapy in each category were significant (low category $p < 0.0001$, medium $p < 0.05$, high $p < 0.05$, McNemar test). To further explore the effect of periodontal treatment on CRP-associated CVD risk categories a binary logistic regression analysis was performed with a dependent variable describing the difference in categories defined as follows: reduced CRP-associated CVD risk (1), no change or increased CRP-associated CVD risk (0) (Table 2). The analysis controlled for potential confounders (age, gender, ethnicity, smoking, body mass index). Individuals who responded better to periodontal treatment (defined by a pocket reduction at 6 months greater than median) were four times more likely (95% CI 1.4–15.8, $p < 0.02$) to reduce their risk category compared to those who did not achieve the same clinical response. Participants who also received extractions of hopeless teeth after baseline had an odds of 1.4 (95%

CI 1.1–1.8, $p < 0.02$) to have a reduction in their risk category.

Discussion

This study observed a significant association between the number of periodontal pockets and increased CRP-associated CVD risk according to a recent AHA/CDC classification (9). Otherwise healthy individuals affected with severe periodontitis had significantly increased odds of being at above average risk (i.e. medium or high risk) for cardiovascular diseases if they presented with more widespread periodontitis defined as higher number of periodontal pockets. This finding is strengthened by the observation that successful non-surgical periodontal therapy resulted in a significant decrease of the CRP-associated CVD risk. Individuals who responded better to periodontal therapy (i.e. those who had above median decreases in the number of periodontal pockets) had increased odds of displaying a decrease in their CRP-associated cardiovascular risk.

Accumulating evidence has associated severe periodontitis with increased odds of future cardiovascular events (11). However a clear aetiologic pathway has not been proven yet. Our report suggests a possible role of untreated severe periodontitis on future atherosclerotic processes via systemic inflammation. Experimental animal data support this hypothesis (15–18). A wide range of pathological stimuli (infection, tissue damage) can cause local host production of inflammatory cytokines that may exert a distant effect and alter the normal vascular homeostasis (6). This insult, also called *endothelial dysfunction,* represents a possible mechanism by which chronic infections such as periodontitis, directly via pathogens or indirectly via their products and host inflammatory defences, may initiate and modulate intravascular accumulation of inflammatory cells and lipids (atherosclerosis) (2, 6).

Patients suffering from severe periodontitis have an increased local production of inflammatory cytokines (IL-1β, TNF-α, IL-6) (19, 20), and a moderate systemic inflammatory response (defined by raised concentrations of CRP, fibrinogen and moderate leucocytosis) (21–24). Whether this is mainly due to a local excessive production of cytokines that may gain access to the circulation or to a metastatic dissemination of periodontal pathogens and their antigenic products through the bloodstream is still unknown. IL-6 local production in the gingiva may exert its systemic anti-inflammatory activity by stimulating the hepatic synthesis of acute phase proteins in order to protect the host against local pathological stimuli (25). CRP is the prototype of these proteins and it is increasingly assuming the leading role of future predictor for CVD events (8, 26). Furthermore CRP may play a direct active role in the atherosclerotic process (27).

The recent AHA/CDC conference confirmed the potential relevance of small serum changes of the concentrations of this marker in healthy individuals or in those already suffering from CVD. However, on the basis of the evidence, the clinical utilization of CRP as a predictive tool for future cardiovascular risk is still considered optional. Randomized controlled clinical trials in primary (healthy individuals) and secondary (patients suffering from CVD) prevention are under way to prove the true utility of this marker.

This study indicated that successful periodontal therapy may reduce CRP-associated cardiovascular risk. Caution is needed in interpreting these results due to the limited number of cases, the variability observed among all participants and the study design. These observations will need to be confirmed in a definitive, prospective, randomized controlled clinical trial. In the meantime, given the high prevalence of periodontitis in the population, these data would caution physicians to be aware of the possible oral source of an increased inflammatory burden both in the context of differential diagnosis and in the context of selection of appropriate therapeutic intervention.

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References

1. Epstein SE, Zhu J, Burnett MS, Zhou YF, Vercellotti G, Hajjar D. Infection and atherosclerosis: potential roles of pathogen burden and molecular mimicry. *Arterioscler Thromb Vasc Biol* 2000;**20:** 1417–1420.
2. Shah PK. Chronic infections and atherosclerosis/thrombosis. *Curr Atheroscler Rep* 2002;**4:**113–119.
3. Anderson JL, Muhlestein JB, Carlquist J *et al.* Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection: The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study. *Circulation* 1999;**99:**1540–1547.
4. Stone AF, Mendall MA, Kaski JC *et al.* Effect of treatment for Chlamydia pneumoniae and Helicobacter pylori on markers of inflammation and cardiac events in patients with acute coronary syndromes: South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). *Circulation* 2002; **106:**1219–1223.
5. Wiesli P, Czerwenka W, Meniconi A *et al.* Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in Chlamydia pneumoniae seropositive men: a randomized, double-blind, placebo-controlled trial. *Circulation* 2002;**105:**2646–2652.
6. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105:**1135–1143.
7. Danesh J, Whincup P, Walker M *et al.* Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000;**321:** 199–204.
8. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation,

aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;**336:**973–979.
9. Pearson TA, Mensah GA, Alexander RW *et al*. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;**107:**499–511.
10. Ebersole JL, Cappelli D. Acute-phase reactants in infections and inflammatory diseases. *Periodontol 2000* 2000;**23:**19–49.
11. Danesh J. Coronary heart disease, Helicobacter pylori, dental disease, Chlamydia pneumoniae, and cytomegalovirus: meta-analyses of prospective studies. *Am Heart J* 1999;**138:**S434–S437.
12. D'Aiuto F, Parkar M, Andreou H *et al*. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res* 2004;**83:**156–160.
13. Mattila K, Vesanen M, Valtonen V *et al*. Effect of treating periodontitis on C-reactive protein levels: a pilot study. *BMC Infect Dis* 2002;**2:**30.
14. Tran SD, Rudney JD. Improved multiplex PCR using conserved and species-specific 16S rRNA gene primers for simultaneous detection of Actinobacillus actinomycetemcomitans, Bacteroides forsythus, and Porphyromonas gingivalis. *J Clin Microbiol* 1999;**37:**3504–3508.
15. Dorn BR, Burks JN, Seifert KN, Progulske-Fox A. Invasion of endothelial and epithelial cells by strains of Porphyromonas gingivalis. *FEMS Microbiol Lett* 2000;**187:**139–144.
16. Li L, Messas E, Batista EL Jr, Levine RA, Amar S. Porphyromonas gingivalis infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation* 2002;**105:**861–867.
17. Lalla E, Lamster IB, Hofmann MA *et al*. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein e-null mice. *Arterioscler Thromb Vasc Biol* 2003;**23:**1405–1411.
18. Qi M, Miyakawa H, Kuramitsu HK. Porphyromonas gingivalis induces murine macrophage foam cell formation. *Microb Pathog* 2003;**35:**259–267.
19. Gorska R, Gregorek H, Kowalski J, Laskus-Perendyk A, Sonohara M, Madalinski K. Relationship between clinical parameters and cytokine profiles in inflamed gingival tissue and serum samples from patients with chronic periodontitis. *J Clin Periodontol* 2003;**30:**1046–1052.
20. Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol* 1996;**1:**821–878.
21. Ebersole JL, Machen RL, Steffen MJ, Willmann DE. Systemic acute-phase reactants, C-reactive protein and haptoglobin, in adult periodontitis. *Clin Exp Immunol* 1997;**107:**347–352.
22. Kweider M, Lowe GD, Murray GD, Kinane DF, McGowan DA. Dental disease, fibrinogen and white cell count; links with myocardial infarction? *Scott Med J* 1993;**38:**73–74.
23. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM. and van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000;**71:**1528–1534.
24. Noack B, Genco RJ, Trevisan M, Grossi S, Zambon JJ, De Nardin E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol* 2001;**72:**1221–1227.
25. Irwin CR, Myrillas TT. The role of IL-6 in the pathogenesis of periodontal disease. *Oral Dis* 1998;**4:**43–47.
26. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;**340:**448–454.
27. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003;**111:**1805–1812.