

Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case–control study

Luigi Nibali^{1,*}, Francesco D’Aiuto^{1,*}, Gareth Griffiths^{1,2}, Kalpesh Patel¹, Jean Suvan¹ and Maurizio S. Tonetti³

¹Periodontology Unit, Eastman Dental Institute and Hospital, University College London, London, UK; ²Department of Adult Dental Care, School of Clinical Dentistry, Sheffield, UK; ³European Research Group on Periodontology (ERGOPero), Berne, Switzerland

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Abstract

Background and Aim: A cluster of metabolic factors defines a syndrome that predisposes to diabetes and cardiovascular disease. Chronic infections such as periodontitis might alter these individual metabolic factors and the systemic inflammatory burden. The aim of this study was to investigate the association between severe periodontitis and increase in inflammatory and metabolic risk factors for cardiovascular disease.

Materials and Methods: We examined 302 patients with severe periodontitis and 183 healthy controls, and we collected a blood sample from each subject in order to investigate differences in inflammatory (leukocyte numbers and differential counts) and metabolic markers (lipids and glucose).

Results: After correcting for differences in age, gender, smoking and ethnicity, periodontitis subjects exhibited a low-grade systemic inflammation (increased white cell counts, $1.10 \pm 1.02 \times 10^9/l$, 95%CI 1.05–1.15, $p = 0.0001$), dyslipidemia [lower high-density lipoprotein cholesterol, 1.14 ± 1.03 mmol/l, 95%CI 1.08–1.20, $p < 0.0001$ and higher low-density lipoprotein cholesterol, 1.12 ± 1.03 , 95%CI 1.05–1.19, $p < 0.0001$] and increased non-fasting serum glucose levels (1.04 ± 1.01 mmol/l, 95%CI 1.02–1.06, $p = 0.01$) when compared with controls. The associations were confirmed in a subpopulation of Caucasian non-smokers. A trend for a dose dependent effect of the number of periodontal pockets on the tested inflammatory and metabolic markers was observed.

Conclusions: These data suggest a possible link between severe generalized periodontitis, systemic inflammation and a dysmetabolic state in otherwise healthy individuals.

Key words: cardiovascular disease; dyslipidemia; insulin resistance; metabolic syndrome; periodontitis; systemic inflammation

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Conflict of interest and source of funding statement

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Compelling evidence has identified a series of metabolic parameters that cluster together and predispose to serious systemic diseases like diabetes or coronary heart disease (CHD). Fifteen years ago, these factors were grouped together to describe the so-called syndrome X (Reaven 2005). Nowadays, coexistence of the same metabolic factors including obesity, dyslipidemia, insulin resistance, high blood pressure and a pro-inflammatory and pro-thrombotic state define the “metabolic syn-

drome” (MS) (Grundy et al. 2004). Diagnosis of MS is made if any of the three following factors are present: insulin resistance (indicated by elevated serum glucose levels), high blood pressure, obesity and dyslipidemia [high plasma triglycerides and low high-density lipoprotein (HDL) cholesterol]. Several studies showed that individuals with MS exhibit increased risk of diabetes (Fernandez-Real & Ricart 2003) and CHD (Bestermann et al. 2005) and new treatment strategies are trying to

*These authors contributed equally to the study.

tackle this risk by reducing the specific factors leading to the MS (Deen 2004).

Low-grade systemic inflammation might represent one of the etiologic factors behind the MS. Indeed inflammatory bio-markers are predictors of future risk of diabetes (Fernandez-Real & Ricart 2003), CHD (Madjid et al. 2004) and MS (Grundy et al. 2004). In particular, increasing evidence suggests that atherosclerosis is an inflammatory disease (Ross 1999). Several studies have shown leukocyte counts, a common marker of systemic inflammation, to be a consistent risk predictor for CHD events (Madjid et al. 2004).

Periodontitis is a common chronic infectious disease affecting the adult population. It is characterized by a progressing gingival inflammatory response to bacterial dental plaque eventually leading to tooth loss. Increasing evidence suggests that the local inflammatory and/or infectious burden might trigger a systemic host response, therefore predisposing subjects with periodontitis to an increased risk of CHD and other systemic diseases. Traditional and novel CHD risk factors, such as leukocyte number and metabolic factors might therefore be affected by the periodontal status. The aim of this study was to compare inflammatory (leukocyte counts) and metabolic markers (serum lipid and glucose levels) between subjects with severe periodontitis and subjects with healthy periodontium.

Materials and Methods

Experimental design

This study had a case-control design. Four hundred and eighty-five individuals were identified among the population referred for care to the Eastman Dental Hospital. Subjects meeting the inclusion/exclusion criteria were invited to take part in the study and were provided with the subject information sheet and consent form. Three hundred and two individuals diagnosed with severe forms of periodontitis were enrolled in the periodontal clinic whereas 183 subjects without periodontitis were invited to participate while attending the oral surgery or restorative clinics and served as non-affected controls. All subjects gave written informed consent and the study protocol had been reviewed and approved by the University College London Hospitals ethics committee.

Experimental population

Our cases were screened from individuals who presented with clinical signs of periodontitis. Inclusion criteria were diagnosis of severe periodontitis, defined as Aggressive Periodontitis (AgP) (Nibali et al. 2006), and severe Chronic Periodontitis (D'Aiuto et al. 2005).

- **Inclusion criteria for AgP patients:** Diagnosis of AgP was based on the 1999 Consensus Classification of Periodontal Diseases, in agreement with the recent Consensus report on definition of periodontitis cases (Armitage 1999, Tonetti & Claffey 2005). Our diagnostic criteria took into consideration only clinical, and not laboratory, evidence. We classified patients as having AgP, when we had evidence of:
 - **Healthy status:** Except from the presence of periodontitis (for example, all subjects with diabetes were excluded).
 - **Rapid attachment loss and bone destruction:** Proven by radiographs obtained at a few years distance. When this was not possible, severe disease at a young age was used, with patients <35 at the time of the initial diagnosis.
 - **Familial aggregation:** We tried to ascertain the familial aggregation, by means of a specific questionnaire and, when possible, by examining first degree relatives. However, patients showing clear clinical signs of AgP but without a positive family history were still included (Llorente & Griffiths 2006).

Patients were diagnosed with Localized AgP (LAgP) or Generalized AgP,

following the 1999 Consensus classification, based on the number of affected teeth (Lang et al. 1999).

- **Inclusion criteria for severe Chronic Periodontitis:** Patients with at least 20 teeth and 50% of sites exhibiting ≥ 5 mm probing pocket depths (PPD) and marginal alveolar bone loss >30%, and who did not fall into the AgP definition, were classified as having severe chronic periodontitis and included in the study. Diabetic subjects were excluded.
- **Inclusion criteria for controls:** The control population was enrolled based upon (i) the absence of clinical and radiographic manifestations of periodontal disease, (ii) at least 20 teeth present, (iii) no history of periodontal treatment, (iv) no history of systemic diseases (e.g. diabetes), (v) no pregnancy, (vi) minimum age of 25 years.

The demographic characteristics of the two groups of patients (severe periodontitis and healthy controls) are presented in Table 1.

Clinical examination

- **Cases:** A comprehensive clinical periodontal examination was performed by three examiners. Full mouth measures of PPD, recession [REC, measured as distance from the cemento-enamel junction (CEJ) to the gingival margin] and LCAL, measured either as a direct measurement of CEJ to the base of the pocket, or as a calculation of PPD+REC) were obtained at six sites per tooth. Full-mouth long-cone periapical radiographs were also obtained from each patient.

Table 1. Subject characteristics and demographic factors

Parameter mean (95% CI)	Healthy (n = 183)	Periodontitis (n = 302)	Significance p-value
Age	39.8 (38–48)	40.8 (39–42)	0.3797*
Gender (Male %)	45.4	45.7	1.0000†
Ethnicity:			
Caucasians %	61.2	63.2	
Asian %	12.0	12.3	
Black %	20.2	18.9	0.9500†
Other %	6.6	5.6	
Smoking			
(Current %)	23.9	24.8	
(Former%)	17.2	28.5	0.0060†
(Never%)	58.9	46.7	

Means and 95% confidence intervals (CI) are reported.

*Two sample *t*-test.

†Comparison between healthy/periodontitis performed by χ^2 test.

Periodontitis patients were sub-classified according to the median number of pockets ≥ 5 mm (median = 68) in higher extent (≥ 68 pockets) and lower extent (< 68 pockets) clusters.

- **Controls:** In order to minimize recruitment bias, we aimed to enrol control subjects who broadly belonged to similar socio-economic groups, and therefore had similar oral health care and awareness as the patient group. Therefore, subjects attending other Departments of the Eastman Dental Hospital were screened for inclusion. Volunteers with known specific genetic diseases or history of periodontal disease or tooth loss due to periodontal disease were not included. A single examiner performed a basic screening periodontal examination on these subjects, using the PSR index and reference to the existing radiographs taken for the clinical problem that resulted in their referral. In the event of detecting codes 3, 4 or * in any sextant, further investigation was performed. This consisted of pocket depth and recession measurements using a UNC 15 probe and further radiographic investigation consisting of either a panoramic view or individual periapical films. Subjects were excluded if they presented with at least one site with PPD and LCAL ≥ 4 mm or radiographic evidence of bone loss.

For both cases and controls, smoking status and ethnic origin were evaluated by a questionnaire.

Blood sampling

A non-fasting blood sample was obtained from each patient via venipuncture of the right arm at the examination visit and processed in a blind fashion for leukocyte [white blood cells (WBC)] and differential counts, total-, low-density lipoprotein (LDL)- and HDL-cholesterol, triglycerides, haemoglobin, red blood cells (RBC) and glucose levels, using standard clinical pathology procedures.

Statistical analysis

SPSS 12.0 package was used for statistical analysis and the α value was set at 0.05. Continuous, normally distributed variables are reported as means \pm standard deviation (SD) and 95% confidence

Table 2. Blood results for inflammatory and metabolic factors in healthy and periodontitis subjects

Parameter mean (95% CI)	Healthy (n = 183)	Periodontitis (n = 302)	Significance p-value
WBC, $10^9/l$	6.0 (5.8–6.2)	6.7 (6.5–6.9)	0.0001
Neutrophils, $10^9/l$	3.5 (3.3–3.7)	3.9 (3.7–4.1)	0.0048
Lymphocytes, $10^9/l$	1.9 (1.8–2.0)	2.1 (2.0–2.1)	0.0050
Monocytes, $10^9/l$	0.4 (0.4–0.4)	0.4 (0.4–0.5)	0.741
Eosinophils, $10^9/l$	0.2 (0.1–0.2)	0.2 (0.2–0.2)	0.118
Basophils, $10^9/l$	0.02 (0.02–0.03)	0.03 (0.02–0.03)	0.259
Cholesterol, mmol/l	5.0 (4.9–5.2)	5.2 (5.0–5.3)	0.506
LDL, mmol/l	2.8 (2.6–2.9)	3.1 (3.0–3.2)	0.0016
HDL, mmol/l	1.6 (1.6–1.7)	1.5 (1.4–1.5)	<0.0001
Triglycerides, mmol/l	1.3 (1.2–1.5)	1.4 (1.3–1.6)	0.439
Glucose, mmol/l	4.8 (4.7–4.9)	5.0 (4.9–5.1)	0.0003
Cholesterol ratio	3.3 (3.1–3.4)	3.9 (3.7–4.1)	<0.0001

Means and 95% confidence intervals (CI) are reported.

The results of a multivariate analysis adjusted for age, gender, smoking and ethnicity are reported in the last column.

HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC, white blood cells.

intervals (CI). In a primary analysis, differences in demographic parameters between groups were assessed by independent *t*-test (continuous variables) and χ^2 testing (categorical variables).

As the outcomes of interest are confounded by age, gender, ethnicity and smoking status, the null hypothesis of lack of association between clinical status and inflammatory and metabolic parameters (logarithmically transformed) was performed by multivariate analysis. Back-transformed adjusted estimated mean differences with 95% CI are reported in the text and in Table 2. Post-hoc analyses were performed using Bonferroni corrections. Furthermore, given the effects of risk factors such as smoking and ethnicity (Schenkein et al. 1995, Tonetti & Mombelli 1999), and the potential for residual confounding, a separate analysis was performed in Caucasian who never smoked (former smokers were not included in this group).

Exploratory analyses were then performed to investigate differences in serum and plasma parameters between all subjects divided into three groups: healthy controls, periodontitis patients higher-extent cluster and periodontitis patients lower-extent cluster.

Results

Patients and controls were balanced for age, gender and ethnicity as assessed by independent *t*-test and χ^2 testing (Table 1). Although the percentage of current smo-

kers was balanced between patients and control, a higher percentage of former smokers was detected in the patient group. The average PPD in all periodontitis patients was 4.31 mm (95% CI = 4.20–4.42), while the average LCAL was 5.01 mm (95% CI = 4.84–5.18) (data not reported in tables). Raw (unadjusted) data for all inflammatory and metabolic parameters are displayed in Table 2. Periodontitis patients exhibited greater adjusted number of leukocytes (WBC) when compared with controls (estimated adjusted mean difference at multivariate analysis $1.10 \times 10^9/l$, 95%CI 1.05–1.15, $p = 0.0001$). This difference was attributable to higher neutrophil (estimated adjusted mean difference $1.10 \times 10^9/l$, 95%CI 1.03–1.18, $p = 0.0048$) and lymphocyte (estimated adjusted mean difference $1.08 \times 10^9/l$, 95%CI 1.03–1.15, $p = 0.0050$) counts. No differences were observed for monocyte, eosinophil or basophil numbers. Current smoking and ethnicity significantly influenced WBC ($p < 0.0001$). Nevertheless, analyses of the subgroup of Caucasian non-smokers (135 subjects) confirmed that severe periodontitis was significantly associated with higher WBC values (estimated adjusted mean difference $1.13 \times 10^9/l$, 95%CI 1.05–1.21, $p = 0.001$).

Periodontitis patients tended to have higher adjusted serum cholesterol and triglycerides levels (NS). Cases also exhibited markedly reduced adjusted HDL cholesterol levels (estimated adjusted mean difference 1.14 mmol/l,

95%CI 1.08–1.20, $p < 0.0001$) and increased total cholesterol/HDL ratios (estimated adjusted mean difference 1.12, 95%CI 1.05–1.19, $p = 0.0007$) irrespective of smoking or ethnic differences. In Caucasian non-smokers, HDL levels were also increased in the patient group (estimated adjusted mean difference 0.83 mmol/l, 95% CI 0.74–0.93, $p = 0.002$). Adjusted LDL cholesterol concentrations were elevated in periodontitis patients ($p = 0.0016$); this difference was independent of known confounders in the subgroup of Caucasian who never smoked (estimated adjusted mean difference 1.15 mmol/l, 95%CI 1.03–1.29, $p = 0.016$). Cases also had higher adjusted glucose levels when compared with controls (estimated adjusted mean difference, 1.04 mmol/l, 95%CI 1.02–1.06, $p = 0.0003$).

Patients with more generalized disease (higher- extent cluster) were older and included a higher percentage of smokers than the lower- extent cluster, although these differences did not reach statistical significance (Table 3). Patients belonging to the higher- extent cluster exhibited a trend towards increased neutrophil counts and cholesterol ratio when compared with patients with less generalized disease (lower- extent). These differences did not reach statistical significance. However, when results relative to healthy subjects, lower- extent periodontitis and higher- extent periodontitis were plotted together (Figs 1 and 2), a trend was evident for increase in inflammatory and metabolic markers. Differences between groups revealed statistical significance for WBC counts between healthy and higher- extent periodontitis ($p = 0.005$, see Fig. 1) and HDL serum levels, both between healthy and higher- extent ($p = 0.001$) and healthy and lower- extent periodontitis ($p = 0.031$, see Fig. 2). No differences were found for RBC and haemoglobin levels.

No difference was observed for any of the studied inflammatory and metabolic parameters based on the clinical diagnoses of Chronic Periodontitis ($n = 173$) and Aggressive Periodontitis ($n = 129$, 88 GAgP, 41 LAgP).

Discussion

The major finding of this investigation is that both routine inflammatory and metabolic parameters of the subjects included in this study were associated

Table 3. Demographic factors and unadjusted blood results for inflammatory and metabolic factors in patients with periodontitis, divided in lower- extent (<68 pockets) and higher- extent (≥ 68 pockets) clusters

Parameter mean (95% CI)	Lower- extent, $n = 151$	Higher- extent, $n = 151$	Significance p -value
Age	37.4 (35–39)	44.4 (42–46)	0.052*
Gender (Male %)	41.4	50.7	0.274†
Ethnicity			
Caucasians %	61.2	65.5	0.977†
Asian %	12.5	12.2	
Black %	20.4	17.6	
Other %	5.9	4.7	
Smoking (Current %)	19.1	31.1	0.051†
WBC, $10^9/l$	6.5 (6.2–6.8)	6.8 (6.5–7.1)	0.098
Neutrophils, $10^9/l$	3.8 (3.5–4.0)	4.0 (3.8–4.3)	0.061
Lymphocytes, $10^9/l$	2.0 (2.0–2.1)	2.1 (2.0–2.2)	0.901
Monocytes, $10^9/l$	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.639
Eosinophils, $10^9/l$	0.2 (0.1–0.2)	0.2 (0.2–0.2)	0.133
Basophils, $10^9/l$	0.03 (0.02–0.03)	0.03 ((0.02–0.03)	0.940
Cholesterol, mmol/l	5.2 (5.0–5.4)	5.2 (5.0–5.4)	0.799
LDL, mmol/l	3.0 (2.9–3.2)	3.1 (2.9–3.3)	0.904
HDL, mmol/l	1.5 (1.5–1.6)	1.4 (1.3–1.5)	0.430
Triglycerides, mmol/l	1.3 (1.1–1.5)	1.5 (1.3–1.8)	0.159
Cholesterol ratio	4.9 (4.8–5.1)	5.0 (4.9–5.2)	0.060
Glucose, mmol/l	3.6 (3.3–3.8)	4.1 (3.8–4.4)	0.659

Means and 95% confidence intervals (CI) are reported. The results of a multivariate analysis for inflammatory and metabolic parameters, adjusted for age, gender, smoking and ethnicity are reported in the last column.

*Comparisons between lower- extent and higher- extent performed by independent t -test.

†Comparison between lower- extent and higher- extent performed by χ^2 test.

HDL, high- density lipoprotein; LDL, low- density lipoprotein; WBC, white blood cells.

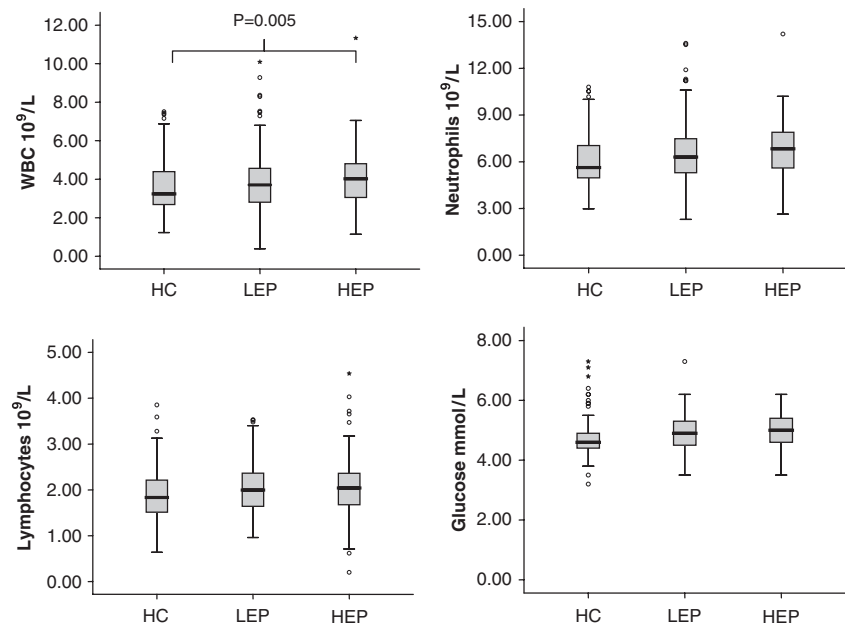


Fig. 1. Plots showing white blood cells (WBC), neutrophil, lymphocyte counts, and serum glucose levels in healthy controls (HC), patients with lower- extent periodontitis (LEP) and patients with higher- extent periodontitis (HEP). Significant p values as obtained by multivariate analysis are shown in the figure.

with their periodontal status. Compared with healthy controls, severe periodontitis patients presented with a low- grade inflammatory state defined by

marked leukocytosis due to increased numbers of circulating neutrophils and lymphocytes. Moreover these individuals also showed a dysmetabolic state

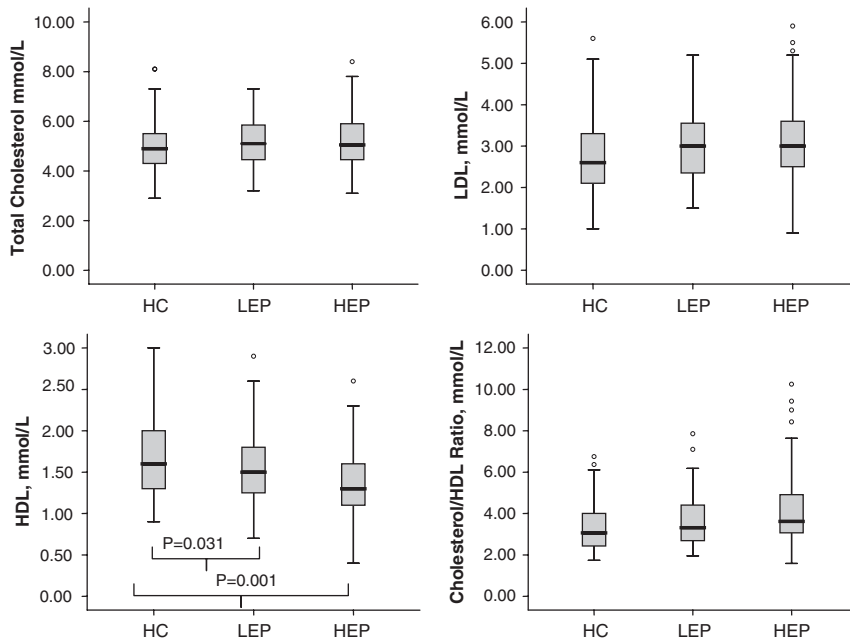


Fig. 2. Plots showing plasma lipid levels (total cholesterol, LDL, HDL and cholesterol/HDL ratio) in healthy controls (HC), patients with lower-extent periodontitis (LEP) and patients with higher-extent periodontitis (HEP). Significant *p* values as obtained by multivariate analysis are shown in the figure. LDL, low-density lipoprotein; HDL, High-density lipoprotein.

characterized by decreased serum HDL levels, raised LDL and mild insulin resistance, crudely assessed by glucose levels. Furthermore, a trend for dose dependency of periodontitis as an exposure was observed: subjects with above median number of pockets displayed higher inflammatory and metabolic markers. This was particularly evident for WBC and neutrophil counts, and for HDL and total cholesterol levels (see Fig. 2). As we are aware of the great impact of body weight on both inflammatory and metabolic markers, we consider the absence of this variable in our analysis an important limitation. However, we previously reported a synergistic effect of periodontal infections and measures of body weight on serum levels of inflammatory markers (D'Aiuto et al. 2004b).

In periodontitis, the presence of subgingival pathogens elicits a local inflammatory response. This is characterized by the formation of a local inflammatory infiltrate characterized by exudation and migration of large number of leukocytes, involved in the first line of defence against bacterial pathogens, towards the affected area. Furthermore, this inflammatory response is amplified due to the production of pro-inflammatory cytokines and prostaglandins. These are produced by a variety of cells

involved in the response to the microbial invasion, such as monocytes/macrophages, neutrophils, lymphocytes, adipocytes and fibroblasts. The release of these substances into the bloodstream stimulates further recruitment of pro-inflammatory mediators and leukocytes at the local site. In addition bacteria and their end-products also trigger a systemic host response; we have already demonstrated that patients with periodontitis have a low-grade systemic inflammatory state (D'Aiuto et al. 2005). Cytokines such as IL-1 and IL-6 produced at the gingival sites might be dumped into the systemic circulation and stimulate a hepatic acute phase response to injury (Gabay & Kushner 1999), and also stimulate haematopoiesis (Revel 1989).

As in the case of acute bacterial infections, the persistent periodontal inflammatory state might have a repercussion on the total numbers of circulating neutrophils, because of increased bone marrow output or mobilization of the marginal granulocyte pool. Whether the increased number of leukocytes is mainly due to bacteraemia or to excessive local production of inflammatory mediators remains unclear. Lymphocyte counts usually increase following an antigenic stimulus or a neoplastic condition. The patients with severe perio-

odontitis included in this study had an increase in leukocytes, especially neutrophils and lymphocytes, reflecting a possible chronic systemic inflammatory stimulus, which could be determined by the persistent periodontal disease. This finding is in keeping with previous studies showing increased levels of neutrophils and lymphocytes in patients with periodontitis (Loos et al. 2000, Christan et al. 2002, Loos et al. 2004). Our group also demonstrated how periodontitis and its treatment can influence leucocytes numbers. An intensive session of periodontal therapy was associated with a sharp increase of neutrophils at 24 h and 1 month after therapy total leukocyte numbers were significantly reduced compared with baseline (D'Aiuto et al. 2005). Further confirmation of these observations comes from the fact that in this report the higher the number of deep pockets in these patients, the higher was their leukocyte number. The relevance of such findings should be discussed within the pivotal role that inflammation might play on future development of serious diseases such as diabetes and CHD. Consistently with the view of atherosclerosis as an inflammatory process, leukocytosis has been shown to be an independent risk factor and prognostic indicator of future CV events in healthy populations. In patients with previous history of CV diseases, leukocyte count also predicts future CV events. Pathogenic mechanisms are poorly understood but may involve biochemical, electrical and biomechanical changes (Madjid et al. 2004).

As well as leukocyte numbers and lipid levels, glucose levels were also found to be altered in the periodontitis subjects included in this study. When compared with healthy controls, periodontitis patients exhibited increased plasma glucose levels (crude difference 0.2 mmol/l, adjusted estimate amounting to approximately 1 mmol/l). These data are not unexpected in the light of the strong relationship between insulin resistance and inflammation (Festa et al. 2000). A chronic activation of the acute-phase response, such as the one which characterizes severe periodontitis, is believed to decrease the action of insulin, with consequent increase in circulating glucose levels (Saito et al. 2004). As part of a vicious circle, insulin resistance may also modulate the inflammatory process (Fernandez-Real & Ricart 2003). A limitation of our analysis

though is based on the inconsistency of blood collection with regards to fasting status, as the fasting time was not standardised. This might have had an important effect on the results, in particular the glucose levels and to a lesser extent on lipid factors. Nevertheless our study did not focus on glucose level per se but rather having a simple measure of indirect insulin sensitivity. In this respect the data and results should be interpreted with caution.

The patients with severe periodontitis included in this study also exhibited a dysmetabolic state, characterized by a large reduction in HDL cholesterol, and an increase in LDL cholesterol levels. This finding confirms previous reports of increased cholesterol (Cutler et al. 1999, Katz et al. 2002) and decreased HDL levels (Buhlin et al. 2003) observed in small samples of periodontitis patients compared with healthy controls. The association between periodontal inflammation and lipid metabolism was particularly evident on the HDL levels: in our population, even subjects with lower-extent disease presented with a sizeable decrease in HDL levels when compared with controls. These differences were even more marked in subjects with more generalized disease (higher-extent cluster). A relationship between infections and lipid metabolism has been widely documented in the past decades. Chronic infectious diseases are now thought to have an impact on lipid plasma levels (Gallin et al. 1969, Alvarez & Ramos 1986, Iacopino & Cutler 2000). This dyslipidemia is thought to be part of a host response aimed at decreasing the toxicity of harmful microbiological agents (Khovidhunkit et al. 2004). This study confirms an association between severe periodontitis and alteration of lipid levels, which may be mediated by the constant activation of the inflammatory process determined by the presence of periodontal pathogens in the periodontal pockets (D'Aiuto et al. 2005, Jain et al. 2003). Bacteria such as *Porphyromonas gingivalis*, one of the most common pathogens present in severe periodontitis patients (Mombelli et al. 2002), are capable of stimulating a continuous release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF- α (Belibasakis et al. 2005, Bodet et al. 2005). These cytokines are believed to have direct or indirect effects resulting in enhanced hepatic lipogenesis, reduced elimination

of LDL and increased tissue lipolysis (Feingold & Grunfeld 1987, Iacopino & Cutler 2000). On the other hand, because of the case-control design of this study, we cannot exclude that the severity of periodontal disease seen in these patients might actually be a result rather than a cause of the altered lipid metabolism. Alterations in lipid metabolism, such as a decrease in HDL levels, have been associated with increased risk of CHD (Grundy et al. 2004).

Evidence from population studies suggests that a cluster of metabolic factors define MS and most of these factors represent useful risk predictors for diabetes, atherosclerosis and CHD (Fernandez-Real & Ricart 2003). The criteria for definition of MS according to the World Health Organization (WHO) are described in Table 4. In our case-control study we observed a possible association of severe periodontitis and some of these factors (insulin resistance and dyslipidemia).

In adults, periodontitis is a common infection. Only a small proportion of individuals however (1–5%) present with severity and extent of periodontitis of magnitude similar to that of the subject of this investigation. Increasing evidence suggests that its local inflammatory and/or infectious burden might trigger a systemic response (D'Aiuto et al. 2004a, D'Aiuto et al. 2005). The observation that traditional and novel cardiovascular risk factors might be influenced by periodontitis may have important clinical consequences. Individual odds for future coronary events not attributable to traditional CV risk factors (Ridker et al. 2004) could be influenced

Table 4. WHO definition of metabolic syndrome (2004)

Insulin resistance:
Type 2 diabetes
Impaired fasting glucose
Impaired glucose tolerance
(≥ 110 mg/dl or ≥ 6.1 mmol/l)
Plus at least 2 of the following:
High blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)
Plasma triglycerides ≥ 150 mg/dl (≥ 1.7 mmol/l)
HDL cholesterol < 35 mg/dl (< 0.9 mmol/l) in men or < 39 mg/dl (< 1.0 mmol/l) in women
BMI > 30 kg/m ² and/or waist: hip ratio > 0.9 in men or > 0.85 in women
Urinary albumin excretion rate ≥ 20 μ g/min or albumin: creatinine ratio ≥ 30 mg/g

HDL, high-density lipoprotein; BMI, body mass index.

by an underlying severe periodontal infection through disruption of metabolic and inflammatory homeostasis. Within the limits of a case-control design, this study supports the association between severe periodontitis and a systemic inflammatory and dysmetabolic state, which may predispose to more serious systemic conditions.

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Address:

Luigi Nibali
 Periodontology Unit
 UCL Eastman Dental Institute
 256 Gray's Inn Road
 London WC1X 8LD
 UK

E-mail: l.nibali@eastman.ucl.ac.uk

Clinical Relevance

Scientific rationale for the study: Numerous studies have associated severe periodontitis with increased risk of cardiovascular events. The mechanisms behind this association remain unclear.

Principal findings: Patients with severe periodontitis exhibited a low-grade systemic inflammation, dyslipidemia and increase in serum glucose levels when compared with healthy subjects with no periodontitis.

Practical implications: Patients with untreated severe periodontitis may have a tendency to increased risk of MS and therefore of cardiovascular diseases.