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Metabolic syndrome, insulin resistance, and periodontitis: a cross-sectional study in a middle-aged French population

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Abstract

Aim: Metabolic syndrome consists of a cluster of clinical and biological abnormalities, influenced by insulin resistance and promoting cardiovascular diseases. We examined the relationships between metabolic syndrome, its various components, insulin resistance, and periodontitis.

Materials and Methods: The study included 276 subjects (35–74 years) recruited within a cross-sectional survey on cardiovascular risk factors. Twenty-one were excluded because of infectious risk or total tooth loss. Clinical attachment loss (CAL), probing pocket depth (PD), gingival and plaque indexes were recorded. Periodontitis was classified into moderate and severe forms.

Results: The mean age was 58, 41% of the subjects had moderate and 39% had severe periodontitis. In univariate comparisons, periodontitis was associated with metabolic syndrome ($p = 0.050$), most of its components, and HOMA index (homoeostasis model assessment of insulin resistance). After adjustment for confounders, only HOMA index remained associated with severe periodontitis (odds ratio [OR] = 3.97 [95% confidence interval: 1.22–12.9], OR = 3.78 [1.14–12.5] for third and fourth *versus* the first quartile of the HOMA index, respectively). The HOMA index was also associated with the number of periodontal sites with CAL $\geqslant$ 4 mm, CAL $\geqslant$ 5 mm, or PD $\geqslant$ 4 mm (greater number for higher HOMA-index values). This relationship disappeared in never-smokers.

Conclusions: Our data support the relationships between metabolic disturbances and periodontitis, with a central role of insulin resistance.

Key words: abdominal obesity; cardiovascular risk factors; insulin resistance; metabolic syndrome; periodontitis

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Conflict of interest and source of funding

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Periodontitis has been associated in previous literature with altered health conditions (Kinane & Marshall 2001, Williams et al. 2008) such as diabetes, obesity, cardiovascular diseases, or preterm birth (Madianos et al. 2002). Recently, studies have suggested that periodontitis could also be associated with increased systemic inflammatory markers (Loos 2005, Montebugnoli et al. 2005), dyslipidaemia (Lösche et al. 2000, Katz et al. 2002), non-fasting serum glucose alterations (Grossi & Genco 1998), and endothelial dysfunction (Tonetti et al. 2007). These disturbances are part of a specific metabolic state, the so-called ''metabolic syndrome''. According to the definition proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (American Heart Association & National Heart,

Lung, and Blood Institute et al. 2005), metabolic syndrome is defined as the presence of at least three of the following five criteria: waist circumference $\geqslant$102 cm in men, $\geqslant$88 cm in women; elevated plasma triglycerides $\geqslant$1.7 mmol/l (150 mg/dl); reduced high-density lipoprotein (HDL) cholesterol below 1 mmol/l (40 mg/dl) in men, 1.3 mmol/l (50 mg/dl) in women; high blood pressure $\geqslant$130/85 mmHg or antihypertensive drug treatment; elevated fasting glucose $\geqslant$5.5 mmol/l (100 mg/dl) or hypoglycaemic drug treatment.

Insulin resistance promoted by obesity plays a central role in the development of metabolic syndrome (American Heart Association & National Heart, Lung, and Blood Institute et al. 2005). Despite a number of studies that have already suggested potential associations between metabolic syndrome and periodontitis (Nibali et al. 2007, D'Aiuto et al. 2008, Li et al. 2009), investigations are still required to better understand the relationships linking these two conditions. The aim of the present cross-sectional analysis was to examine the relationships between metabolic syndrome, its various components, insulin resistance, and periodontitis in a middle-aged population recruited in France.

Materials and Methods

Study population

The study was conducted in Toulouse University Hospital, France, in a sub-sample of the MONA LISA survey (MOnitoring NAtionaL du rISque Artériel), a cross-sectional study carried out to estimate the prevalence of cardiovascular risk factors in the general French population (Ferrières et al. 2009). Briefly, participants, aged 35–74 years, were recruited from polling lists between 2006 and 2007 in three French centres located in Northern (Lille), North-Eastern (Strasbourg), and South-Western (Toulouse) France. The recruitment was stratified on centre, town size, age, and gender, in order to get 200 men and 200 women in each centre and a 10-year age stratum. Thus, 4800 subjects were recruited to participate in the MONA LISA study.

In the Toulouse Centre, 1625 subjects were recruited, a quarter of whom were offered to undergo additional examinations including a clinical oral exam. This sub-sample corresponds to those people who were available for data collection on the dates at which the dental exams were scheduled. Those with a risk of endocarditis (18 subjects), fever, or other symptoms of infectious disease (two subjects) were excluded as was a subject with total tooth loss. The present analyses were performed on 255 subjects, who signed an informed consent form after having received oral and written information about the study. The protocol was approved in March 2006 by the appropriate French National Ethics Committee (CCPPRB). The study was conducted in agreement with French law and the Declaration of Helsinki.

Questionnaires

All participants had a guided, face-to-face interview. Information on socio-economic characteristics and living standards (number of years at school after the age of seven, highest diploma, occupational activity, and income tax level), previous medical histories, cardiovascular risk factors (smoking habits, hypertension, diabetes, and hypercholesterolaemia), drug intake, alcohol consumption, and family history of cardiovascular disease were recorded. Smokers were divided into three categories: non-smokers, former, and current smokers. All smoking practices were considered (cigarettes, cigarillos, cigars, and pipe). Alcohol consumption led to separation of the subjects into three groups: teetotallers, moderate alcohol drinkers (1–30 g/day), and heavy drinkers ($>$30 g/day).

Clinical examination: anthropometric data and blood pressure measurement

Subjects' height and weight were measured. The body mass index (BMI) was calculated as weight (kg) divided by height squared. BMI was categorized into normal weight (BMI $<$ 25 kg/m^2), overweight (25 $\leqslant$ BMI $<$ 30 kg/m^2) and obesity (BMI $\geqslant$ 30 kg/m^2). The waist circumference was measured using a tape at mid distance between the last rib and the iliac crest, subjects being in a standing position and breathing normally (Després et al. 2001). Abdominal obesity was defined as a waist circumference $\geqslant$102 cm in men and $\geqslant$88 cm in women (Grundy et al. 2004). Two blood pressure measurements were taken after a 5-min. rest, at least, on the subject's right arm, in a seated position, using an automatic sphygmomanometer (OMROM 705, Kruisweg, the Netherlands). Heart pulses per minute were measured twice using the same automatic sphygmomanometer. Means of the two measurements were used for statistical analyses.

Clinical oral examination

Clinical oral examinations were performed by a single dentist who used standardized methods. The number of teeth was recorded. Using an examination probe and mirror, the number of filled and carious teeth was assessed. Periodontal examination used a manual periodontal probe PCP 127 (Hu-Friedy, Chicago, IL, USA). Four parameters of periodontal disease were recorded on four sites (mesiobuccal, midbuccal, distobuccal, and midlingual or midpalatal) of each tooth present, except third molars: plaque index (PI), gingival index (GI), probing pocket depth (PD), and clinical attachment loss (CAL). PD was measured from the gingival margin to the base of the clinical pocket, and CAL was recorded as a distance from the cement-enamel junction to the base of the clinical pocket, with the probe tip parallel to the long axis of the tooth. Periodontitis was classified into moderate and severe forms according to the clinical criteria suggested by Page & Eke (2007): Moderate periodontitis was defined as two or more inter-proximal sites with CAL $\geqslant$ 4 mm, not on the same tooth, or two or more inter-proximal sites with PD $\geqslant$ 5 mm, not on the same tooth. Severe periodontitis required two or more inter-proximal sites with CAL $\geqslant$ 6 mm, not on the same tooth, and one or more inter-proximal site with PD $\geqslant$ 5 mm.

Repeatability

Tests of repeatability were performed on a sample of 20 persons (10 men and 10 women) by the dentist who was recruited to examine participants in the MONA LISA study. The 20 subjects underwent two periodontal examinations, 14 days apart. At each examination, PI, GI, PD, and CAL were assessed as described above. The intra-class correlation coefficients were 0.96 for PI, 0.99 for GI, 0.97 for PD, and 0.99 for CAL.

Biological measurements

A venous blood sample was drawn on disodium EDTA after a fasting period of

at least 10 h. Blood cell count (white and red cells and platelets) was performed by the Toulouse University Hospital Laboratory. Other biological measurements were performed at the Pasteur Institute of Lille. Glucose was measured using a standard glucose hexokinase method (Olympus, Eastleigh, UK). The plasma total cholesterol and triglyceride levels were measured by enzymatic methods (Olympus). HDL cholesterol was assessed with an enzymatic colorimetric method (Olympus). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation (Friedewald et al. 1978) when triglycerides were below 4.6 mmol/l (400 mg/dl). Plasma insulin was measured by enzyme immuno-assay (Beckman Coulter, Villepinte, France), and C-reactive protein (CRP) was measured by a nephelometric method (Dade Behring, Courbevoie, France).

Definition of cardiovascular risk indicators and metabolic syndrome

Hypertension was defined as systolic blood pressure $\geqslant$140 mmHg or diastolic blood pressure $\geqslant$90 mmHg or use of antihypertensive drugs. Diabetes was defined as serum fasting glucose $\geqslant$7 mmol/l (126 mg/dl) or use of hypoglycaemic drugs. Hypercholesterolaemia was defined as LDL-C$\geqslant$4.1 mmol/l (160 mg/dl) or use of hypocholesterolaemic drugs, and hypertriglyceridaemia was defined as triglycerides $\geqslant$1.7 mmol/l (150 mg/dl). Abdominal obesity was defined as a waist circumference $\geqslant$102 cm in men or $\geqslant$88 cm in women. Metabolic syndrome was assessed according to the 2005 definition proposed by the NCEP ATP III (American Heart Association & National Heart, Lung, and Blood Institute et al. 2005), as detailed in the introduction of this paper. Insulin resistance was evaluated by the HOMA index for insulin resistance (homoeostasis model assessment of the insulin resistance index) defined as fasting insulin (mIU/l) multiplied by fasting glucose (mmol/l) and divided by 22.5 (Matthews et al. 1985).

Statistical analyses

Statistical analyses were performed using STATA statistical software (release 9.2, Stata Corporation, College Station, TX, USA). Variables associated with periodontitis in univariate comparisons were assessed using the χ^2 test for qualitative variables (or Fischer's exact test in the case of small expected numbers). ANOVA was used for quantitative variables. Multinomial logistic regression models were built to estimate the risk of periodontitis. Odds ratios (OR) were estimated with 95% confidence intervals (95% CI). In the first model, the explanatory variable was metabolic syndrome and the model was adjusted for traditional risk markers for periodontitis (age, gender, educational level, smoking habits, alcohol consumption, CRP, and dental plaque). Then, this procedure was repeated several times, using each component of the metabolic syndrome (waist circumference, hypertension, glycaemia, plasma triglycerides, and plasma HDL cholesterol) and HOMA index, as successive explanatory variables, in place of metabolic syndrome. Interactions between periodontitis, metabolic syndrome, HOMA index, and the various adjustment variables were tested in final regression models. Finally, in order to study the impact on the whole periodontium, we also conducted analyses considering the number of sites affected by CAL$\geqslant$4 mm, CAL$\geqslant$5 mm, or PD$\geqslant$4 mm, as the outcome variables. A negative binomial regression analysis was used (nbreg STATA procedure) to provide relative risks (RR) and 95% CI. Negative binomial regression was preferred to Poisson regression because of over-dispersion of the data.

Results

Table 1 shows the main characteristics of the study sample regarding data collected during the clinical oral examination. The median number of missing teeth was 2, with a minimum of 0 and a maximum of 27. The mean percentage of sites with PD$\geqslant$4 mm, PD$\geqslant$5 mm, and CAL$\geqslant$4 mm was 10% $\pm$ 13; 5% $\pm$ 9; and 24% $\pm$ 23, respectively. Tables 2 and 3 show univariate comparisons with periodontitis. Male gender, current smoking, regular alcohol drinking, obesity, hypertension, and metabolic syndrome were more frequent in subjects with periodontitis, as well as in those with a PI and a number of sites with CAL$\geqslant$4 mm, CAL$\geqslant$5 mm, or PD$\geqslant$4 mm, above median. Age, waist circumference, systolic blood pressure, and diastolic blood pressure increased with the severity of periodontal disease (Table 2). Low HDL cholesterol, high fasting glycaemia, and high HOMA index were also linked with periodontitis (Table 3).

After full adjustment for confounders, having a metabolic syndrome was no longer associated with periodontitis (Table 4). Subjects in the fourth quartile of HDL cholesterol remained associated with moderate periodontitis (OR = 0.23 [0.05–0.92] for the fourth *versus* the first quartile of HDL cholesterol), but no association was found with severe

Table 1. Characteristics of the 255 participants (clinical oral examination)

	N = 255
Number of filled teeth	
Mean $\pm$ SD	11.0 $\pm$ 5.3
Median [IQR] [min.; max.]	11 [7–15] [min. 0; max. 22]
At least one filled tooth, *n* (%)	250 (98%)
Number of carious teeth	
Mean $\pm$ SD	0.2 $\pm$ 0.7
Median [IQR] [min.; max.]	0 [0–0] [min. 0; max. 6]
At least one carious lesion, *n* (%)	36 (14%)
Number of missing teeth	
Mean $\pm$ SD	3.4 $\pm$ 4.5
Median [IQR] [min.; max.]	2 [0–5] [min. 0; max. 27]
At least one missing tooth, *n* (%)	189 (74%)
Periodontitis, n (%)	
No; moderate; severe	54 (21%); 102 (40%); 99 (39%)
Sites with PD$\geqslant$4 mm	
Mean % $\pm$ SD	9.7% $\pm$ 12.7
Median % [IQR] [min.; max.]	4.62% [1–14] [min. 0; max. 62]
Sites with PD$\geqslant$5 mm	
Mean % $\pm$ SD	5.3% $\pm$ 9.2
Median % [IQR] [min.; max.]	1% [0–6] [min. 0; max. 51]
Sites with CAL$\geqslant$4 mm	
Mean % $\pm$ SD	23.7% $\pm$ 23.1
Median % [IQR] [min; max]	16% [4–38] [min. 0; max. 94]

SD, standard deviation; IQR, inter-quartile range; Min., minimum; Max., maximum; CAL, clinical attachment loss; PD, probing pocket depth.

Table 2. Univariate comparisons with periodontitis (socio-economic characteristics, cardiovascular risk indicators, and plaque index)

	No periodontitis ($N = 54$)	Moderate periodontitis ($N = 102$)	Severe periodontitis ($N = 99$)	p-value
Age (years)	53.0 ± 9.8	59.6 ± 9.8	58.9 ± 8.2	<0.001
Male gender, *n* (%)	21 (38.9%)	56 (54.9%)	63 (63.6%)	0.013
Finished high school, *n* (%)	31 (57.4%)	50 (49.0%)	42 (42.4%)	0.204
School period (years)	14.4 ± 3.6	13.6 ± 3.6	13.6 ± 4.7	0.376
Payment of income tax, *n* (%)	48 (88.9%)	87 (85.2%)	86 (86.9%)	0.819
More than 2 children, *n* (%)	11 (20.4%)	18 (17.6%)	27 (27.3%)	0.244
Smoking, *n* (%)				0.021
Never	35 (64.8%)	45 (44.1%)	38 (38.8%)	
Former	13 (24.1%)	39 (38.2%)	36 (36.4%)	
Current	6 (11.1%)	18 (17.6%)	25 (25.2%)	
Alcohol consumption, *n* (%)				0.050
No consumption	20 (37.0%)	24 (23.8%)	26 (26.3%)	
0–30 g/day	26 (48.1%)	68 (67.3%)	53 (53.5%)	
>30 g/day	8 (14.8%)	9 (8.9%)	20 (20.2%)	
Body mass index (BMI), *n* (%)				0.050
BMI < 25 kg/m^2	31 (57.4%)	47 (46.1%)	34 (34.3%)	
BMI (25–30 kg/m^2)	18 (33.3%)	43 (42.2%)	45 (45.5%)	
BMI ⩾ 30 kg/m^2	5 (9.3%)	12 (11.8%)	20 (20.2%)	
Abdominal obesity, *n* (%)*	12 (22.2%)	31 (30.4%)	28 (28.3%)	0.552
Waist (cm)	86.3 ± 10.9	90.5 ± 10.7	92.6 ± 10.6	0.003
Heart rate (pulse/min.)	67.2 ± 9.6	65.0 ± 9.8	65.3 ± 9.7	0.369
SBP (mmHg)	124.8 ± 16.7	130.3 ± 16.9	135.6 ± 19.7	0.002
DBP (mmHg)	78.4 ± 9.4	80.7 ± 10.1	83.0 ± 10.3	0.023
Hypertension, *n* (%)†	14 (25.9%)	38 (37.2%)	48 (48.5%)	0.021
Diabetes, *n* (%)	1 (1.9%)	8 (7.8%)	8 (8.1%)	0.278
Hypercholesterolaemia, *n* (%)‡	22 (40.7%)	43 (42.2%)	54 (54.5%)	0.131
Hypertriglyceridaemia, *n* (%)§	8 (14.8%)	21 (20.6%)	29 (29.3%)	0.099
Metabolic syndrome, *n* (%)	9 (16.7%)	29 (28.4%)	35 (35.3%)	0.050
Plaque index, *n* (%)¶	12 (22.2%)	46 (45.1%)	68 (68.6%)	<0.001
Sites with PD ⩾ 4 mm, *n* (%)¶	0 (0.0%)	40 (39.2%)	87 (87.9%)	<0.001
Sites with CAL ⩾ 4 mm, *n* (%)¶	1 (1.8%)	39 (38.2%)	87 (87.9%)	<0.001
Sites with CAL ⩾ 5 mm, *n* (%)¶	1 (1.8%)	32 (31.4%)	94 (94.9%)	<0.001

Results are given as mean ± SD or *n* (%).

*Waist circumference ⩾ 102 cm in men, ⩾ 88 in women.

†SBP ⩾ 140 or DBP ⩾ 90 mmHg or antihypertensive drug treatment.

‡LDL-cholesterol ⩾ 4.1 mmol/l or hypocholesterolaemic drug treatment.

§Triglycerides ⩾ 1.7 mmol/l.

¶Percentage of subjects with a mean plaque index (or a mean number of sites with PD ⩾ 4 mm, CAL ⩾ 4 mm, or CAL ⩾ 5 mm) above the median value in the sample.

LDL, low-density lipoprotein; PD, probing pocket depth; CAL, clinical attachment loss; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Table 3. Univariate comparisons with periodontitis (biological parameters)

	No periodontitis ($N = 54$)	Moderate periodontitis ($N = 102$)	Severe periodontitis ($N = 99$)	p-value
Total cholesterol (mmol/l)	5.83 ± 0.92	5.73 ± 0.95	5.67 ± 1.00	0.664
LDL-cholesterol (mmol/l)	3.67 ± 0.77	3.67 ± 0.84	3.62 ± 0.89	0.847
HDL-cholesterol (mmol/l)	1.59 ± 0.33	1.41 ± 0.30	1.38 ± 0.28	0.001
Triglycerides (mmol/l)	1.20 ± 0.96	1.30 ± 0.84	1.42 ± 0.68	0.301
Glycaemia (mmol/l)	5.27 ± 0.50	5.49 ± 0.82	5.63 ± 0.87	0.029
Insulinaemia (mUI/l)	4.52 ± 3.01	5.40 ± 3.94	5.94 ± 4.02	0.085
HOMA-index for insulin resistance	1.07 ± 0.74	1.36 ± 1.07	1.50 ± 1.02	0.038
CRP (mg/l)	1.60 ± 1.87	1.68 ± 1.65	2.27 ± 2.30	0.053

Results are given as mean ± SD.

CRP, C-reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

periodontitis (Table 4). A high HOMA index remained associated with severe periodontitis (OR = 3.97 [1.22–12.92] for the third *versus* the first quartile of HOMA index and OR = 3.78 [1.14–12.57] for the fourth *versus* the first quartile) (Table 4). None of the other components of the metabolic syndrome were associated with periodontitis after adjustment.

Negative binomial regression analysis showed that subjects in the highest quartile of the HOMA index had a 48% increased risk of having additional sites with CAL ⩾ 4 mm, as compared with subjects in the lowest quartile (and a 73% and a 74% increased risk to have additional sites with CAL ⩾ 5 mm or

Table 4. Relationships between periodontitis and the various components of metabolic syndrome

	Moderate periodontitis ($N = 102$)		Severe periodontitis ($N = 99$)	
	OR	95% CI	OR	95% CI
Waist circumference				
I Quartile	1		1	
II Quartile	1.49	(0.54–4.10)	1.33	(0.45–3.92)
III Quartile	2.00	(0.63–6.34)	1.99	(0.59–6.75)
IV Quartile	0.93	(0.29–2.91)	1.32	(0.40–4.26)
Hypertension	0.83	(0.34–1.99)	1.22	(0.50–2.98)
Glycaemia				
I Quartile	1		1	
II Quartile	0.59	(0.22–1.61)	0.60	(0.19–1.82)
III Quartile	1.06	(0.33–3.41)	1.92	(0.57–6.49)
IV Quartile	0.88	(0.27–2.81)	1.55	(0.46–5.25)
Triglycerides				
I Quartile	1		1	
II Quartile	1.48	(0.52–4.23)	2.43	(0.78–7.56)
III Quartile	1.18	(0.42–3.30)	2.05	(0.68–6.14)
IV Quartile	1.46	(0.48–4.42)	2.32	(0.72–7.44)
HDL-cholesterol				
I Quartile	1		1	
II Quartile	0.38	(0.10–1.40)	0.39	(0.10–1.47)
III Quartile	0.33	(0.08–1.24)	0.35	(0.09–1.34)
IV Quartile	0.23	(0.05–0.92)	0.24	(0.06–1.02)
HOMA index				
I Quartile	1		1	
II Quartile	0.65	(0.24–1.74)	1.38	(0.46–4.11)
III Quartile	2.16	(0.74–6.33)	3.97	(1.22–12.9)
IV Quartile	1.28	(0.41–3.98)	3.78	(1.14–12.5)
Metabolic syndrome	1.54	(0.59–4.01)	1.97	(0.74–5.23)

Waist circumference, hypertension, glycaemia, triglycerides, HDL-cholesterol, HOMA index, and metabolic syndrome were explanatory variables in 7 independent models adjusted for age, gender, educational level, smoking habits, alcohol consumption, CRP, and dental plaque.

HDL, high-density lipoprotein; CRP, C-reactive protein; OR, odds ratio; 95% CI, 95% confidence interval.

PD $\geqslant$ 4 mm, respectively) (Table 5). Trends from the lowest to the highest quartile of the HOMA index were significant. These relationships were modified only marginally when diabetic subjects were excluded (Table 5). When analyses were stratified on smoking status, the HOMA index was linked to periodontal parameters, only in current or past smokers (Table 6). The metabolic syndrome or its various components were not associated with periodontitis when negative binomial regression was used for data analysis.

Discussion

The data analysed in this paper were collected from a sub-sample recruited within the Toulouse MONA LISA study. The subjects analysed were quite similar to the entire Toulouse MONA LISA sample, with regard to gender (55% of men *versus* 51% in the Toulouse MONA LISA sample), smoking habits (46% of non-smokers in both groups), or educational level (13.8 years spent at school or university in average, *versus* 13.5), but the mean age was higher (58.0 *versus* 55.1 years). Our study population was characterized by a rather homogeneous socio-economic level and relatively good living conditions and medical follow-up: 48% of the sample completed high school, 87% paid income tax, 92% declared they had blood pressure monitored during the past 12 months, and 73% had cholesterol and 94% had glycaemia checked.

To determine the presence of periodontitis, we first used the consensus definition proposed by Page & Eke (2007). Periodontitis was classified into moderate and severe forms based on the presence of inter-proximal sites affected by CAL and/or PD (Page & Eke 2007). Such a definition is appealing because it is close to the diagnosis of periodontitis made in clinical practice. Differentiating moderate and severe forms according to thresholds of CAL and PD enhances case definitions and thus provides more satisfactory estimates for the prevalence of clinical periodontitis. However, one limitation is the exclusion of buccal and/or lingual sites, which is problematic because general health conditions such as metabolic syndrome or insulin resistance may have a wide impact overall on periodontal tissue (Li et al. 2009). From this point of view, considering the number of sites affected by CAL $\geqslant$ 4 mm, CAL $\geqslant$ 5 mm, or PD $\geqslant$ 4 mm as the outcome variables, and distinguishing these three situations, could be more appropriate. This latter strategy also makes stratified analyses easier (because of power concerns) to better elucidate the role of confounding factors.

Actually, both approaches appear to be complementary, but using different definitions for periodontitis compelled us to use different statistical methods and risk estimates (OR for multinomial logistic regression and RR for negative binomial regression), which made comparability difficult. First, OR represents the increase in the risk of having moderate or severe periodontitis in exposed compared with unexposed subjects (for instance, in subjects with metabolic syndrome compared with those without), whereas RR represents the increase in the risk of having an additional site with CAL $\geqslant$ 4 mm, CAL $\geqslant$ 5 mm, or PD $\geqslant$ 4 mm, in exposed compared with unexposed subjects. Then, OR should be interpreted with caution as it is a poor approximation of risk increase (compared with RR), generally leading to an overestimation. Nevertheless, whatever be the definition and the type of analyses used, high HOMA index was associated consistently with severe periodontal disease, whereas other components of metabolic syndrome were not. Furthermore, we found little difference in the magnitude of the RRs estimated for CAL $\geqslant$ 4 mm, PD $\geqslant$ 4 mm and CAL $\geqslant$ 5 mm. Overall, our results point out the key role of insulin resistance.

To improve the comparability of the results, all models were adjusted systematically for the same variables: age, gender, educational level, smoking habits, alcohol consumption, CRP, and dental plaque. These covariates were chosen as they are described in the literature to be involved in the development of periodontal diseases. In particular, age, alcohol consumption, and socio-economic level are well-established

Table 5. Relationships of HOMA index (homeostasis model assessment of insulin resistance) with the number of sites with CAL ⩾ 4 mm, PD ⩾ 4 mm, and CAL ⩾ 5 mm

		Number of sites with CAL ⩾ 4 mm		Number of sites with PD ⩾ 4 mm		Number of sites with CAL ⩾ 5 mm	
		RR	95% CI	RR	95% CI	RR	95% CI
HOMA index for insulin resistance							
Total population							
I	Quartile	1.00		1.00		1.00	
II	Quartile	1.07	0.74–1.54	1.14	0.73–1.76	1.20	0.74–1.95
III	Quartile	1.41	0.97–2.06	1.37	0.87–2.16	1.48	0.89–2.46
IV	Quartile	1.48	1.02–2.15	1.74	1.11–2.73	1.73	1.05–2.84
			$p = 0.018$*		$p = 0.007$*		$p = 0.022$*
Non-diabetics subjects ($n = 238$)							
I	Quartile	1.00		1.00		1.0	
II	Quartile	1.05	0.72–1.54	1.05	0.67–1.66	1.17	0.71–1.92
III	Quartile	1.31	0.88–1.94	1.27	0.79–2.04	1.26	0.74–2.13
IV	Quartile	1.52	1.02–2.27	1.61	1.00–2.61	1.82	1.08–3.07
			$p = 0.021$*		$p = 0.027$*		$p = 0.023$*
Non-smoker subjects ($n = 204$)							
I	Quartile	1.00		1.00		1.0	
II	Quartile	1.11	0.72–1.71	1.07	0.64–1.78	1.25	0.71–2.21
III	Quartile	1.15	0.72–1.82	1.09	0.62–1.92	1.19	0.64–2.23
IV	Quartile	1.26	0.82–1.96	1.46	0.86–2.48	1.44	0.81–2.57
			$p = 0.309$*		$p = 0.131$*		$p = 0.240$*

Model was adjusted for age, gender, educational level, smoking habits, alcohol consumption, CRP, and dental plaque.

*p-value for trend.

CAL, clinical attachment loss; PD, probing pocket depth; RR, relative risks; 95% CI, 95% confidence interval; CRP, C-reactive protein.

Table 6. Relationships of HOMA index (homeostasis model assessment of insulin resistance) with the number of sites with CAL ⩾ 4 mm, PD ⩾ 4 mm, and CAL ⩾ 5 mm among subjects who had never smoked ($n = 116$) and among former and current smokers ($n = 137$)

		Number of sites with CAL ⩾ 4 mm		Number of sites with PD ⩾ 4 mm		Number of sites with CAL ⩾ 5 mm	
		RR	95% CI	RR	95% CI	RR	95% CI
Never smoked ($n = 116$)							
I	Quartile	1.00		1.00		1.0	
II	Quartile	1.30	0.73–2.31	1.09	0.53–2.26	1.36	0.64–2.88
III	Quartile	0.80	0.42–1.52	0.76	0.34–1.72	0.67	0.28–1.60
IV	Quartile	1.14	0.61–2.13	1.15	0.52–2.51	1.05	0.46–2.37
			$p = 0.992$*		$p = 0.872$*		$p = 0.751$*
Former and current smokers ($n = 137$)							
I	Quartile	1.00		1.00		1.0	
II	Quartile	0.75	0.49–1.16	1.04	0.62–1.74	0.82	0.45–1.49
III	Quartile	1.99	1.28–3.07	1.96	1.16–3.30	2.32	1.27–4.24
IV	Quartile	1.78	1.16–2.73	2.43	1.45–4.05	2.26	1.26–4.06
			$p < 0.001$*		$p < 0.001$*		$p < 0.001$*

Model was adjusted for age, gender, educational level, smoking habits, alcohol consumption, CRP, and dental plaque.

*p-value for trend.

CAL, clinical attachment loss; PD, probing pocket depth; RR, relative risks; 95% CI, 95% confidence interval; CRP, C-reactive protein.

risk indicators for periodontitis and have also been associated with metabolic syndrome (Razzouk & Muntner 2009). The role of gender is more controversial but adjustment for this covariate is relevant as a surrogate for other confounding situations.

Smoking is a major risk factor for periodontitis but its relationships with metabolic syndrome and insulin resistance are more complex. On the one hand, nicotine stimulates energy expenditure and enhances satiety. On the other hand, body weight is frequently greater in heavy smokers compared with light or non-smokers, reflecting a number of behaviours leading to weight gain, such as poor diet and low physical activity (Chiolero et al. 2008). Furthermore, smoking has also been associated with insulin resistance in the early stages of glucose disturbances (Fagard & Nilsson 2009). Consequently, our models were adjusted for smoking habits, but a stratified analysis on smoking status was also required, to fully eliminate confounding and better elucidate the role of tobacco. While a high HOMA-index value was clearly linked with periodontitis among current and past smokers, the association disappeared among never-smokers. Similar relationships were found for metabolic syndrome (data not shown). These data support the hypothesis that smoking may promote or strengthen the link between insulin resistance and periodontitis, or at least, that smokers have specific characteristics promoting this link.

Adjustment for CRP was decided because, on the one hand, this inflammatory marker has clearly been associated with obesity (Visser et al. 1999), insulin resistance (Marques-Vidal et al. 2002), and metabolic syndrome (Tamakoshi et al. 2003), and, on the other hand, CRP is increased in serum and gingival crevicular fluid among subjects with periodontal diseases (Noack et al. 2001, Linden et al. 2008, Fitzsimmons et al. 2009). Accordingly, it has been suggested that CRP may play the role of a mediator between metabolic disturbances and periodontal lesions, especially among smokers (Hanyu et al. 2009). Considering CRP as an adjustment covariate was thus warranted.

Despite this extensive adjustment, remaining confounders may exist, such as other inflammatory biomarkers (interleukins for instance), poor toothbrushing habits (oral hygiene), or periodontal pathogens. The latter has been partly taken into account through adjustment for PI.

Metabolic syndrome is a constellation of interrelated risk factors of a metabolic origin, promoting the development of atherosclerotic cardiovascular diseases and type 2 diabetes. Papers considering the relationship of periodontitis with metabolic syndrome as a whole entity are recent and scarce (Pozharitskaia et al. 2004, Holmlund et al. 2007, Nibali et al. 2007, Shimazaki et al. 2007, D'Aiuto et al. 2008, Janket et al. 2008, Li et al. 2009). In the paper of D'Aiuto

et al. (2008) that reports data from a very large US population, an association was found between severe periodontitis and metabolic syndrome in people aged 44 or older. The authors suggested the potential key role of insulin resistance. Our study provides further information in an older French population, by providing data on the HOMA index, a biological marker of insulin resistance. Insulin resistance is central in the development of the metabolic disturbances encountered in the metabolic syndrome and is linked closely with glucose disorders (Matthews et al. 1985). Given that poor glycemic control is likely involved in the development of periodontitis (Tsai et al. 2002), insulin resistance may also play a central role.

Obesity is also a key factor in the occurrence of metabolic syndrome and is strongly linked with insulin resistance (Eckel et al. 2005, Grundy 2005). Based on an experimental, controlled, animal study, Amar et al. (2007) have suggested that obesity may disturb immune host defence to periodontal pathogens such as *Porphyromonas gingivalis*, and thus promote periodontitis. Mice with a diet-induced obesity and experimentally infected with this bacteria, developed increased alveolar bone loss associated with a paradoxical blunted inflammatory response with reduced expression of pro-inflammatory cytokines. In human studies, a high BMI and a high waist–hip ratio have been related to periodontitis or deep pockets in various populations including young and older subjects, men and women (Saito et al. 2001, 2005, Al-Zahrani et al. 2003, Wood et al. 2003, Dalla Vecchia et al. 2005, Nishida et al. 2005, Reeves et al. 2006, Linden et al. 2007). A dose-dependent relationship between the BMI and deep periodontal pockets has also been described in low-risk middle-aged subjects such as non-diabetic, non-smoking people (Ylöstalo et al. 2008). Our data do not support the fact that obesity may act directly to promote periodontitis (we found no association between obesity and periodontitis after adjustment). Preferentially, we hypothesize that the role of insulin resistance is predominant: insulin resistance, which increases with obesity, could mediate the association between obesity and periodontitis, as suggested previously in the literature (Genco et al. 2005).

Extensive medical and biological data were recorded in our study through standardized medical examinations and questionnaires; hence, a great number of variables were available for our analyses, in particular, markers of insulin resistance such as the HOMA index. The main limitation is the cross-sectional design of the study, making it impossible to define the direction of the link between insulin resistance and periodontitis. However, although periodontitis may have an impact on systemic metabolic parameters such as insulin resistance, it is more likely that insulin resistance could play a trigger role in periodontitis, at least in smokers (as the relationship disappeared in non-smokers). Further research is required to specify the role of tobacco and to determine whether causal relationship exists, and if so, to investigate the impact of therapeutic actions taken to reduce the effect of insulin resistance on periodontal disease.

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Clinical Relevance

This study suggests that insulin resistance and severe periodontitis are two conditions that are prone to coexist in an individual.
Scientific rationale for the study: While previous literature has associated periodontitis with various cardiovascular risk factors, less is known about the relationships with metabolic syndrome or insulin resistance.
Principal findings: In former and current smokers, we found that periodontitis was associated with a high HOMA index (a biological marker of insulin resistance.)
Practical implications: Subjects with dysmetabolic profile due to insulin resistance may be at an increased risk for periodontitis and should be screened for periodontal disease.