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Association of periodontitis and metabolic syndrome in the Baltimore Longitudinal Study of Aging

Mark J. Nesbitt[1], **Mark A. Reynolds**[2], **Harlan Shiau**[2], **Kyong Choe**[2], **Eleanor M. Simonsick**[1], and **Luigi Ferrucci**[1]

[1]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, University of Maryland, Dental School, Baltimore, MD, USA

[2]Department of Periodontics, University of Maryland, Dental School, Baltimore, MD, USA

Abstract

Background and aims—Metabolic syndrome (MetS) comprises central obesity, insulin resistance, hypertension and dyslipidemia, interrelated metabolic risk factors for diabetes and cardiovascular disease. A state of low-grade systemic inflammation may underlie this constellation of risk factors. Chronic inflammatory conditions, such as periodontal disease, may contribute to systemic inflammation and development of MetS. This study examines the association of periodontitis with MetS with and without consideration of systemic inflammatory status.

Methods—The association of alveolar bone loss (none/slight *vs* moderate/severe) determined from panoramic radiographs and MetS parameters were analyzed using logistic regression, adjusting for age, sex, ethnicity, and smoking in 112 men and 78 women (mean±SD age 56.7±13.3 and 60.0±12.1, respectively) participating in the Baltimore Longitudinal Study of Aging.

Results—Participants with radiographic evidence of moderate to advanced alveolar bone loss were significantly more likely to have MetS than those with minimal or no bone loss (OR 2.61, 95% CI 1.1–6.1, $p<0.05$). No significant differences in systemic inflammation were found between periodontal groups.

Conclusions—The association of alveolar bone loss to MetS is consistent with the hypothesis that destructive periodontal disease may contribute to the development of MetS and elevations in systemic inflammation. Longitudinal studies are necessary to clarify the role of periodontal disease in the development of MetS and conditions associated with chronic inflammation.

Keywords

Inflammation; metabolic syndrome; obesity; periodontal disease; periodontitis

INTRODUCTION

Metabolic syndrome (MetS) is characterized by a group of metabolic conditions including central obesity, insulin resistance, hypertension, and dyslipidemia, which comprise key risk factors for type 2 diabetes and cardiovascular disease (1). Clustering of multiple MetS components appears to have a greater impact on vascular parameters and risk for cardiovascular-related morbidity and mortality than the expected risk based on an additive

Correspondence: Luigi Ferrucci, MD, PhD, Longitudinal Studies Section, Clinical Research Branch, Harbor Hospital, 3001 Hanover Street, Baltimore, MD 21225, USA. ferruccilu@grc.nia.nih.gov.

model (2,3). Multiple age-related conditions have been associated with elevations in serum markers of inflammation, which may constitute a key factor underlying the co-occurrence of multiple MetS components (4,5). Elevations in circulating levels of multiple biologic mediators, such as pro-inflammatory cytokines and acute phase proteins, are thought to be important markers of a chronic inflammatory state and increased risk of mortality (6). Increases in white blood cell (WBC) count, for example, have been associated with poorer survival in the general population and patients with coronary heart disease (6,7).

Periodontal disease is characterized by an inflammatory and immune response to microbial biofilm formation. Periodontitis is a destructive, often chronic form of periodontal disease that results in connective tissue degradation and alveolar bone resorption, ultimately leading to tooth loss in a susceptible host. Periodontitis has been associated with significant elevations in circulating levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (8).

Chronic inflammation has been postulated as the basis for the association between periodontal disease and other systemic inflammatory conditions. Associations have been observed between periodontitis and obesity (9), triglyceride levels (10), diabetes (11), and systemic inflammation (12). Moreover, persons with periodontitis have increased risk for endothelial dysfunction and cardiovascular disease (13). The pathogenesis of destructive periodontal disease and MetS, therefore, may be related through common underlying and interacting inflammatory cascades; however, few studies have evaluated this possible pathway (14–17).

This study examines the association between periodontitis and MetS in participants in the Baltimore Longitudinal Study of Aging (BLSA). We hypothesized that persons with advanced periodontal destruction, defined as moderate or severe alveolar bone loss, would be more likely to exhibit MetS than those with minimal or no evidence of periodontal breakdown. In addition, WBC count, a general marker of systemic inflammation, was examined in relation to periodontitis and MetS.

METHODS

Study population

Participants were community-dwelling volunteers enrolled in the BLSA, an ongoing observational study of normal aging initiated in 1958. Beginning in 1978, detailed dental data were collected on 692 BLSA participants, of which 320 had panographic radiographs taken. Two hundred participants with radiographs and complete data on MetS parameters constitute the study population.

Measurements

Periodontal status was determined from panographic images taken as part of the dental examination. Alveolar bone loss was measured by two trained examiners. Distance from the cemento-enamel junction (CEJ) to the alveolar crest was measured on the interproximal surface of each tooth. The average of these linear measurements was calculated and participants were scored as having none or slight (1–2 mm), moderate (3–4 mm), or severe (≥5 mm) alveolar bone loss based on radiographic assessment of crestal bone height (excluding 3rd molars). For analysis purposes, alveolar bone loss was dichotomized as none-slight and moderate-severe with periodontal disease defined as moderate-severe bone loss. Participants with less than ten teeth were excluded from the study.

Assessment of MetS was based on blood pressure, waist circumference, triglyceride levels, and fasting glucose levels (Table 1). Blood pressure measurements were recorded in both arms with participants in a seated position following a 5-minute quiet rest period using a mercury sphygmomanometer and appropriately sized cuff. The average of the second and third

measurements from both arms were used in this analysis. Systolic and diastolic blood pressure values were defined by Kortokoff phases I and V, respectively. Waist circumference was measured as the minimal circumference between the inferior rib cage and iliac crests. Blood samples were drawn after an overnight fast to assess lipid profiles. Participants were not allowed to smoke, engage in significant physical activity, or take medications prior to blood collection. The fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments, Inc., Fullerton, CA). The concentration of plasma triglycerides was determined by an enzymatic method (Abbott Laboratories, ABA-200 ATC Biochromatic Analyzer, Irving, TX). Triglyceride data were unavailable for 62 participants on the date of the panoramic examination; therefore, triglyceride values were used from the closest adjacent visit (759±170 days).

MetS was defined using a modified version of the Adult Treatment Panel III (ATP III) criteria. In particular, participants with 2 or more of the following criteria were considered to have MetS: waist circumference ≥102 cm for men and ≥88 cm for women, triglyceride level ≥150 mg/dL, fasting glucose ≥110 mg/dL, and blood pressure ≥130/85 mmHg or documented use of antihypertensive therapy. High density lipoprotein (HDL) values were not collected in the BLSA prior to 1985; therefore, the MetS criteria based on HDL level could not be considered in this analysis.

Total WBC count (cells/mm^3) was performed with standard automated clinical methodologies. In a previous study of BLSA participants, Ruggiero et al. found a WBC of greater than 6000 to be associated with an increased risk of mortality (18). Therefore, participants were classified according to the following WBC levels (cut points): 3500, 6000, and 10,000 cells/mm^3. Smoking status was obtained from self-report, and participants were categorized as nonsmoker or smoker. Body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2).

Statistical analysis

Inter-examiner agreement for radiographic measurements was evaluated using the Kappa statistic. The association of demographic and clinical measures to periodontal disease status was examined using independent *t*-tests and chi-square tests. Logistic regression analysis was used to assess the cross-sectional association of MetS and individual MetS components with periodontal status, adjusting for age, sex, ethnicity and smoking status. The logistic regression analysis was modeled separately with and without WBC. Statistical analysis was performed using SAS (Version 8.02; Cary, NC); statistical significance was set at $p<0.05$.

RESULTS

There was high concordance between the examiners that evaluated radiographic measurements of alveolar bone loss (kappa=0.94, CI 0.89–0.98). Overall, the study population was middle-aged (56.8±12.7 yrs) and comprised a slightly higher proportion of men (58%) (Table 2). Participants exhibiting moderate-severe bone loss (n=43) were more likely to be men, significantly older and demonstrated greater waist circumference and higher systolic blood pressure than those without evidence of advanced alveolar bone loss (Table 2). Participants with MetS demonstrated a greater mean WBC count (OR 2.9, 95% CI 1.2–7.2, $p=0.02$) than those without MetS. Mean WBC count was comparable in participants with and without periodontal disease.

Participants with advanced alveolar bone loss were significantly more likely to exhibit MetS than those without periodontal disease (OR 2.6, 95% CI 1.1–6.1, $p<0.02$; Table 3, Model I). Periodontal disease demonstrated similar but non-significant associations with 2 components of MetS; namely, abdominal obesity (OR 2.7, 95% CI 0.9–7.9, $p=0.07$) and elevated blood

pressure (OR 2.1, 95% CI 0.9–4.8, p=0.07). The association between periodontal disease and MetS remained essentially unchanged after adjusting for WBC count (OR 2.4, 95% CI 1.3–5.7, p<0.04; Table 3, Model II).

DISCUSSION

Chronic inflammation is an important factor in the pathophysiology of periodontal disease and may be the link between alveolar bone loss and MetS components (4,5). In the present study, participants with advanced periodontal breakdown were approximately 2.5 times more likely to manifest dysmetabolic parameters than those without periodontitis. The odds ratio observed between periodontitis and MetS in the BLSA study population – a homogeneous, high-income, high-educated population – was found to be similar to that derived from the National Health and Nutrition Examination (NHANES III), a national probability sample of noninstitutionalized, nonmilitary American adults (17). The majority of BLSA participants diagnosed with periodontitis were men. This finding is in keeping with results from the NHANES III survey and other epidemiologic studies on periodontal disease (19). Severity of periodontal breakdown has also been found positively associated with several components of MetS in women, consistent with a common molecular pathway underlying these seemingly disparate conditions.

A joint position statement of the American Diabetes Association and European Association for the Study of Diabetes called for a reappraisal of MetS as a discrete entity, reflecting, in part, a lack of evidence establishing an underlying pathophysiology (20). Recent studies suggest that visceral adipocytes may be a primary source of inflammatory, dysglycemia-promoting adipokines (TNF-α, IL-6, resistin), which also inhibit the production of adiponectin, perpetuating inflammation (21,22). In the present study, waist circumference was found to be significantly greater in persons with periodontitis, in agreement with studies documenting a relationship between obesity and periodontal destruction (23,24). The relationship of periodontal bone loss with abdominal obesity and other components of MetS, such as systolic blood pressure, is compatible with the hypothesis that local and systemic factors may contribute to a chronic inflammatory state, perhaps in a multiplicative manner, increasing the likelihood of developing MetS and cardiovascular disease. However, the extent to which other risk factors, such as type 2 diabetes, may underlie the mutual development of these conditions remains incompletely understood (25).

Age and gender have been shown to affect the severity and progression of periodontitis (19, 26), with men and older adults appearing to carry a disproportionate risk for periodontitis. Interestingly, a nation-wide, population based study in Taiwan found that women were first to develop a single isolated MetS component but presented with MetS at an older age when compared to men (27). In humans, both obesity and metabolic syndrome are associated with increased markers of systemic inflammation as well as periodontitis (28–30).

Leucocytes are major mediators of inflammation and have a key role in host defense, such as in periodontal infection, and elevations in WBC count provide a clinically convenient marker of systemic inflammation. Elevations in WBC count have been associated with both periodontal disease and MetS (31). In this study WBC count was found to be significantly associated with MetS and was modestly but not significantly higher (5%) in individuals with periodontal disease. Nibali et al. (14) found that subjects with generalized severe periodontitis exhibited a significantly higher WBC count (11.7%) than healthy controls. Inoue et al. (32) observed an association of periodontitis with increased WBC count and blood pressure among Japanese manufacturing workers. Interestingly, Nagasawa et al. (33) found that the strength of association between WBC count and MetS increased with the number of clustering component factors.

Contrary to the literature, in our study WBC count was not significantly associated with periodontitis. We predicted that the association between alveolar bone loss and MetS would be attenuated after adjusting for systemic inflammation in the regression model. However, inclusion of WBC count in the analysis did not attenuate the association. Although leukocytes are involved in the first line of defense against bacterial infections, it is pro-inflammatory cytokines (IL-6, TNF-α) that stimulate further amplification of the inflammatory cascade. Further, WBC count is affected by medications and is correlated with various measures of haemostatic function. WBC count, therefore, may not be the most sensitive measure of systemic inflammation and may not capture the critical aspect of inflammation that is causative in the development of MetS. Further, the progression of periodontal destruction is often variable, with periods of remission and exacerbation. Because this study was a retrospective analysis of prospectively collected data, we did not have access to other inflammatory markers.

Panoramic radiographs underestimate the extent of bone loss when compared to direct measurements (34,35), with the greatest potential underestimation associated with early marginal bone destruction (35). Nevertheless, panoramic radiographs provide measures of bone loss that correlate highly with both clinical attachment level (36) and the Community Periodontal Index of Treatment Needs (37). In this study, therefore, it was not possible to unequivocally identify participants without periodontitis. Hence, the comparison of participants based on none-slight and moderate-severe periodontitis may have resulted in an underestimate in the observed differences between periodontal disease and individual MetS components.

CONCLUSIONS

The observed association between periodontitis and MetS is compatible with the hypothesis that chronic inflammation is an important underlying factor in the pathophysiology of these conditions. Moreover, the association of alveolar bone loss with MetS components, such as waist circumference, suggests that local and systemic conditions may mutually contribute to a chronic inflammatory state, increasing the likelihood of developing MetS and cardiovascular disease.

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Table 1

Individual MetS parameters and periodontal status of participants in relation to MetS.

Characteristic	Without MetS (n=165)	With MetS (n=35)	*p**
Waist circumference, cm	84.0±10.5	93.7±13.1	<0.001
Systolic blood pressure, mmHg	122.6±21.2	141.6±21.5	<0.001
Diastolic blood pressure, mmHg	77.4±10.5	83.5±10.2	0.002
Serum triglycerides, mg/dL	85.3±47.1	148.2±74.0	<0.001
Fasting glucose, mg/dL	97.7±16.9	115.4±26.0	<0.001
Moderate-severe bone loss, %	17.6	40.0	0.003

* Comparisons calculated using *t*-tests for continuous variables, and chi-square tests for dichotomous variables.

Table 2

Demographic and clinical characteristics of participants in relation to periodontal disease.

Characteristic	Total (n=200)	None-Slight bone loss (n=157)	Moderate-Severe bone loss (n=43)	*p**
Age, yrs	56.8±12.7	55.4±12.9	61.8±11.0	0.001
Sex, % male	57.5	52.2	76.7	0.004
Race, % black	2.5	1.9	4.7	0.31
Non smoker, %	42.5	45.9	30.2	0.06
Waist circumference, cm	85.7±11.6	84.0±10.6	91.6±13.1	0.001
Systolic blood pressure, mmHg	126.0±22.4	123.8±21.9	133.7±22.8	0.01
Diastolic blood pressure, mmHg	78.5±10.7	78.1±9.6	79.8±14.2	0.47
Serum triglycerides, mg/dL	96.4±57.7	94.4±58.7	103.3±54.2	0.35
Fasting glucose, mg/dL	100.8±19.9	99.4±17.9	105.9±25.7	0.12
White blood cell count, /mm^3	6638.5±1340.8	6571.3±1289.8	6883.7±1503.6	0.22

* Comparisons calculated using *t*-tests for continuous variables, and chi-square tests for dichotomous variables.

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Table 3

Adjusted logistic regression models for association of periodontal disease with metabolic syndrome and metabolic syndrome components.

	Model I			Model II		
Outcome variable	**Point estimate**	**95% CI**	***p***	**Point estimate**	**95% CI**	***p***
Metabolic syndrome	2.61	(1.1–6.1)	0.02	2.42	(1.0–5.7)	0.04
Abdominal obesity	2.67	(0.9–7.9)	0.07	2.66	(0.9–8.1)	0.08
High blood pressure	2.12	(0.9–4.8)	0.07	1.97	(0.9–4.5)	0.10
High fasting glucose	1.59	(0.6–4.0)	0.32	1.55	(0.6–3.9)	0.35
High triglycerides	1.30	(0.5–3.7)	0.64	1.30	(0.4–3.8)	0.64

Model I adjusted for age, sex, race, and smoking status; Model II adjusted for model I confounders + inflammation.