Association of the Metabolic Syndrome with Severe Periodontitis in a Large U.S. Population-Based Survey

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Context: Metabolic syndrome and periodontitis both have an increasing prevalence worldwide; however, limited information is available on their association.

Objective: The objective of the study was to assess the association between periodontitis and the metabolic syndrome in a cross-sectional survey of a nationally representative sample of the non-institutionalized civilians in the United States.

Design, Setting, and Participants: Data analysis from the Third National Health and Nutrition Examination Survey on 13,994 men and women aged 17 yr or older who received periodontal examination were studied.

Main Outcome Measures: Association of diagnosis and extent of periodontitis (gingival bleeding, probing pocket depths) with the metabolic syndrome and its individual component conditions (central obesity, hypertriglyceridemia, low high-density lipoprotein-cholesterol, hypertension, and insulin resistance) were measured. Adjustment for age, sex, years of education, poverty to income ratio, ethnicity, general conditions, and smoking were considered.

Results: The prevalence of the metabolic syndrome was 18% [95% confidence interval (CI) 16–19], 34% (95% CI 29–38), and 37% (95% CI 28–48) among individuals with no-mild, moderate, and severe periodontitis, respectively. After adjusting for confounders, participants aged older than 45 yr suffering from severe periodontitis were 2.31 times (95% CI 1.13–4.73) more likely to have the metabolic syndrome than unaffected individuals. Diagnosis of metabolic syndrome increased by 1.12 times (95% CI 1.07–1.18) per 10% increase in gingival bleeding and 1.13 times (95% CI 1.03–1.24) per 10% increase in the proportion of periodontal pockets.

Conclusions: Severe periodontitis is associated with metabolic syndrome in middle-aged individuals. Further studies are required to test whether improvements in oral health lead to reductions in cardiometabolic traits and the risk of metabolic syndrome or vice versa. **(*J Clin Endocrinol Metab* 93: 3989–3994, 2008)**

The metabolic syndrome, a clustering within individuals of several cardiovascular risk factors, is becoming a common disorder among U.S. citizens and worldwide (1–3). A diagnosis of metabolic syndrome is associated with doubling in risk for future cardiovascular diseases and type 2 diabetes mellitus (4, 5). According to Adult Treatment Panel III and recent consensus workshops, the metabolic syndrome is defined as the concurrence of hypertension and atherogenic lipid profiles [hypertri-

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Abbreviations: CI, Confidence interval; HDL, high-density lipoprotein; NHANES III, third National Health and Nutrition Examination Survey; OR, odds ratio.

glyceridemia and low high-density lipoprotein (HDL)-cholesterol] but also obesity and insulin resistance (6, 7). A proinflammatory and procoagulant state may also coexist in this syndrome, with elevation of C-reactive protein and fibrinogen (8, 9). The exact mechanisms behind this systemic response remain uncertain. There is evidence to also suggest that this chronic inflammatory state is associated with endothelial dysfunction, which might contribute to the increased cardiovascular risk of people affected by this disorder and with the increased risk of type 2 diabetes (10–13).

Periodontitis is a common chronic infection of the adult population characterized by an exaggerated gingival inflammatory response against a pathogenic bacterial microflora, resulting in alveolar bone and eventually tooth loss (14). Periodontitis has also been associated with systemic alterations such as low-grade inflammation (15, 16), dyslipidemia (17), glucose intolerance (18, 19), a procoagulant state (20), and endothelial dysfunction (21). A growing body of evidence also indicates that periodontitis is associated with measures of body weight in youth (22) as well as insulin resistance (23). Because both periodontitis and the metabolic syndrome are associated with systemic inflammation and insulin resistance, these two diseases may be linked through a common pathophysiological pathway. This could explain the almost 20% increased risk of cardiovascular diseases reported in patients with periodontitis (24). Little information, however, is available on the possible association between periodontitis and the metabolic syndrome as sole clinical entity (25). Our aim was therefore to ascertain the association between the metabolic syndrome and periodontal diseases in a cross-sectional survey of a nationally representative sample of the noninstitutionalized civilians in the United States.

Subjects and Methods

Data were derived from the third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988–1994 on a national probability sample of noninstitutionalized, nonmilitary American population (26). We used data pertaining to the population aged 17 yr and older, excluding pregnant women and those individuals reporting cardiac condition or any medical condition requiring antibiotic coverage before the dental examination. From a total of 13,994 subjects who had periodontal assessment, our final study sample was of 13,677 individuals.

Assessment of metabolic syndrome was based on the following five components: central obesity (waist circumference >102 cm for males and >88 cm for females); hypertriglyceridemia (triglycerides >150 mg/dl); low HDL-cholesterol (<40 mg/dl for men and <50 for women); high blood pressure (systolic: >130 mm Hg or diastolic: >85 mm Hg or on blood pressure medication); and high plasma glucose (>110 g/dl) (7). Metabolic syndrome was considered present in participants exceeding the threshold limits for at least three of these components (7).

Reproducible periodontal measures were done on dentate participants on randomly assigned half-mouths by calibrated examiners as previously described in the NHANES procedures manuals (26). Among a plethora of case definitions of periodontitis (27, 28), we used a recently reported definition of periodontitis suited for epidemiologic surveys (28) as follows: moderate periodontitis = two sites not on the same tooth with loss of periodontal attachment 4 mm or greater or one site with gingival probing depth 4 mm or greater and severe periodontitis = two sites not on the same tooth with loss of periodontal attachment 6 mm or greater and at least one site with gingival probing depth 4 mm or greater (28). We also used continuous measures of periodontal health/disease as proxy for systemic exposure of periodontitis (29). Proportion of periodontal sites with periodontal pockets 4 mm or greater per number of examined sites and proportion of gingival bleeding sites per number of examined sites were included in the analyses.

The STATA 8.0 (StataCorp, College Station, TX) statistical program was used for all analyses (estimated prevalence, logistic regression), taking into account population weights and adjustment for the complex sampling design. Logistic regression analyses were used to assess the associations between the presence of metabolic syndrome and its components (dependent variables) with the different measures of periodontal disease adjusted for the effect of other variables (age, sex, years of education, poverty to income ratio, ethnicity, general conditions, and smoking) were used as covariates in all multivariate models. General conditions were assessed by aggregate binary variables to note the presence of chronic heart diseases, cancer, diabetes, stroke, emphysema, asthma, arthritis, lupus, thyroid disease, and goiter (30). Participants were grouped into three groups according to cigarette smoking: current smokers, nonsmokers, and no respondents. Analyses were performed in the all study sample and the subgroup of middle-aged individuals (presenting with the highest prevalence of periodontitis and the metabolic syndrome; see Table 1) and never-smokers (defined as persons who reported having smoked <100 cigarettes during their lifetime). For each outcome variable (metabolic syndrome and each of the individual components), analyses were conducted for the whole available sample, and the different regression models were based on the same number of subjects to ensure comparability.

Results

Baseline characteristics of subjects among subgroups of periodontitis are reported in Table 2. Substantial differences in most the variables examined were observed, and therefore, only adjusted multivariate estimates are reported. Diagnosis of no-mild, moderate, or severe periodontitis was associated with a linear increase in the prevalence of the metabolic syndrome; 18% [95% confidence interval (CI) 16–19] among

TABLE 1. Frequency distribution of periodontitis (no-mild, moderate, and severe) and the metabolic syndrome in different age groups

	Age groups (yr) Frequency (95% CI)			
	17–30	31–44	45–65	>66
Periodontitis				
No or mild	35.2 (32.9–37.5)	35.5 (33.5–37.7)	21.7 (20.1–23.3)	7.6 (6.4–9.0)
Moderate	6.0 (4.1–8.7)	22.7 (19.3–26.3)	46.3 (43.1–49.6)	25.0 (21.9–28.7)
Severe	4.1 (1.4–11.2)	25.9 (17.3–36.8)	49.0 (40.6–57.6)	21.0 (15.1–28.5)
Metabolic syndrome	8.1 (6.9–9.5)	23.8 (21.2–26.6)	41.2 (38.6–43.9)	26.9 (24.2–29.7)

TABLE 2. Baseline characteristics of subjects by diagnosis of periodontitis (n = 13,677) (pregnant women are excluded from all analyses

Variable	Mild or no periodontitis (n = 11758)	Moderate periodontitis (n = 1582)	Severe periodontitis (n = 337)
		(95% CI)	
Age (mean)	38.7 (37.8–39.5)	54.2 (53.0–55.5)	52.3 (49.8–55.3)
Gender, females (%)	51.2 (50.3–52.2)	40.0 (35.7–44.3)	31.7 (23.9–40.0)
Ethnicity, white (%)	74.8 (72.1–77.4)	68.7 (63.8–73.2)	61.4 (51.3–70.6)
Current smoker (%)	27.6 (25.8–29.5)	44.5 (39.4–49.8)	53.1 (44.9–61.3)
Education, yr (mean)	12.7 (12.5–12.9)	11.3 (11.1–11.6)	10.7 (10–11.4)
Poverty, income ratio (mean)	3.2 (3.0–3.3)	2.9 (2.7–3.1)	2.5 (2.1–2.8)
Poor to fair health, self-reported (%)	10.9 (9.9–12.0)	24.0 (20.8–27.4)	34.2 (25.8–43.8
Mean of waist circumferences (%)	89.8 (89.3–90.3)	96.5 (95.5–97.5)	97.9 (95.0–100.8)
Mean of serum HDL cholesterol (mg/dl)	50.6 (49.9–51.3)	48.6 (47.2–50.0)	47.4 (44.0–50.7)
Mean of serum triglycerides (mg/dl)	134.3 (129.8–138.9)	167.4 (150.5–184.3)	162.9 (140.1–185.7)
Mean C-reactive protein	3.7 (3.5–3.8)	4.7 (4.2–5.2)	5.1 (4.2–5.9)
Mean systolic blood pressure, mm Hg	118.9 (118.2–119.7)	129.7 (128.0–131.4)	129.6 (126.9–132.3)
Mean diastolic blood pressure, mm Hg	73.6 (73.2–74.0)	76.0 (75.2–76.8)	76.9 (75.2–78.6)

participants with no or mild periodontitis, 34% (95% CI 29–38) and 37% (95% CI 28–48) among those with moderate and severe periodontitis had metabolic syndrome, respectively ($P < 0.01$ for linear trend). Similarly, among individuals with moderate and severe periodontitis, there was a higher prevalence of obesity (48–54%, 95% CI 44–63 *vs.* 31%, 95% CI 30–33), hypertension (51–56%, 95% CI 47–64 *vs.* 27%, 95% CI 25–29), and high glucose levels (18–24%, 95% CI 15–30 *vs.* 8%, 95% CI 8–9) (all $P < 0.001$), compared with those with no or mild periodontitis.

After adjusting for the effect of age, sex, years of education, poverty to income ratio, ethnicity, general conditions, and smoking in multiple logistic regression, among participants with severe periodontitis, the odds for the metabolic syndrome was 1.45 (95% CI 0.91–2.33), compared with those with no or mild periodontitis (Table 3). In the middle aged group (45 yr or older), severe periodontitis was mildly associated with the metabolic syndrome [odds ratio (OR) 1.74, 95% CI 1.10–2.76, $P < 0.05$, n = 263], and the magnitude of this association increased in the subgroup of never-smokers (OR 2.31, 95% CI 1.13–4.73, $P < 0.05$, n = 61). A consistent positive association between severe periodontitis diagnosis and insulin resistance was observed. Indeed adjusted ORs of 1.71 (95% CI 1.16–2.54, $P < 0.01$, n = 337), 1.74 (95% CI 1.10–2.78, $P < 0.05$, n = 263), and 4.74 (95% CI 2.05–10.97, $P < 0.01$, n =

TABLE 3. Adjusted associations between diagnosis of periodontitis (no-mild, moderate, and severe) and the metabolic syndrome and its individual components

Periodontitis		All sample (n = 11,029)[a]	>44 yr (n = 4,003)[a]	Never-smokers (n = 2,318)[b]
Metabolic syndrome	Mild-no[e]			
	Moderate	1.07 (0.84–1.36)	1.06 (0.83–1.34)	0.91 (0.56–1.48)
	Severe	1.45 (0.91–2.33)	1.74 (1.10–2.76)[c]	2.31 (1.13–4.73)[c]
Central obesity	Mild-no			
	Moderate	1.12 (0.89–1.41)	1.11 (0.90–1.35)	1.11 (0.78–1.60)
	Severe	1.54 (0.99–2.40)	1.25 (0.70–2.23)	1.50 (0.49–4.61)
Hypertriglyceridemia	Mild-no			
	Moderate	1.02 (0.77–1.35)	1.08 (0.82–1.44)	0.81 (0.54–1.25)
	Severe	0.96 (0.61–1.51)	1.16 (0.71–1.90)	1.54 (0.74–3.18)
Low HDL cholesterol	Mild-no			
	Moderate	1.42 (1.13–1.78)	1.26 (1.01–1.58)	1.08 (0.67–1.74)
	Severe	1.35 (0.87–2.09)	1.36 (0.81–2.29)	2.02 (0.86–4.74)
High blood pressure	Mild-no			
	Moderate	0.94 (0.74–1.20)	0.93 (0.71–1.22)	0.75 (0.49–1.15)
	Severe	1.29 (0.85–1.98)	1.36 (0.80–2.33)	0.39 (0.14–1.06)
High glucose	Mild-no			
	Moderate	1.13 (0.84–1.53)	1.08 (0.81–1.44)	0.93 (0.60–1.45)
	Severe	1.71 (1.16–2.54)[d]	1.74 (1.10–2.78)[c]	4.74 (2.05–10.97)[d]

[a] Model adjusted for age, sex, years of education, poverty ratio, ethnicity, general conditions, and smoking.

[b] Model adjusted for age, sex, years of education, poverty ratio, ethnicity, and general conditions.

[c] $P < 0.05$.

[d] $P < 0.01$.

[e] Mild-no is the reference category, OR = 1.

61) for hyperglycemia were found in all the sample, the middle-aged group, and the subgroup of nonsmokers with severe periodontitis respectively.

Both continuous measures of periodontal disease examined (bleeding and pocket scores) were associated with higher odds of components of the metabolic syndrome (Fig. 1). A 10% increase in gingival bleeding extent was associated with an OR for metabolic syndrome of 1.12 (95% CI 1.07–1.18, $P < 0.001$) and a 10% increase in the periodontal pocket extent with and OR of 1.13 (95% CI 1.03–1.24, $P < 0.05$). Moreover, there was evidence to suggest a positive association of each periodontal marker with each individual component of the metabolic syndrome, with all associations with the exception of hypertriglyceridemia remaining significant, even after adjusting for confounders (Fig. 1).

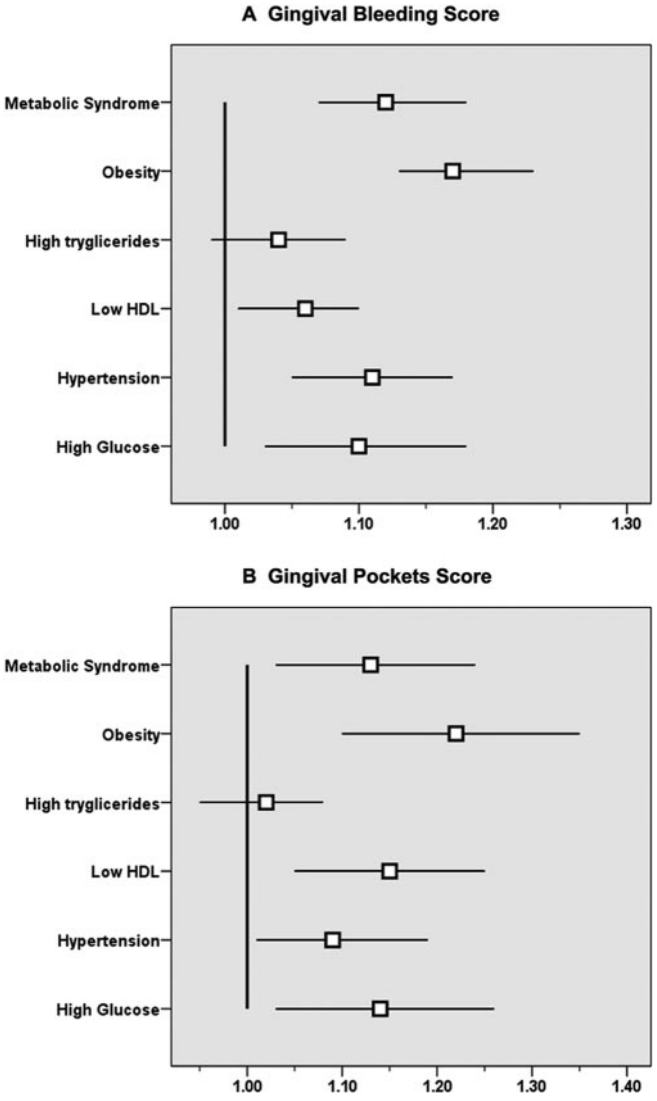

FIG. 1. Odds ratios (95% CIs) of metabolic syndrome and individual components calculated for clinical measures of periodontal disease (A and B). For gingival bleeding and pocket depth scores, OR is for 10% increase. ORs are presented as adjusted values (□) for age, sex, years of education, poverty ratio, ethnicity, general conditions, and smoking.

Discussion

This analysis provides evidence of a positive association between continuous measures of gingival health and the metabolic syndrome and its components in all age groups of this study sample. We also confirmed an association between diagnosis of severe periodontitis with the metabolic syndrome and in particular with the insulin resistance component in middle-aged never-smoker individuals.

Over the past decade, accumulating evidence suggests that periodontitis may be associated with an increased risk of future cardiovascular events and type 2 diabetes in otherwise healthy individuals (24, 31). The magnitude of this association, however, seems to be strongly affected by the inadequacy of current definitions of periodontitis and the use of multiple clinical criteria to ascertain its grade of severity. The strength of our findings lies in having found an association between periodontitis and the metabolic syndrome and its components using both a very conservative case definition of periodontitis and continuous measures of gingival health. However, these data raise the hypothesis of a possible nonlinear relationship between different measures of gingival health and components of the metabolic syndrome. Indeed, a linear association between gingival bleeding/pockets and most metabolic factors in particular obesity was observed at all age groups, whereas when a case definition of periodontitis was used, only measures of insulin resistance were associated with severe periodontitis in middle-aged individuals. Nevertheless, these finding are not surprising because of the bulk of experimental and clinical evidence in support of an association between periodontitis and most of the individual components of the metabolic syndrome. A recent analysis of the same data set both in young individuals and all of the population showed that periodontitis and measures of adiposity are closely linked (22, 32). Furthermore, data from experimental models suggests that adiposity could influence the host response to periodontal bacteria, and it has been proposed as a potential mechanisms explaining this association (33).

Clinical evidence has been produced on the association between periodontitis and measures of insulin resistance (18), lipid alterations (17), and vascular dysfunction (21). Few studies have also reported on a possible positive association between periodontitis, arterial blood pressure, endothelial dysfunction (34, 35), and a dyslipidemic state (36). A bulk of experimental data derived from animal models and epidemiological and intervention trials support the hypothesis that periodontitis triggers a state of low-grade systemic inflammation (37). A complex interplay of the host inflammatory response to periodontal infections, adiposity, and alterations of lipid levels might be responsible for the state of insulin resistance reported in individuals with periodontitis (23) as we also observed in this analysis. We hypothesize that this finding could also explain the reported association among periodontal diseases, the metabolic syndrome, and future increased risk of vascular diseases (38) and diabetes (31). Our group recently showed that 6 months after treatment of severe forms of periodontitis, a substantial improvement in measures of endothelial function was observed (21). Limited and inconclusive evidence, however, has been reported on the potential impact of treatment of periodontitis on other components of the metabolic syndrome in particular blood pressure (39).

Our analysis, however, has several limitations. The cross-sectional nature of the NHANES study does not allow for causal interpretations because the data indicate a strong association without inferring any information as to the direction of a potential causal pathway. It should also be noted that the diagnostic criteria used to define periodontitis as well as definitions of each component of the metabolic syndrome including use of different medications are intentionally conservative. Periodontitis prevalence, therefore, may have been underestimated. The partial (half mouth) recordings available in this data set might also play a role in this. In addition, many other factors (*e.g.* genetics, oral health behavior) that could be associated with both conditions have not been assessed. We cannot therefore exclude the possibility of a spurious association between periodontitis and metabolic syndrome due to other unmeasured confounding factors (residual confounding). A word of caution in interpreting our results is due in particular with regard to the role of cigarette smoking as a major confounder of this association and due to the limited number of individuals included in the analysis. Nonetheless, it should be noted that despite its limitations, this report emphasizes the possible impact that poor oral health might have on systemic parameters, and this might have important implications for the health of the public. Further intervention studies aimed at controlling periodontal infections are required to test whether improvements in oral health lead to reductions in cardiometabolic traits and the risk of metabolic syndrome.

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References

1. **Bray GA, Bellanger T** 2006 Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine 29:109–117
2. **Ford ES, Giles WH, Dietz WH** 2002 Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 287:356–359
3. **Kereiakes DJ, Willerson JT** 2003 Metabolic syndrome epidemic. Circulation 108:1552–1553
4. **Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM** 2007 Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 49:403–414
5. **Lorenzo C, Williams K, Hunt KJ, Haffner SM** 2007 The National Cholesterol Education Program-Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 30:8–13
6. **Alberti KG, Zimmet P, Shaw J** 2006 Metabolic syndrome–a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 23:469–480
7. **Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F** 2005 Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735–2752
8. **Ford ES** 2003 The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 168:351–358
9. **Wannamethee SG, Lowe GD, Shaper AG, Rumley A, Lennon L, Whincup PH** 2005 The metabolic syndrome and insulin resistance: relationship to haemostatic and inflammatory markers in older non-diabetic men. Atherosclerosis 181:101–108
10. **Arcaro G, Cretti A, Balzano S, Lechi A, Muggeo M, Bonora E, Bonadonna RC** 2002 Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 105:576–582
11. **Kim JA, Montagnani M, Koh KK, Quon MJ** 2006 Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 113:1888–1904
12. **Sjoholm A, Nystrom T** 2005 Endothelial inflammation in insulin resistance. Lancet 365:610–612
13. **Grundy SM** 2007 Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab 92:399–404
14. **Williams RC** 1990 Periodontal disease. N Engl J Med 322:373–382
15. **Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS** 2000 Acute-phase inflammatory response to periodontal disease in the US population. J Dent Res 79:49–57
16. **Slade GD, Ghezzi EM, Heiss G, Beck JD, Riche E, Offenbacher S** 2003 Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. Arch Intern Med 163:1172–1179
17. **Katz J, Flugelman MY, Goldberg A, Heft M** 2002 Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. J Periodontol 73:494–500
18. **Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, Koga T** 2004 The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. J Dent Res 83: 485–490
19. **Nibali L, D'Aiuto F, Griffiths G, Patel K, Suvan J, Tonetti MS** 2007 Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case-control study. J Clin Periodontol 34:931–937
20. **Taylor BA, Tofler GH, Carey HM, Morel-Kopp MC, Philcox S, Carter TR, Elliott MJ, Kull AD, Ward C, Schenck K** 2006 Full-mouth tooth extraction lowers systemic inflammatory and thrombotic markers of cardiovascular risk. J Dent Res 85:74–78
21. **Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J** 2007 Treatment of periodontitis and endothelial function. N Engl J Med 356:911–920
22. **Reeves AF, Rees JM, Schiff M, Hujoel P** 2006 Total body weight and waist circumference associated with chronic periodontitis among adolescents in the United States. Arch Pediatr Adolesc Med 160:894–899
23. **Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y** 2005 A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontol 76(Suppl 11):2075–2084
24. **Scannapieco FA, Bush RB, Paju S** 2003 Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. Ann Periodontol 8:38–53
25. **Shimazaki Y, Saito T, Yonemoto K, Kiyohara Y, Iida M, Yamashita Y** 2007 Relationship of metabolic syndrome to periodontal disease in Japanese women: the Hisayama Study. J Dent Res 86:271–275
26. **National Centre for Health Statistics** 1994 Third National Health and Nutrition Examination Survey. 1988–1994. [1.22a]. NCHS CD-ROM Series 11, No 1. Ref Type: Data File
27. **Borrell LN, Papapanou PN** 2005 Analytical epidemiology of periodontitis. J Clin Periodontol 32 Suppl 6:132–158
28. **Page RC, Eke PI** 2007 Case definitions for use in population-based surveillance of periodontitis. J Periodontol 78(7 Suppl):1387–1399
29. **Andriankaja OM, Genco RJ, Dorn J, Dmochowski J, Hovey K, Falkner KL, Scannapieco F, Trevisan M** 2006 The use of different measurements and definitions of periodontal disease in the study of the association between periodontal disease and risk of myocardial infarction. J Periodontol 77: 1067–1073
30. **Netuveli G, Wiggins RD, Hildon Z, Montgomery SM, Blane D** 2006 Quality of life at older ages: evidence from the English longitudinal study of aging (wave 1). J Epidemiol Community Health 60:357–363
31. **Demmer RT, Jacobs Jr DR, Desvarieux M** 2008 Periodontal disease and in-

cident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care 31:1373–1379

32. **Wood N, Johnson RB, Streckfus CF** 2003 Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III). J Clin Periodontol 30:321–327
33. **Amar S, Zhou Q, Shaik-Dasthagirisaheb Y, Leeman S** 2007 Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. Proc Natl Acad Sci USA104:20466–20471
34. **Angeli F, Verdecchia P, Pellegrino C, Pellegrino RG, Pellegrino G, Prosciutti L, Giannoni C, Cianetti S, Bentivoglio M** 2003 Association between periodontal disease and left ventricle mass in essential hypertension. Hypertension 41: 488–492
35. **Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, Takemoto H, Nakamura S, Soga J, Chayama K, Yoshizumi M, Taguchi A** 2008 Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. Hypertension 51:446–453
36. **Losche W, Karapetow F, Pohl A, Pohl C, Kocher T** 2000 Plasma lipid and blood glucose levels in patients with destructive periodontal disease. J Clin Periodontol 27:537–541
37. **Pihlstrom BL, Michalowicz BS, Johnson NW** 2005 Periodontal diseases. Lancet 366:1809–1820
38. **Janket SJ, Jones JA, Meurman JH, Baird AE, Van Dyke TE** 2008 Oral infection, hyperglycemia, and endothelial dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 105:173–179
39. **D'Aiuto F, Parkar M, Nibali L, Suvan J, Lessem J, Tonetti MS** 2006 Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial. Am Heart J 151: 977–984