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Metabolic Syndrome and Periodontal Disease Progression in Men

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Abstract

Metabolic syndrome, a cluster of 3 or more risk factors for cardiovascular disease, is associated with periodontal disease, but few studies have been prospective in design. This study's aim was to determine whether metabolic syndrome predicts tooth loss and worsening of periodontal disease in a cohort of 760 men in the Department of Veterans Affairs Dental Longitudinal Study and Normative Aging Study who were followed up to 33 y from 1981 to 2013. Systolic and diastolic blood pressures were measured with a standard mercury sphygmomanometer. Waist circumference was measured in units of 0.1 cm following a normal expiration. Fasting blood samples were measured in duplicate for glucose, triglyceride, and high-density lipoprotein. Calibrated periodontists served as dental examiners. Periodontal outcome events on each tooth were defined as progression to predefined threshold levels of probing pocket depth (≥5 mm), clinical attachment loss (≥5 mm), mobility (≥0.5 mm), and alveolar bone loss (≥40% of the distance from the cementoenamel junction to the root apex, on radiographs). Hazards ratios (95% confidence intervals) of tooth loss or a periodontitis event were estimated from tooth-level extended Cox proportional hazards regression models that accounted for clustering of teeth within individuals and used time-dependent status of metabolic syndrome. Covariates included age, education, smoking status, plaque level, and initial level of the appropriate periodontal disease measure. Metabolic syndrome as defined by the International Diabetes Federation increased the hazards of tooth loss (1.39; 1.08 to 1.79), pocket depth ≥5 mm (1.37; 1.14 to 1.65), clinical attachment loss ≥5 mm (1.19; 1.00 to 1.41), alveolar bone loss ≥40% (1.25; 1.00 to 1.56), and tooth mobility ≥0.5 mm (1.43; 1.07 to 1.89). The number of positive metabolic syndrome conditions was also associated with each of these outcomes. These findings suggest that the metabolic disturbances that comprise the metabolic syndrome may play a role in the development or worsening of periodontitis.

Keywords: periodontitis, bone loss, epidemiology, risk factors, systemic health/disease, Metabolic Syndrome X

Introduction

Metabolic syndrome (MetS) refers to a cluster of physical risk factors that are associated with increased risks of cardiovascular disease (Lockhart et al. 2012), type 2 diabetes (Ford et al. 2008), and other chronic diseases (Chen et al. 2004, 2014; McEvoy et al. 2012). MetS is commonly defined as the presence of 3 or more of the following 5 metabolic abnormalities: elevated levels of blood glucose, serum triglycerides, and blood pressure; low serum high-density lipoprotein (HDL); and large waist circumference (Alberti et al. 2009).

As summarized in a recent review, the majority of studies of MetS and periodontal diseases published before 2014 showed that these diseases frequently co-occur (Watanabe and Cho 2014). Several studies published subsequent to that review (Thanakun et al. 2014; Iwasaki et al. 2015; Minagawa et al. 2015), but not all (LaMonte et al. 2014), also reported significant associations. However, there was considerable variation in the periodontal disease measures and the definitions of MetS used, and few studies were prospective in design. Therefore, it is not clear whether MetS or its components contribute to increased risk of periodontal disease or, conversely, if periodontal disease promotes the onset of MetS.

Presence of at least 1 periodontal pocket ≥4 mm at baseline was associated with a 40% increase in odds of any positive MetS components among Japanese adults after 4 y of

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follow-up and a >2-fold increase in odds of ≥2 components (Morita et al. 2010). Brushing one's teeth at least 3 times per day was related to lower odds of MetS after 3 y (Kobayashi et al. 2012). Together, these 2 longitudinal studies suggest that deep periodontal pockets and insufficient oral hygiene increase the risk of developing MetS, possibly through enhancement of the host inflammatory response (Kobayashi et al. 2012). Two studies assessed the evidence for an association in the opposite direction (i.e., whether presence of MetS increased the risk for periodontal disease progression or tooth loss). Japanese adults with a positive MetS diagnosis at baseline were 2.6 times more likely to develop periodontal disease, as defined by loss of attachment ≥3 mm, after 3 y than those without MetS (Iwasaki et al. 2015), and having 3 or more MetS components increased the risk of tooth loss by approximately 50% relative to no components (Furuta et al. 2016).

Extended longitudinal studies are needed to better understand the dynamic relationship between these 2 diseases. MetS is a progressive disease, and the individual components of a MetS diagnosis, several of which independently raise the risk of periodontitis, are not likely to all arise at the same time. Therefore, risk of periodontitis may already be elevated before a definite diagnosis is made. Furthermore, a MetS diagnosis is changeable; weight loss and adoption of a heart-healthy diet, for example, may result in reversal of 1 or more of the MetS components. The purpose of this study was to determine whether there is evidence that MetS is a risk factor for periodontal disease in men, using time-dependent repeated assessments of MetS components and periodontal disease measures.

Materials and Methods

Study Participants

Participants were selected from the Department of Veterans Affairs (VA) Dental Longitudinal Study (DLS), a closed-panel, observational cohort study of aging and oral health among initially healthy men that began in 1969 in a subset of men enrolled in the VA Normative Aging Study (NAS) (Kapur et al. 1972; Feldman et al. 1986). The men's oral health, weight, medical health, and lifestyle are monitored approximately every 3 y. Although most DLS participants are veterans, they are not patients of the VA healthcare system and they receive dental and medical care from the private sector.

All 5 measurements needed to determine MetS status were available from medical examinations conducted between 1981 and 2013. Of the 1,231 men initially enrolled in the DLS, 807 men had complete MetS and dental data at their first dental examination during this interval; of these, 760 were dentate. Baseline examinations for these men occurred between 1981 and 2011, although 90% occurred between 1981 and 1987. Follow-up examinations of 683 men continued until 2013. Mean follow-up time was 17 ± 8 y and ranged from 2 to 33 y.

The institutional review boards of Boston University Medical Center and the VA Boston Healthcare System approved the protocol. All participants gave informed consent on approved forms before each examination. This report complies with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies.

Dental Examinations

During follow-up, 3 calibrated periodontists performed the dental examinations. The current examiner has served since 1984. Presence or absence of each tooth was recorded at each examination. Plaque was measured on an ordinal scale (0, none; 1, interproximal surfaces only; 2, interproximal surfaces continuing onto facial or lingual sites; and 3, all surfaces covering more than two-thirds of the tooth) after rinsing with a disclosing solution. Tooth mobility was assessed by pressing instrument handles on the buccal and lingual surfaces of the tooth and movement was recorded on an ordinal scale (0, none; 1, <0.5 mm; 2, 0.5 to 1.0 mm; and 3, >1.0 mm). Probing pocket depth (PPD) and clinical attachment loss (CAL) were measured in millimeters using a Williams probe at 6 sites per tooth (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual) at each examination. Bleeding on probing was noted and recorded. Prior to 1987, only the maximum PPD and CAL values per tooth were recorded on an interval scale (0, ≤2 mm; 1, >2 to ≤3 mm; 2, >3 to <5 mm; and 3, ≥5 mm). From 1987 onward (examination cycles 7 through 12), values at all sites were recorded in millimeters. The maximum value per tooth and the maximum of mesiobuccal and distolingual interproximal sites were computed.

Radiographs were taken using a paralleling technique with Rinn holders. Radiographic alveolar bone loss (ABL) was measured on the mesial and distal aspects of each tooth from periapical radiographs by superimposing a transparent ruler on the tooth image with reference points at the cementoenamel junction (CEJ) and root apex. A modified Schei ruler method was used (Schei et al. 1959) to record ABL in increments of 20% of the CEJ–root apex distance. The maximum of the mesial and distal measures on each tooth was computed.

Interexaminer agreement for pocket depth and mesial and distal bone loss scores was 41%, 71%, and 67%, and Cohen's kappa values were 0.22, 0.45, and 0.42, respectively, based on repeat assessments on 25 participants (Alman et al. 1986). Third molars were excluded from all analyses.

Medical Examinations

NAS examinations included measurements of blood pressure and anthropometry and a fasting blood draw. Systolic and diastolic blood pressures were measured to the nearest 2 mmHg with a standard mercury sphygmomanometer on both left and right arms while the participant was seated. Averages from the 2 arms were computed. For waist circumference, the participant wore little clothing and stood erect, relaxed, with arms at the sides and feet together. An inelastic tape measure was placed around the narrowest part of the torso keeping the tape horizontal to the floor and circumference was measured in units of 0.1 cm at the end of a normal expiration. Fasting blood samples were measured in duplicate for glucose, triglyceride,

and high-density lipoprotein (HDL) (all in milligrams per decaliter) on autoanalyzers at the VA Boston Healthcare System clinical laboratory. HDL measurements began in 1981.

Other Information

Information on medication use and diabetes diagnoses was obtained during examinations conducted by NAS physicians. Participants completed questionnaires concerning oral hygiene, smoking habit, and education.

Definition of MetS

MetS is defined as the presence of 3 or more of 5 metabolic risk factors: hyperglycemia, hypertension, hypertriglyceridemia, low HDL, and abdominal obesity (Alberti et al. 2009). The criteria for the first 4 factors have been standardized as follows: fasting serum glucose ≥100 mg/dL or antidiabetic drug use, systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg or antihypertensive drug use, serum triglycerides ≥150 mg/dl or hypertriglyceridemia drug use, and serum HDL <40 mg/dl in male individuals. For men of European descent, the International Diabetes Federation (IDF) defines high waist circumference as ≥94 cm, whereas the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) uses a cut-off of ≥102 cm (Grundy et al. 2005).

Of the 424 participants without MetS (IDF criteria) at baseline, 383 were followed for at least 2 y and 206 subsequently met the above criteria at some point during follow-up. However, 48% of men who had MetS anytime during follow-up reverted to absence of MetS at a later time. Because these changes in status may have been due to random error in measurement of the metabolic risk factors rather than true reversal, change in MetS status was determined to be genuine if it was consistent at 2 consecutive examinations, and the maximum number of positive conditions at 2 consecutive examinations was carried over if the number declined. Using these criteria, 179 men genuinely changed status from no MetS to MetS during follow-up. Similar rates of change in MetS status were observed with the NCEP-ATP III definition.

Statistical Methods

Exposures of interest were MetS diagnosis and number of positive MetS components at each examination. The length of time a participant was exposed to MetS was calculated from the first examination when a positive MetS status was recorded until the end of follow-up or until a genuine reversal in status occurred, otherwise he was considered unexposed. Sensitivity analyses in which exposure time was calculated from the second consecutive examination with positive MetS status did not result in substantially different results.

The primary periodontal outcome events on each tooth were progression of PPD, CAL, mobility, and ABL to predefined threshold levels: PPD and CAL ≥5 mm (based on ordinal scores prior to 1987; categorization of maximum millimeter value after 1987), mobility ≥0.5 mm, and ABL ≥40%. Another defined outcome event was loss of the tooth. Because several years elapsed between dental examinations and we did not know reasons for tooth loss in this cohort, we also computed a composite periodontal disease event, defined as either reaching the periodontal measure threshold or loss of the tooth.

Means and frequencies of baseline characteristics were compared among categories of number of positive MetS components present at baseline and statistical significance determined by analysis of variance or the chi-square statistic, as appropriate. For longitudinal analyses, hazards of tooth loss and each periodontitis event were estimated from separate tooth-level extended Cox proportional hazards regression models that accounted for clustering of teeth within individuals. For teeth that experienced an event, time to event was computed from the baseline dental examination to the examination at which the event was first recorded. For teeth that did not experience an event (censored observations), time to event was computed from the baseline dental examination to the last available examination (dropped out, became edentulous, or end of study period). Variables in the tooth loss models included baseline age, education, and time-varying values of MetS status (or number of positive components), cigarette use (no/yes), cigar use (no/yes), plaque level per tooth (none/interproximal only versus interproximal and at least 1 other surface), and number of decayed or filled surfaces per tooth. Models for the distinct periodontal disease outcomes included age, education, baseline value of the appropriate periodontal disease, and time-varying values of MetS, cigarette use, cigar use, and plaque. Models without baseline periodontal disease measures were also constructed. Models for the composite events included all variables in the tooth loss models plus the appropriate baseline periodontal disease values. Teeth that had already reached the threshold value at baseline were excluded from longitudinal analyses. The models were constructed so that any changes in MetS status and covariates always preceded any tooth loss or the incident periodontitis event. Sensitivity analyses were conducted that limited the PPD and CAL outcomes to data collected after 1987 when they were recorded on a continuous scale.

Results

Demographic and clinical characteristics of the cohort by baseline MetS status are shown in Table 1. Overall prevalence of MetS was 44% using IDF criteria and 37% using NCEP-ATP III criteria. High waist circumference (IDF definition), hyperglycemia, and hypertension were the most common positive components at baseline. Baseline characteristics of the cohort by number of positive IDF MetS components are shown in Table 2. Results were similar using the NCEP-ATP III definition (Appendix Table 1).

Men who were excluded from prospective analyses because of lack of follow-up were older (68 ± 10 y), had more positive MetS components (2.7 ± 1.2), had fewer teeth (19 ± 8), and were more likely to be cigarette smokers (22%) compared with the men who were included.

Overall, 31% of teeth were lost, and 15%, 25%, 8%, and 5% of teeth reached the disease thresholds for pocket depth, CAL,

Table 1. Baseline Demographic and Clinical Characteristics of Dental Longitudinal Study Participants by MetS Status (IDF Criteria).[a]

Characteristic	No MetS	MetS
Number of participants	424	336
Age, y	61 ± 9	61 ± 9
Systolic/diastolic blood pressure, mm Hg	123 ± 15/75 ± 8	135 ± 16/81 ± 9
Serum triglycerides, mg/dL	112 ± 51	213 ± 113
Fasting blood glucose, mg/dL	98 ± 12	112 ± 26
HDL, mg/dL	53 ± 12	42 ± 12
Waist circumference, cm	91 ± 7	100 ± 8
Met criteria for NCEP-ATP-III definition of MetS[b]	0	76
Participants with college education or higher[c]	29	36
Cigarette smokers	12	11
Cigar or pipe smokers[c]	5	11
Whole-mouth mean pocket depth score (*n*)[d]	0.6 ± 0.6 (419)	0.8 ± 0.7 (332)
Teeth with pocket depth >3 mm, %[d]	16 ± 22	23 ± 27
Teeth with pocket depth ≥5 mm, %[d]	5 ± 12	8 ± 15
Whole-mouth mean attachment loss score (*n*)[d]	0.8 ± 0.8 (391)	0.9 ± 0.8 (315)
Teeth with attachment loss >3 mm, %[d]	21 ± 28	27 ± 30
Teeth with attachment loss ≥5 mm, %	10 ± 19	13 ± 22
Whole-mouth mean alveolar bone loss score (*n*)[d]	0.9 ± 0.6 (394)	1.1 ± 0.7 (319)
Teeth with alveolar bone loss ≥40%, %	6 ± 13	7 ± 14
Teeth with alveolar bone loss ≥60%, %	1 ± 5	2 ± 8
Whole-mouth mean mobility score (*n*)[d]	0.2 ± 0.3 (422)	0.3 ± 0.4 (336)
Teeth with mobility ≥0.5 mm[d]	3 ± 9	5 ± 13
Teeth with mobility ≥1 mm	1 ± 4	2 ± 8

Data are given as percentages or means ± SDs unless otherwise specified.
HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III.
[a]IDF criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥94 cm (men).
[b]NCEP-ATP III criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥102 cm (men).
[c]Percentages differ between groups ($P < 0.05$, chi-square test).
[d]Means differ between groups ($P < 0.05$, independent-samples *t* test).

Table 2. Baseline Characteristics of Dental Longitudinal Study Participants by Number of Positive MetS Components (IDF Criteria).

	Number of Positive MetS Conditions at Baseline				
	0	1	2	3	4 or 5
Number	82	124	195	190	169
Age, y[a]	58 ± 8	60 ± 8	62 ± 8	60 ± 8	62 ± 9
Number of teeth[a]	23 ± 6	22 ± 6	21 ± 6	21 ± 7	21 ± 6
Number of teeth with specified conditions					
≥1 decayed/filled surface	13 ± 5	13 ± 5	13 ± 5	12 ± 5	13 ± 5
Bleeding on probing[a]	4 ± 5	6 ± 6	6 ± 7	6 ± 6	9 ± 7
Plaque on interproximal plus at least 1 other surface	1.9 ± 4.6	2.3 ± 5.0	2.1 ± 4.7	2.3 ± 5.2	2.5 ± 5.5
Pocket depth ≥5 mm (*n*)[a]	0.6 ± 1.3 (82)	0.9 ± 2.4 (123)	1.1 ± 2.1 (193)	1.3 ± 2.6 (189)	1.9 ± 3.3 (164)
Clinical attachment loss ≥5 mm (*n*)[a]	1.0 ± 2.1 (76)	1.6 ± 3.4 (112)	2.1 ± 3.3 (182)	1.7 ± 3.2 (179)	2.3 ± 3.5 (157)
Alveolar bone loss ≥40% (*n*)	0.8 ± 1.5 (80)	1.1 ± 2.6 (113)	1.0 ± 1.7 (180)	1.1 ± 2.0 (182)	1.1 ± 1.6 (158)
Mobility ≥0.5 mm[a]	0.5 ± 1.3	0.5 ± 1.2	0.7 ± 1.7	0.7 ± 1.8	1.0 ± 1.9

Data are given as percentages or means ± SDs. IDF criteria: presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥94 cm (men).
HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome.
[a]Linear trend ($P < 0.05$, from analysis of variance).

Table 3. Adjusted Hazards Ratios for Tooth Loss and Periodontal Disease Outcomes Attributable to MetS Status, from Tooth-Level, Time-Varying Proportional Hazards Regression Models.

	IDF Criteria[a]		NCEP-ATP III Criteria[b]	
Disease Outcome	Disease Event Only	Composite Event[c]	Disease Event Only	Composite Event[c]
Tooth loss[d]	1.39 (1.08 to 1.79)		1.44 (1.11 to 1.87)	
Pocket depth ≥5 mm[e]	1.37 (1.14 to 1.65)	1.32 (1.21 to 1.55)	1.32 (1.08 to 1.60)	1.25 (1.05 to 1.49)
Clinical attachment loss ≥5 mm[f]	1.19 (1.00 to 1.41)	1.22 (1.04 to 1.42)	1.12 (0.93 to 1.35)	1.20 (1.02 to 1.41)
Alveolar bone loss ≥40%[g]	1.25 (1.00 to 1.56)	1.28 (1.08 to 1.53)	1.10 (0.88 to 1.39)	1.28 (1.06 to 1.54)
Tooth mobility ≥0.5 mm[h]	1.43 (1.07 to 1.89)	1.41 (1.14 to 1.75)	1.43 (1.07 to 1.90)	1.43 (1.13 to 1.80)

Data are presented as adjusted hazard ratios (95% confidence intervals).
HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III.
[a]IDF criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥94 cm (men).
[b]NCEP-ATP III criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥102 cm (men).
[c]Composite event defined as either the periodontal measure reached the threshold level or the tooth was lost.
[d]Adjusted for baseline age and highest level of education completed (high school, some college, college) and time-dependent values of cigarette use (no/yes), cigar use (no/yes), plaque on tooth (none/interproximal only versus interproximal plus at least 1 other surface), and number of decayed/filled surfaces per tooth.
[e]Disease event adjusted for baseline age, education, pocket depth score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[f]Disease event adjusted for baseline age, education, clinical attachment loss score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[g]Disease event adjusted for baseline age, education, alveolar bone loss score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[h]Disease event adjusted for baseline age, education, mobility score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.

ABL, and mobility, respectively. Using IDF criteria, the presence of MetS predicted greater hazards of tooth loss and all of the individual periodontal disease outcomes (Table 3). Hazards estimates for tooth loss, pocket depth, CAL, and mobility were very similar regardless of how MetS was defined or whether the outcome was periodontal disease only or the composite event. The effect of excluding baseline periodontal disease values as covariates was to increase the hazards ratios (Appendix Table 2). Other covariates consistently related to tooth loss and periodontal diseases were cigarette use (15%–25% increase), age (2%–5% increase per year), and less than high school education (20%–25% increase relative to college education).

Hazards of tooth loss, periodontal disease outcomes, and composite outcomes also tended to rise per each additional positive IDF or NCEP-ATP III risk factor (Table 4).

As seen with the ordinal measures, the average millimeters of pocket depth and CAL increased as the number of IDF MetS components increased (Appendix Table 3). IDF MetS was associated with increased hazards of pocket depth and interproximal pocket depth progression but not CAL (Appendix Table 4), but estimates were attenuated relative to the corresponding ordinal measures.

Discussion

MetS status and number of positive MetS components, regardless of their definition, predict long-term increases in risk of tooth loss and moderate to severe events of periodontitis as measured by pocket depth, CAL, tooth mobility, and ABL.

Various criteria have been used over the years to define MetS, ranging from a simple tally of the number of metabolic abnormalities to the mandatory inclusion of 1 key component, such as central obesity or insulin resistance, along with any other 2 risk factors (Alberti et al. 2009). The most recent set of guidelines is a consensus of the IDF and American Heart Association/National Heart, Lung, and Blood Institute to define MetS as any 3 of 5 risk factors (hyperglycemia, hypertriglyceridemia, hypertension, low HDL, and abdominal obesity) without a required component. Cut-off values for the first 4 components are uniform; however, differing opinions exist with respect to how abdominal obesity should be defined, with the IDF recommending a lower cut-off than the NCEP-ATP III. The IDF value captures more men who are overweight rather than obese but are still at high risk of metabolic disease (Alberti et al. 2009). Estimates of MetS prevalence in the United States derived from the National Health and Nutrition Examination Survey (NHANES) are based on the NCEP-ATP III definition (Mozumdar and Liguori 2011). Changing waist circumference cut-off points had minimal impact on the strength of associations between MetS and tooth loss or periodontal disease progression in this cohort.

The link between MetS and periodontal disease is not remarkable, given that the individual cardiovascular disease risk factors that comprise MetS are also associated with periodontal diseases. Obesity is a predictor of periodontitis

Table 4. Adjusted Hazards Ratios for Tooth Loss and Periodontal Disease Outcomes per Each Additional Positive MetS Component, from Tooth-Level, Time-Varying Proportional Hazards Regression Models.

	IDF Criteria[a]		NCEP-ATP III Criteria[b]	
Disease Outcome	Disease Event Only	Composite Event[c]	Disease Event Only	Composite Event[c]
Tooth loss[d]	1.14 (1.03 to 1.26)		1.18 (1.06 to 1.30)	
Pocket depth ≥5 mm[e]	1.14 (1.05 to 1.23)	1.13 (1.06 to 1.20)	1.11 (1.03 to 1.20)	1.12 (1.05 to 1.19)
Clinical attachment loss ≥5 mm[f]	1.05 (0.99 to 1.12)	1.08 (1.02 to 1.14)	1.05 (0.98 to 1.12)	1.08 (1.02 to 1.14)
Alveolar bone loss ≥40%[g]	1.11 (1.01 to 1.21)	1.15 (1.07 to 1.23)	1.12 (1.02 to 1.22)	1.18 (1.10 to 1.26)
Tooth mobility ≥0.5 mm[h]	1.17 (1.04 to 1.32)	1.28 (1.18 to 1.39)	1.16 (1.03 to 1.31)	1.31 (1.21 to 1.42)

Data are presented as adjusted hazard ratios (95% confidence intervals).
HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; NCEP-ATP III, National Cholesterol Education Program Adult Treatment Panel III.
[a]IDF criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥94 cm (men).
[b]NCEP-ATP III criteria include the presence of 3 or more conditions: hypertension, impaired glucose tolerance, low HDL, hypertriglyceridemia, or waist circumference ≥102 cm (men).
[c]Composite event defined as either the periodontal measure reached the threshold level or the tooth was lost.
[d]Adjusted for baseline age and highest level of education completed (high school, some college, college), and time-dependent values of cigarette use (no/yes), cigar use (no/yes), plaque on tooth (none/interproximal only versus interproximal plus at least 1 other surface), and number of decayed/filled surfaces per tooth.
[e]Disease event adjusted for baseline age, education, pocket depth score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[f]Disease event adjusted for baseline age, education, clinical attachment loss score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[g]Disease event adjusted for baseline age, education, alveolar bone loss score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.
[h]Disease event adjusted for baseline age, education, mobility score, and time-dependent values of cigarette use, cigar use, and plaque. Composite event additionally adjusted for number of decayed/filled surfaces per tooth.

progression in prospective studies (Gorman et al. 2012; Jimenez et al. 2012). Periodontitis is correlated with hyperlipidemia (Fentoğlu et al. 2009) and hypertension (Rivas-Tumanyan et al. 2013). The association with insulin resistance may be bidirectional. Periodontal disease and tooth loss are known complications of diabetes and insulin resistance (Lamster et al. 2014), whereas periodontitis may exacerbate impaired glucose (Demmer et al. 2010) and lead to incident diabetes (Demmer et al. 2008). A similar dynamic may occur between MetS, tooth loss, and periodontitis. Morita et al. (2010) reported that people with periodontal pockets ≥4 mm were 40% more likely to have developed 1 or more MetS conditions 4 y later. They found no association between tooth loss and MetS, however. Conversely, adults with MetS were more likely than those without MetS to have developed loss of attachment ≥3 mm after 3 y (Iwasaki et al. 2015) or to have lost 1 or more teeth during 5 y of follow-up (Furuta et al. 2016).

Insulin resistance and inflammation have been proposed as the primary causal mechanisms that lead to the association between MetS and periodontitis, but dyslipidemia may also play a role. Hyperglycemia impairs the regulation of the host inflammatory response via deposition of advanced glycated endproducts in tissues, including the periodontium, and stimulation of proinflammatory cytokines (Preshaw et al. 2012). These actions are thought to heighten the body's response to infection by periodontal pathogens and cause damage to periodontal tissues. In addition, proinflammatory cytokines and hormones produced in excess by adipose tissue may also intensify the response to periodontal infection. Accumulation of cholesterol and lipids in arterial walls, macrophages, and immune cells triggers an inflammatory response that may be amplified if levels of HDL, which function to remove lipids from arterial walls, are insufficient. Alternatively, local production of proinflammatory cytokines and markers in periodontal disease can enter the systemic circulation and potentially contribute to insulin resistance (Genco et al. 2005; Preshaw et al. 2012), which in turn can set off a continuing cycle of inflammation.

Major strengths of this study are the prospective design, extended follow-up period, and control for multiple potential confounders. A major limitation of the study is the poor to moderate reproducibility of ordinal periodontal disease scores among examiners. Even after dichotomizing the scores, the lack of reproducibility would result in some misclassification of the outcomes. However, there is no reason to believe that such misclassification would be differentially related to MetS status. Rather, the effect of random misclassification in measurements is an attenuation of the hazard estimates.

Other limitations include the all-male, predominantly white ethnic makeup of the cohort and self-selection by participants to enroll in the DLS, which restrict the ability to generalize these findings to a larger, diverse population. However, NCEP-ATP III MetS prevalence among male DLS participants (37% at baseline and 49% ever) was similar to that in male

participants in NHANES surveys over a similar time period. Nationally, prevalence rates of MetS in non-Hispanic white men aged 40 to 59 y and ≥60 y were 37% and 50%, respectively, in 1988 to 1992 and increased to 51% among men aged ≥60 y in 1999 to 2006 (Mozumdar and Liguori 2011).

In summary, MetS is a predictor of tooth loss and worsening periodontal disease in men. More longitudinal studies are needed to confirm this association in other populations, more fully address the directionality of the association, and uncover the biological mechanisms responsible for the relationship.

Author Contributions

E.K. Kaye, contributed to conception, design, and data acquisition, drafted and critically revised the manuscript; N. Chen, contributed to data analysis and interpretation, critically revised manuscript; H.J. Cabral, contributed to design, data analysis, and interpretation, critically revised manuscript; P. Vokonas, contributed to data acquisition and interpretation, critically revised manuscript; R.I. Garcia, contributed to conception, design, data acquisition and interpretation, critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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