Tooth Loss is Related to the Presence of Metabolic Syndrome and Inflammation in Elderly Subjects: A Prospective Study of the Vasculature in Uppsala Seniors (PIVUS)

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Purpose: To investigate how the number of remaining teeth relates to the presence of metabolic syndrome (MetS) and markers of inflammation.

Materials and Methods: A population-based prospective investigation of the vasculature in Uppsala seniors (PIVUS) study was carried out on 1016 subjects, aged 70.

Results: The number of teeth was self-reported in 947 subjects and was found to be less in those with MetS using National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) criteria (n = 219, mean 17.7 ± 9.0 [SD]), compared with n = 728, mean 20.7 ± 7.2 in those without MetS ($p < 0.0001$), and in proportion to the number of criteria fulfilled ($p < 0.0001$). The number of teeth was also inversely related to markers of inflammation ($r = -0.15$, $p < 0.0001$ for leukocyte count; $r = -0.10$, $p = 0.0023$ for C-reactive protein). In a multiple regression analysis, the presence of MetS, smoking, educational level, leukocyte count and height were independent predictors of the number of teeth.

Conclusions: In addition to established risk factors for tooth loss, the presence of MetS and inflammation were independent predictors of the number of teeth in an elderly population.

Key words: C-reactive protein (CRP), inflammation, metabolic syndrome, oral health, teeth

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Over the last decade, oral health, and especially periodontitis, has been suggested to be a possible risk factor for a number of general health conditions such as diabetes, cardiovascular disease, lower respiratory disease and premature birth (Beck et al, 1998; Scannapieco et al, 2003; Saito et al, 2004; Moliterno et al, 2005). However, the biological mechanism underlying these associations still remains unclear. Periodontitis is a chronic infection in the supporting tissue of the teeth, creating an inflammatory response that will cause bone loss and soft tissue degradation around the teeth, eventually leading to tooth loss (Page, 1991). Another oral disease that causes tooth loss is caries, but in middle-aged and elder individuals periodontal disease seems to be the most important reason for removing teeth (Reich and Hiller, 1993).

Elevated levels of circulating inflammation markers, such as white blood cells (WHC), fibrinogen and high-sensitivity C-reactive protein (Hs-CRP), have been found in individuals with periodontitis compared with those with periodontal health. This indicates that periodontitis may cause a systemic low-grade inflammation that can be one link between periodontal disease

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and the abovementioned general conditions (Loos et al, 2000; Sahingur et al, 2003).

Metabolic syndrome (MetS) is a syndrome consisting of different combinations of cardiovascular risk factors, such as high blood pressure, dyslipidemia, abnormal glucose control and abdominal obesity. Subjects with this syndrome are at increased risk of developing cardiovascular disease (Grundy et al, 2004; Savage et al, 2005), and insulin resistance has been suggested as a common denominator of the syndrome (Reaven, 1988).

Although periodontitis and tooth loss have been associated with different components included in MetS, no previous study has related tooth loss to the presence of the syndrome.

As MetS has also been associated with increased levels of inflammatory markers, the aim of the present study was to investigate how self-reported tooth loss relates to the presence of MetS as well as to general markers of inflammation. For this purpose we used data collected in the prospective investigation of the vasculature in Uppsala seniors (PIVUS) study, a large population-based study on elderly subjects.

MATERIALS AND METHODS

Subjects

All subjects aged 70 living in the municipality of Uppsala, Sweden, were eligible. The subjects were chosen from the register of community living and were invited in a randomised order. The subjects received an invitation by letter within 2 months prior to their 70th birthday. Of the 2025 subjects invited, 1016 subjects participated, giving a participation rate of 50.1%. The number of teeth was self-reported by 947 of the participants.

The study was approved by the Ethics Committee of the University of Uppsala, and the participants gave informed consent.

Basic investigation

At the time of the medical examination, the participants were asked to answer a questionnaire about their medical history, smoking habits, regular medication and the number of remaining teeth (excluding wisdom teeth, which give a maximum number of 28). The educational level was divided into three different categories: six years in school or less, between 7 and 12 years, and university studies.

All subjects were examined in the morning after an overnight fast. No medication or smoking was allowed after midnight. After recordings of height, weight, abdominal and hip circumference, an arterial cannula was inserted in the brachial artery for blood sampling.

Blood pressure was measured by a calibrated mercury sphygmomanometer in the non-cannulated arm, to the nearest mmHg, after at least 30 minutes of rest, and the average of three recordings was used. Lipid variables, leukocyte count and fasting blood glucose were measured by standard laboratory techniques. Hs-CRP was measured in human serum by an ultrasensitive particle enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland) on a Konelab 20 autoanalyser (Thermo Clinical Labsystems, Espoo, Finland). The inter-assay coefficient of variation was 3.2%.

MetS was defined according to the NECP/ATP III (National Cholesterol Education Program/Adult Treatment Panel III) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Three of the following five criteria should be fulfilled:

- blood pressure >130/85 mmHg or antihypertensive treatment;
- fasting blood glucose > 5.6 mmol/l;
- serum triglycerides >1.7 mmol/l;
- waist circumference > 102 cm in men and >88 cm in women;
- HDL-cholesterol < 1.0 mmol/l in men and <1.3 in women.

As the participation rate in this cohort was only 50%, we carried out an evaluation of cardiovascular disorders and medications in 100 consecutive non-participants. The prevalence of cardiovascular drug intake, history of myocardial infarction, coronary revascularisation, antihypertensive medication, statin use and insulin treatment were similar to those in the investigated sample, while the prevalence of diabetes, congestive heart failure and stroke tended to be higher among the non-participants (see Table 2).

Statistics

Non-normally distributed variables were log-transformed to achieve a normal distribution. Differences between groups were evaluated with ANOVA. Relationships between pairs of variables were evaluated by Pearson's correlation coefficient. Multiple regression

analysis was applied to relate several independent variables to a dependent variable. Two-tailed significance values were given with $p < 0.05$ regarded as significant. The statistical programme package StatView (SAS, NC, USA) was used.

RESULTS

Mean values for studied variables are given in Table 1. History of diseases and medication are shown in Table 2. The number of teeth was reported by 947 of the subjects. The mean (± SD) number was 20.0 ± 8.0. The data showed no differences in the major studied variables between subjects who reported the number of teeth and those who did not (results not shown). MetS was present in 23% of the subjects and of these, 63% were women and 37% men.

The number of teeth did not significantly differ between men and women (19.6 ± 7.7 in women, and 20.4 ± 7.8 in men, $p = 0.11$).

The number of teeth was significantly lower in subjects with MetS (n = 219) compared with those without ($p < 0.0001$) (Fig 1), and was also significantly related to the number of criteria included in the definition of MetS ($p < 0.0001$) (Fig 2).

The number of teeth was also related to the educational level (18.3 ± 8.2 in those with only 6 years in school, n = 527; 21.6 ± 7.0 in those with 7–12 years in school, n = 167; and 22.7 ± 6.3 in subjects with a university degree, n = 236). The number of teeth was significantly reduced in current smokers compared with non-smokers (15.2 ± 9.7 in smokers versus 20.6 ± 7.3 in non-smokers, $p < 0.0001$).

When the number of teeth was related to continuous variables in univariate analysis, dental status was significantly correlated with CRP, leukocyte count, intercellular adhesion molecule-1 (ICAM-1), Framingham risk score, waist circumference, body mass index (BMI), serum triglycerides, heart rate and fasting blood glucose in an inverse way and to height in a positive way (Table 3). Blood pressure, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were not significantly related to the number of teeth.

In a backwards stepwise multiple regression analysis with the number of teeth as dependent variable and the abovementioned significant variables as independent variables, the presence of MetS, smoking, low education level, leukocyte count and height were independent predictors of the number of teeth (Table 4).

Table 1 Basic characteristics, major cardiovascular risk factors and measures of endothelium-dependent vasodilation in the total sample (means ± SD)

Parameter measured	Total sample
n	1016
Females (%)	50.2
Height (cm)	169 ± 9.1
Weight (kg)	77 ± 14
Waist circumference (cm)	91 ± 12
BMI (kg/m2)	27.0 ± 4.3
Waist/hip ratio	0.90 ± 0.075
SBP (mmHg)	150 ± 23
DBP (mmHg)	79 ± 10
Heart rate (beats/min)	62 ± 8.7
Serum cholesterol (mmol/l)	5.4 ± 1.0
LDL-cholesterol (mmol/l)	3.3 ± 0.88
HDL-cholesterol (mmol/l)	1.5 ± 0.42
Serum triglycerides (mmol/l)	1.3 ± 0.60
Fasting blood glucose (mmol/l)	5.3 ± 1.6
Current smoking (%)	11
Leukocyte count	5.7 ± 1.5
CRP	2.5 ± 5.2
Framingham risk score	11.1 ± 3.3

BMI, body mass index
DBP, diastolic blood pressure
SBP, systolic blood pressure

Table 2 Self-reported history of cardiovascular disorders and regular drug intake given in percentage of the investigated sample and in 100 non-attendees

	Total investigated sample (%)	Not attending (%)
n	1016	100
Myocardial infarction	7.1	7.9
Stroke	3.7	6.7
Angina pectoris	8.1	13.8
CABG/PTCA	5.3	5.6
Congestive heart failure	3.8	6.9
Diabetes	8.7	16.9
Any regular drug	70	64
Any cardiovascular drug	45	52
Any antihypertensive medication	32	36
Beta-blockers	22	26
Calcium antagonists	11	12
Diuretics	13	19
ACE-inhibitors	8.5	11
Angiotensin II-blockers	8.3	9.1
GTN	3.0	3.4
Digoxin	2.1	9.2
Statins	15	17
Other antihyperlipidemic drugs	1.2	4.5
Insulin	1.8	1.1
Oral antidiabetic drugs	6.1	12
Warfarin	3.2	6.8
Aspirin/clopidogrel	18	21
Other antiarythmic drugs	0.2	0

ACE, angiotensin converting enzyme
CABG/PTCA, coronary revascularisation
GTN, any nitro-glycerine preparation

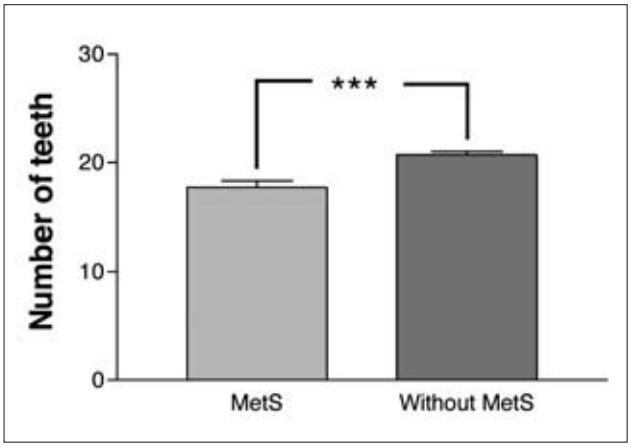

Fig 1 Number of teeth in subjects with metabolic syndrome (MetS, n = 219) and in those without (n = 728) (means + SEM; ***p < 0.001).

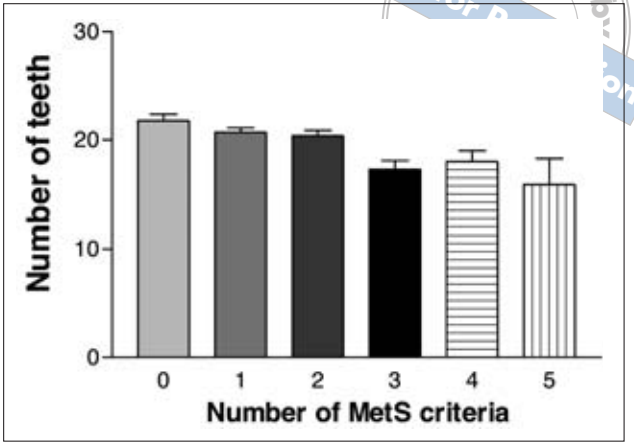

Fig 2 Number of teeth in relation to the number of criteria included in the NCEP/ATP III definition of metabolic syndrome (MetS) (means ± SEM) (p < 0.0001 for trend).

Table 3 Univariate correlations between the number of teeth and risk factors for metabolic syndrome and cardiovascular disease

Variable	r-value	p-value
Height	0.12	0.0003
BMI	-0.10	0.0028
Waist circumference	-0.07	0.028
SBP	-0.01	0.83
DBP	0.02	0.47
Heart rate	-0.08	0.029
Fasting blood glucose	-0.11	0.0008
LDL-cholesterol	0.03	0.39
HDL-cholesterol	0.02	0.58
Serum triglycerides	-0.07	0.038
ICAM-1	-0.14	0.0001
CRP	-0.10	0.0023
Leukocyte count	-0.15	0.0001
Framingham risk score	-0.09	0.0058

DBP, diastolic blood pressure
SBP, systolic blood pressure

Table 4 Backwards stepwise multiple regression analysis with number of teeth as dependent variable and only significant independent variables retained in the model

Independent variables	Correlation coefficient	p-value
Metabolic syndrome	-0.15	0.0001
Smoking	-0.19	0.0001
Education level	0.21	0.0001
Height	0.07	0.019
Leukocyte count	-0.07	0.043

DISCUSSION

To our knowledge, the present study is the first to report a relationship between number of self-reported teeth and MetS. Subjects with MetS reported an average of three less teeth than those without the syndrome. This finding was still valid after adjustment for known confounders such as smoking and education level. The number of teeth was furthermore related to markers of inflammation in this population-based cohort of elderly subjects.

One of the major reasons for tooth loss is periodontal disease (periodontitis) and recent data show that the number of teeth removed reflects the severity of the periodontal disease (Desvarieux et al, 2003, 2004). After the age of 40, periodontitis has been reported to be a major reason for loss of teeth (Reich and Hiller, 1993) and it has been shown that the number of teeth is a valid marker regarding self-estimation of oral health (Buhlin et al, 2002).

Thus, the number of teeth may be a way to describe the lifetime accumulation of oral infections. In periodontal disease, local levels of inflammatory mediators are raised (Gamonal et al, 2003; Holmlund et al, 2004) and it is possible to assume that these cytokines can enter the circulation and contribute to a low-grade systemic inflammatory response. In the present study the number of remaining teeth was correlated to circulating levels of CRP, leukocyte count and ICAM-1. A relationship between oral health and markers of systemic inflammation has previously been reported (Loos et al, 2000).

Low-grade inflammation has been suggested as one of the pathogenic events in the development of

MetS (Ridker et al, 2003; Salmenniemi et al, 2004). Thus a pro-inflammatory status might be a link in the association between tooth loss and MetS, although causality cannot be explored in epidemiological studies. However, this does not seem to be the sole explanation of the association between tooth loss and MetS, as multiple regression analysis showed that leukocyte count and MetS are independent predictors of the number of remaining teeth. In the present study, the number of teeth was related to the number of components of MetS, suggesting that the number of teeth is not related to a single risk factor, but rather to the sum of several risk factors. This is in line with reports that periodontitis is related to diabetes (Iacopino, 2001) and abdominal obesity (Wood et al, 2003).

The Framingham risk score is a tool to calculate the risk for future coronary heart disease by combining the risk factors age, blood pressure, smoking, cholesterol and diabetes (Wilson et al, 1998). That tooth loss in this study correlates to Framingham risk score further strengthens findings from other studies regarding an association between tooth loss and coronary heart disease (Elter et al, 2004).

Education level as well as smoking were also independent predictors for the number of teeth in this study, which is in accord with other studies and underlines the importance of lifestyle factors regarding both oral and general health (Krall et al, 1997; Haugejorden et al, 2003; Klein et al, 2004).

Limitation of the study

The present sample is limited to Caucasians aged 70. Therefore caution should be used in inferring conclusions to other ethnic and age groups. Furthermore, the study design is cross-sectional, which limits the ability to draw causal conclusions from the results, but the results suggest a possible association that deserves further investigation. Number of teeth was self-reported, but as previously mentioned, people are good at estimating their remaining number of teeth (Buhlin et al, 2002). As stated above, the authors are aware that the self-reported number of teeth has its limitations. However, this could only underestimate any potential relationships investigated and create false negative results. We therefore think that the results presented are valid although they might have been underestimated.

The present study had a moderate participation rate. However, an analysis of non-participants showed the present sample to be fairly representative of the total population regarding several cardiovascular disorders and drug intake. Unfortunately, the non-participants were not asked about the number of remaining teeth. In health studies, health is often worse among non-participants than participants, also indicated in this study. The same pattern would probably be seen for oral health and number of remaining teeth. This would, if anything, lead to an underestimation rather than an overestimation of the relationship presented in this study.

In conclusion, tooth loss was significantly related to MetS. One pathogenic factor might be a low-grade systemic inflammation, but other factors are also likely to be involved in the link between tooth loss and MetS. Whatever the underlying cause, oral health can be an important indicator for a deranged general health and individuals suffering from periodontal disease or extensive tooth loss should be considered for a general medical examination.

REFERENCES

1. Beck JD, Offenbacher S, Williams R, Gibbs P, Garcia R. Periodontitis: a risk factor for coronary heart disease? Ann Periodontol 1998;3:127-141.
2. Buhlin K, Gustafsson A, Andersson K, Hakansson J, Klinge B. Validity and limitations of self-reported periodontal health. Community Dent Oral Epidemiol 2002;30:431-437.
3. Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR Jr, Papapanou PN et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). Stroke 2003;34:2120-2125.
4. Desvarieux M, Schwahn C, Volzke H, Demmer RT, Ludemann J, Kessler C et al. Gender differences in the relationship between periodontal disease, tooth loss, and atherosclerosis. Stroke 2004;35:2029-2035.
5. Elter JR, Champagne CM, Offenbacher S, Beck JD. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. J Periodontol 2004;75:782-790.
6. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii). J Am Med Assoc 2001;285:2486-2497.
7. Gamonal J, Sanz M, O'Connor A, Acevedo A, Suarez I, Sanz A et al. Delayed neutrophil apoptosis in chronic periodontitis patients. J Clin Periodontol 2003;30:616-623.
8. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433-438.
9. Haugejorden O, Klock KS, Trovik TA. Incidence and predictors of self-reported tooth loss in a representative sample of Norwegian adults. Community Dent Oral Epidemiol 2003;31:261-268.

10. Holmlund A, Hanstrom L, Lerner UH. Bone resorbing activity and cytokine levels in gingival crevicular fluid before and after treatment of periodontal disease. J Clin Periodontol 2004; 31:475-482.
11. Iacopino AM. Periodontitis and diabetes interrelationships: role of inflammation. Ann Periodontol 2001;6:125-137.
12. Klein BE, Klein R, Knudtson MD. Life-style correlates of tooth loss in an adult Midwestern population. J Public Health Dent 2004;64:145-150.
13. Krall EA, Dawson-Hughes B, Garvey AJ, Garcia RI. Smoking, smoking cessation, and tooth loss. J Dent Res 1997;76:1653-1659.
14. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol 2000;71:1528-1534.
15. Moliterno LF, Monteiro B, Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. J Clin Periodontol 2005;32:886-890.
16. Page RC. The role of inflammatory mediators in the pathogenesis of periodontal disease. J Periodontal Res 1991;26:230-242.
17. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.
18. Reich E, Hiller KA. Reasons for tooth extraction in the western states of Germany. Community Dent Oral Epidemiol 1993; 21:379-383.
19. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107:391-397.
20. Sahingur SE, Sharma A, Genco RJ, De Nardin E. Association of increased levels of fibrinogen and the -455G/A fibrinogen gene polymorphism with chronic periodontitis. J Periodontol 2003;74:329-337.
21. Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, Koga T. The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. J Dent Res 2004;83:485-490.
22. Salmenniemi U, Ruotsalainen E, Pihlajamaki J, Vauhkonen I, Kainulainen S, Punnonen K et al. Multiple abnormalities in glucose and energy metabolism and coordinated changes in levels of adiponectin, cytokines, and adhesion molecules in subjects with metabolic syndrome. Circulation 2004;110:3842-3848.
23. Savage PD, Banzer JA, Balady GJ, Ades PA. Prevalence of metabolic syndrome in cardiac rehabilitation/secondary prevention programs. Am Heart J 2005;149:627-631.
24. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for nosocomial bacterial pneumonia and chronic obstructive pulmonary disease. A systematic review. Ann Periodontol 2003;8:54-69.
25. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-1847.
26. Wood N, Johnson RB, Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National Health and Nutrition Examination Survey (NHANES III). J Clin Periodontol 2003;30:321-327.