CLINICAL INVESTIGATIONS

Tooth Loss and Atherosclerosis: The Nagahama Study

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Abstract: Several epidemiologic studies have suggested that oral disease is a risk factor for cardiovascular disease (CVD). However, whether a clinically significant association exists between the 2 disorders remains controversial. Here, we investigated the association between tooth loss, as an indicator of oral disease, and arterial stiffness, as a marker of atherosclerosis, in Japanese adults. Cross-sectional data were collected for 8,124 persons aged 30 to 75 y with no history of tooth loss for non-inflammatory reasons, such as orthodontic treatment, malposition, and trauma. Participants received a comprehensive dental examination and extensive in-person measurements of CVD risk factors, and arterial stiffness was evaluated using the cardio-ankle vascular index (CAVI). We examined the association between CAVI and tooth loss using general linear models with adjustment for age, sex, body mass index, smoking status, hemoglobin A1c, and a history of insulin or hypoglycemic medication depending on the model. In addition, we performed an analysis that included interaction terms of the centered variables tooth loss, sex, and age. The results of the multiple regression analysis that included the interaction terms detected that the relationship between CAVI and

tooth loss was dependent on sex, with only men showing a positive correlation (β for interaction = 0.04; 95% confidence interval, 0.02–0.06). The findings from this study suggest that a linear relationship exists between tooth loss and degree of arterial stiffness and that the association differed depending on sex.

Key Words: arterial stiffness, epidemiology, inflammation, periodontal disease, cross-sectional analysis, cardiovascular diseases.

Introduction

Cardiovascular disease (CVD) is the most common cause of death and disability in industrialized nations and has a high cost to society. The coincidence of cardiovascular and oral disease is relatively high, and numerous studies have reported that a positive association exists between these 2 diseases (Beck et al. 1998; Beck et al. 2001; Hujoel et al. 2001; Desvarieux et al. 2003; Pussinen et al. 2003; Desvarieux et al. 2004; Ylostalo et al. 2006; Tonetti et al. 2007; Tu et al. 2007; Dietrich et al. 2008; Senba et al. 2008; Choe et al. 2009; de Oliveira et al. 2010; Kim et al. 2010). However, as a significant

relationship was not detected in several studies (Hujoel et al. 2000; Lavelle 2002; Colhoun et al. 2008), it remains controversial whether a clinically significant association exists between the 2 diseases (Hujoel et al. 2000; Lavelle 2002; Lockhart et al. 2012).

Inflammation plays an important role in the pathogenesis of CVD. Systemic inflammation may represent the underlying mechanism that links oral and cardiovascular diseases. Oral disease, such as periodontal disease, is characterized by chronic systemic inflammation and often results in tooth loss due to the breakdown of periodontal tissue. Therefore, tooth loss is a useful proxy for the accumulated burden of inflammatory disease (Desvarieux et al. 2003; Houshmand et al. 2012).

Elderly people and men carry a disproportionate burden of CVD and oral disease. Therefore, age and sex adjustment must be performed when evaluating the potential link between oral disease and CVD. Moreover, as oral disease and CVD share common risk factors, including smoking, diabetes, hypertension, and obesity, the potential for confounding is substantial. Thus, the power for detecting effect modification is limited in small population studies.

Arterial stiffness, as assessed by the cardio-ankle vascular index (CAVI), is

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a measure of CVD (Kadota et al. 2008). CAVI was developed to overcome the dependency of pulse-wave velocity (PWV) measurements on blood pressure. The underlying principle of CAVI measurement is based on the stiffness parameter β and is calculated using the Bramwell-Hill formula, which is basically independent of blood pressure (Yambe et al. 2004; Shirai et al. 2006; Takaki et al. 2008; Shirai et al. 2011). Thus, CAVI is an easily administered arterial stiffness screening test that ensures good reproducibility as a diagnostic tool for CVD. Here, we investigated the relationship between tooth loss and arterial stiffness using baseline survey data in a population-based cohort.

Methods

Ethics Statement

This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, the Ad Hoc Review Board of the Nagahama Study, and the Nagahama Municipal Review Board of Personal Information Protection. Appointments for health examinations were made by telephone by the municipal government staff, and participant registration was performed at the site of the health examinations. Written informed consent was also obtained from all participants prior to their health examination.

Study Design and Population

The Nagahama Prospective Genome Cohort for the Comprehensive Human Bioscience (the Nagahama Study) is a population-based prospective cohort study of a broad range of chronic illnesses and was conducted in Nagahama City, Shiga Prefecture, Japan (Tabara et al. 2013). The present study is a prospective study that collected data by means of questionnaires, anthropometric and physiologic measures, biochemical measurements of blood samples, genomic information, and oral examinations. The Nagahama Study participants were recruited from apparently healthy community residents living in Nagahama City, a largely rural city of approximately 125,000 inhabitants in Shiga Prefecture,

which is located in central Japan. A baseline survey was conducted between fiscal years 2008 and 2010. Information on the project was provided to potential participants by newsletters, newspaper flyers, and brochures and on the homepages of the local government and citizen organizations. Information sessions for the residents were also held by researchers and city employees, who explained the project to interested residents. Residents of Nagahama City who fulfilled the following criteria were recruited for the cohort study: 1) age between 30 and 74 years old at the time of recruitment, 2) able to participate in the health examinations independently, 3) no difficulties in communication in Japanese, 4) no serious diseases/symptoms or health issues, and 5) voluntarily decided to participate in the project. We performed a complete case analysis, so only participants with complete information for subjective measures of tooth loss, CAVI, and all other examined covariates were included in the analytical sample. As no variables were missing from more than 5% of the total number of cases, and the missing data were random, the missing data are not considered to have markedly influenced the outcomes of the analysis. A total of 1,670 participants were excluded from the adjusted analyses because of missing data, and participants who reported that tooth loss was due to orthodontic treatment, malpositioned teeth, or trauma were also excluded. Therefore, the analyses reported in the present study included a total of 8,124 participants.

Risk Factor Assessment

Trained physicians and research assistants administered standardized questionnaires, performed anthropomorphic measurements, and collected fasting blood specimens using standardized protocols. Subjects were interviewed and completed a questionnaire regarding sex, age, cardiovascular risk factors, and other medical conditions.

Height and weight measurements were determined with calibrated scales. Body mass index (BMI) was calculated using the obtained height and weight data. Trained nurses measured blood

pressure using a calibrated automated sphygmomanometer (HEM-9000; Omron Healthcare Co., Ltd., Kyoto, Japan). All measurements were taken at least twice in a sitting position, and the last measurement among the data measured without error was used in the analysis. Fasting blood glucose level, high-density lipoprotein (HDL) cholesterol (HDL-C), low-density lipoprotein (LDL) cholesterol (LDL-C), and hemoglobin A1c (HbA1c) were measured using the collected blood samples from all subjects. Participants were categorized as current smokers, former smokers, or never smokers based on self-report.

Hypertension was defined as a systolic blood pressure (SBP) of ≥ 140 mm Hg or a diastolic blood pressure (DBP) of ≥ 90 mm Hg, or the self-report of history of antihypertensive drug use. HbA1c values (%) are reported according to the National Glycohemoglobin Standardization Program. Diabetes mellitus was defined by a history of insulin or hypoglycemic medication, or a fasting glucose level ≥ 126 mg/dL or random plasma glucose level ≥ 200 mg/dL, or HbA1c ≥ 6.5 (HbA1c $\geq 6.1\%$), according to the Japan Diabetes Society criteria (Seino et al. 2010).

Measurement of CAVI

CAVI was recorded using a Vasera VS-1500 vascular screening system (Fukuda Denshi Ltd., Tokyo, Japan) with the participant resting in the supine position, as described in a previous report (Shirai et al. 2006). Briefly, electrocardiograph electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around both arms and ankles. After automatic measurements, obtained data were analyzed using VSS-10 software (Fukuda Denshi Ltd.), and values of the right and left CAVI were calculated. Averages of the right and left CAVI were used for analysis.

Dental History and Oral Examination

At baseline, subjects were interviewed and underwent a complete examination of the oral cavity administered by 1 of 2

Table 1.
Characteristics of Study Participants

Variable	Men (<i>n</i> = 2680)	Women (<i>n</i> = 5444)	All Participants (<i>N</i> = 8124)
Age, y	56.0 (28.9–83.1)	53.3 (27.2–79.5)	54.2 (53.9–54.5)
Tooth loss	4.3 (0–18.3)	3.2 (0–14.4)	3.6 (0–15.8)
CAVI	7.9 (5.4–10.3)	7.2 (5.2–9.3)	7.4 (5.2–9.7)
Hypertension	1,066 (39.8)	1,549 (23.5)	2,420 (29.8)
Diabetes	226 (8.4)	170 (2.6)	377 (4.6)
Former smoker	1,184 (44.2)	454 (8.3)	1,638 (20.2)
Current smoker	827 (30.9)	345 (6.4)	1,172 (14.4)
BMI, kg/m ²	23.4 (17.3–29.5)	21.8 (15.3–28.3)	22.3 (15.8–28.9)
SBP, mm Hg	128.6 (91.9–160.3)	119.4 (85.6–153.3)	122.4 (88.2–156.7)
DBP, mm Hg	79.9 (58.4–101.3)	73.5 (52.1–94.9)	75.6 (53.3–97.8)
HDL-C, mg/dL	57.7 (26.2–89.2)	68.7 (36.3–101.2)	65.1 (31.3–98.8)
LDL-C, mg/dL	123.0 (60.4–185.7)	123.8 (61.36–186.2)	123.5 (61.1–181.0)
HbA1c	5.2 (3.9–6.5)	5.1 (4.2–6.0)	5.1 (4.0–6.2)
Glucose, mg/dL	94.3 (51.9–136.7)	88.8 (63.2–114.4)	90.6 (58.1–123.2)
Antihypertensive medication	598 (22.3)	843 (15.5)	1,441 (17.7)
Hypoglycemic medication	141 (5.3)	88 (1.6)	229 (2.8)
Insulin	14 (0.5)	14 (0.3)	28 (0.3)

Values are presented as the mean (reference range: mean -2 SD to mean $+2$ SD) or *n* (%).

BMI, body mass index; CAVI, cardio-ankle vascular index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

trained, calibrated dentists, who were randomly assigned to subjects. The same 2 dentists performed the dental examinations during the study period. During the oral examination, the number of missing teeth was counted. Congenitally missing and impacted teeth were excluded from the count of tooth loss. Third molars were excluded from counts of tooth loss, because third molars tend to be completely impacted or congenitally missing.

Statistical Analysis

Continuous variables are reported as means (reference range: mean -2 SD to mean $+2$ SD), and categorical variables are given as counts (percentages). The number of teeth showed right-skewed distributions and was therefore logarithmically transformed before analyses and back transformed to the original scale

when presented. We examined the association between CAVI and tooth loss using general linear models with adjustment for age, sex, BMI, smoking status, HbA1c, and a history of insulin or hypoglycemic medication depending on the model, having excluded the presence of multicollinearity. In addition, the models were compared with and without interaction terms. To investigate possible effect modification with sex, age, and tooth loss, we added interaction terms using the centered variables tooth loss, sex, and age (<60 and ≥ 60 years). We checked the linear relationship identified in this multiple regression model by visual examination of plots of standardized residuals.

Probability values of less than 0.05 were considered indicative of statistical significance. Statistical analyses were performed using the STATA version 11

software package (Stata Corp., College Station, TX).

Results

General Characteristics

Table 1 lists demographic information of the study participants, including data for the known risk factors of arteriosclerosis and tooth loss. The mean (reference range) age of the 8124 participants was 54.2 y (27.7–80.8 y), and 67.0% were women. Men were significantly older than women (56.0 [28.9–83.1] vs. 53.3 [27.2–79.4] y) and had a high prevalence of arteriosclerosis risk factors, including hypertension, diabetes, smoking status, and obesity. CAVI values were higher for men than for women (7.9 [5.4–10.3] vs. 7.2 [5.2–9.3], respectively). The mean

Table 2.

Multivariable Linear Regression Models for CAVI and Tooth Loss Adjusted for Age, Sex, BMI, Smoking Status, Hemoglobin A1c, a History of Insulin or Hypoglycemic Medication, and Interactions

	Unadjusted Model		Adjusted Model ^a			
			Model 1		Model 2	
	β	95% CI	β	95% CI	β	95% CI
Tooth loss	0.47	(0.45 to 0.50)	0.04	(0.02 to 0.06)	0.03	(0.01 to 0.06)
Sex	−0.65	(−0.70 to −0.60)	−0.48	(−0.53 to −0.43)	−0.48	(−0.53 to −0.43)
Age	0.06	(0.06 to 0.06)	0.06	(0.05 to 0.06)	0.06	(0.05 to 0.06)
Tooth loss × sex^b					0.05	(0.02 to 0.09)
Tooth loss × age category^c					−0.04	(−0.08 to 0.01)

Tooth loss was logarithmically transformed.

CAVI, cardio-ankle vascular index; CI, confidence interval; BMI, body mass index.

^aMultivariable linear regression analysis, adjusting for body mass index, smoking status, hemoglobin A1c, and a history of insulin or hypoglycemic medication.

^bSex (0: male, 1: female).

^cAge category (0: <60 years, 1: ≥60 years).

(reference range) tooth loss was higher in men 4.3 (0–18.3) than in women 3.2 (0–14.3).

Association between Tooth Loss and CAVI

Table 2 shows the results of the regression modeling for the association between tooth loss and CAVI, as reported by coefficient β (β) and 95% confidence intervals (CIs). For the unadjusted analysis, a significant relationship was detected between tooth loss and CAVI ($\beta = 0.47$; 95% CI, 0.45–0.50).

Multiple regression modeling after adjustment for age, sex, BMI, smoking status, HbA1c, and a history of insulin or hypoglycemic medication was also performed (model 1, Table 2). The adjusted multiple regression analysis detected a significant positive association between CAVI and tooth loss ($\beta = 0.04$; 95% CI, 0.02–0.06). As the residuals were randomly scattered around 0 (horizontal line) and exhibited a relatively even distribution, the association between CAVI and tooth loss appeared to be linear (data not shown).

Interaction Effects of Sex, Age, and Tooth Loss

We introduced the interaction between sex, age, and tooth loss in the multiple

regression analysis by examining the association between CAVI and tooth loss (model 2, Table 2). The analysis revealed that the relationship between CAVI and tooth loss differed depending on sex, with only men showing a positive correlation (β for interaction = 0.04; 95% CI, 0.02–0.06).

Discussion

The present large-scale epidemiologic study has identified that a significant positive correlation exists between tooth loss and arterial stiffness, even after adjustment for age, sex, and other confounding factors. Notably, we found an association between tooth loss and CAVI, although the association differed depending on sex. Our data provide evidence that oral disease and CVD may be positively related in men, who had higher rates of tooth loss and arterial stiffness than did women.

Previous reports examining the association between tooth loss and CVD have treated tooth loss as a nominal variable and have primarily focused on the presence or absence of CVD (Choe et al. 2009; Desvarieux et al. 2004). In contrast, here we treated both tooth loss and the primary outcome

of atherosclerosis, arterial stiffness, as numeric variables. Our analysis revealed that the severity of atherosclerosis is linearly related to tooth loss, which often results from the breakdown of periodontal tissue caused by periodontal disease. As tooth loss is a marker of current and long-term cumulative effects of periodontal disease (Desvarieux et al. 2003; Houshmand et al. 2012), our findings suggest that periodontal disease may play a role in the pathogenesis of atherosclerosis progression. In this study, we excluded noninflammatory reasons for tooth loss such as traumatic or orthodontic procedures, because we considered that noninflammatory tooth loss may bias the association between tooth loss and CAVI. However, we considered that the influence of excluding noninflammatory tooth loss on the findings from this study was not significant, because the number of individuals who were excluded for noninflammatory tooth loss was small.

Several potential mechanisms have been proposed in the literature for the association between periodontal disease, including tooth loss, and CVD. The findings from animal and epidemiologic studies suggest that infectious agents, including those associated with periodontal disease, increase

inflammatory cytokine production and platelet aggregation (Herzberg and Meyer 1996), which contribute to arteriosclerosis and thrombosis. In the present study cohort, age was the most important covariate for the relationship between tooth loss and arterial stiffness. Elderly people are more likely to develop periodontal disease and ensuing tooth loss, and they have increased arterial stiffness. We detected a positive association between tooth loss and CAVI and also found that the association differed depending on sex.

We investigated the factors of sex, age, and tooth loss as potential effect modifiers and found that sex that appeared to modify the association of interest. The identified sex difference in the association between clinical periodontal disease, tooth loss, and systemic disease has several potential explanations (Desvarieux et al. 2004; Demmer et al. 2008). Findings from clinical studies and laboratory research have suggested that estrogen is associated with beneficial cardiovascular effects in women (Kannel et al. 1976; Barrett-Connor and Bush 1991) as it reduces the development of atherosclerotic plaque. However, it is also possible that oral inflammation has little or no causal relationship with arteriosclerosis in women.

Progression of atherosclerosis is closely related with increased pulse pressure (Nichols et al. 1985; Sako et al. 2009), which therefore represents an important surrogate marker of arterial stiffness. Pulse pressure is a function of SBP and DBP (pulse pressure [P] = SBP – DBP) and was incorporated into the equation used to calculate CAVI as follows: $CAVI = a[(2p/\Delta P) \times \ln(SBP/DBP)PWV^2] + b$, where ΔP = SBP – DBP, p is blood density, a and b are constants to match aortic PWV. Therefore, pulse pressure is an independent determinant of CAVI (Okura et al. 2007). In CAVI, the rate of increase is reportedly approximately 0.05 per year (Shirai et al. 2011). In the present study, the coefficient β of the multiple regression analysis was 0.04; the loss of 5 teeth corresponds to the amount that CAVI increases in a 4-y period. This

finding suggests that the relationship between CAVI and tooth loss is clinically significant.

This study has several limitations that are inherent to cross-sectional analyses. First, the relationships reported here, while robust, should not be interpreted as causal. Our cross-sectional study design lacked information on the time sequence of events and therefore did not permit identification of causal relationships. To confirm the relationship between tooth loss and subclinical atherosclerosis, it is necessary to follow a cohort of middle-age adults until death. Second, we did not measure dietary habits. Increased tooth loss often leads to decreased masticatory performance and a change of dietary habit, which is related to risk factors of atherosclerosis, such as diabetes and hypertension. For this reason, we conducted multivariate analyses with adjustment for potential confounding factors, including hypertension and diabetes. Finally, information related to socioeconomic factors, such as education and income, were not collected in this cohort. Although previous studies have attempted to delineate the influence of socioeconomic differences on mortality, morbidity, and risk factors of disease, the Japanese population may not necessarily reflect the same pattern of relationships observed in other developed countries (Kagamimori et al. 2009). For example, an association between higher education and health is not strongly expressed among the Japanese population (Kagamimori et al. 2009; Lahelma et al. 2010). This may be partly due to the fact that a compulsory insurance system covers all people living in Japan, thereby minimizing differences in access to health care based on socioeconomic status.

In conclusion, our results suggest that the progression of atherosclerosis is linearly related to increased tooth loss and further strengthen the suggested association between these 2 factors. Notably, the age and sex differences in atherosclerosis prevalence seemed to be related to not only the distribution but also the differing contributions of oral inflammatory disease to atherosclerosis

across sexes. These findings have profound clinical and public health implications, as they provide further evidence that implementing strategies for preventing periodontal disease, which is both preventable and treatable, might help prevent atherosclerosis. Preventable and treatable contributors of CVD would add to the existing options available to clinicians and public health practitioners for the control of CVD. Educating patients in methods for preventing periodontal disease and improving personal oral hygiene is expected to benefit not only their oral but also their systemic health.

Author Contributions

K. Asai, contributed to conception and design, performed the experiments, contributed to data analysis, drafted manuscript; M. Yamori, contributed to conception and design, performed the experiments, drafted manuscript, initially revised manuscript; T. Yamazaki, contributed to conception and design, performed the experiments, contributed to data analysis, initially revised manuscript; A. Yamaguchi, S. Kosugi, contributed to conception and design, critically revised manuscript; K. Takahashi, contributed to conception and design, performed the experiments, critically revised manuscript; A. Sekine, contributed to conception and design, contributed reagents/materials/tools for analysis, critically revised manuscript; F. Matsuda, T. Nakayama, contributed to conception and design, performed the experiments, initially revised manuscript; K. Bessho, contributed to conception and design, critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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