Tertiary lymphoid structures are associated with favorable survival outcomes in patients with endometrial cancer

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Association Between Tooth Loss and Longitudinal Changes in B-Type Natriuretic Peptide Over 5 Years in Postmenopausal Women: The Nagahama Study

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Abstract: There is disparity between the sexes in cardiovascular diseases including heart failure (HF). This study aimed to investigate the effect of periodontal disease (PD) on plasma B-type natriuretic peptide (BNP) concentration across sex, age, and menopausal status, as well as the interaction effect of PD and diabetes mellitus (DM) on BNP. This large-scale prospective cohort study enrolled 7539 individuals with no myocardial infarctions or angina pectoris at baseline from the general Japanese population. The association between baseline number of missing teeth (MT) and the longitudinal changes in BNP over 5 years (ΔBNP) was evaluated according to sex and menopausal status. Among 7539 participants, 3190 were postmenopausal women with a mean age ± standard deviation of 61.1 ± 7.6 at baseline. Multivariate analysis revealed a positive association between MT and ΔBNP among postmenopausal women even after adjusting for covariates, including traditional HF risk factors (coefficient, 0.210; 95% confidence interval [CI], 0.107 to 0.312; $P < 0.001$), but not in men aged > 50. Including an interaction term (MT × DM) in the multivariate model revealed a positive interaction between MT and DM in ΔBNP among postmenopausal women (coefficient for interaction, 1.365; 95% CI, 0.902 to 1.827; P for interaction < 0.001). In conclusion, our study showed a positive association between MT and ΔBNP, as well as a positive effect of the interactive association between MT and DM, among postmenopausal women. Our results suggest a sex difference of an adverse effect of PD on initial myocardial wall stress in the ventricles. (Curr Probl Cardiol 2022;47:100997.)

Introduction

Heart failure (HF) is primarily a progressive disease whose prevalence and mortality/morbidity burden are increasing worldwide.[1,2] Since the prevention of HF from the early stage is

important[1], understanding its underlying mechanisms and high-risk groups is required. The overall lifetime risk of HF is fairly comparable between the sexes;[3] however, the pathophysiology of HF reportedly differs according to sex as well as menopausal status.[3–5] Accumulating evidence also suggests that women have higher risk of developing cardiovascular diseases (CVD) including HF associated with diabetes mellitus (DM) than men.[6–8]

Systemic inflammation produces pathophysiological changes, such as endothelial dysfunction or myocardial damage, that promote the development of CVD, including HF.[9–11] Periodontal disease (PD) is a common oral infection and is characterized by the accumulating burden of low-grade systemic inflammation or bacteremia, in addition to the consequent gradual destruction of tooth-supporting tissues.[12–14] Moreover, DM and PD are chronic diseases that mutually exacerbate one another's course with systemic inflammation.[15]

While the causal relationship between PD and CVD has not been delineated,[16] accumulating evidence suggests an association between PD and atherosclerotic disease, which is associated with CVD.[10,17–20] However, there is less evidence of mechanisms linking PD to CVD including HF, focused on the differences of sex and menopausal status.[21,22] Furthermore, because evidence regarding effective treatments especially for HF with preserved ejection fraction (HFpEF) (which more often occurs in older women) is scarce,[2,4,5] it is important to identify modifiable risk factors other than the currently known traditional risk factors (TRFs), such as DM and hypertension (HT).[2] This study aimed to investigate the effect of an association of the number of missing teeth (MT), which is indicative of the highest stage of PD,[13] on myocardial wall stress across sex, age, and menopausal status, as well as that of an interactive association between MT and DM.

We used plasma B-type natriuretic peptide (BNP) as our marker of myocardial wall stress.[2] BNP is an objective and sensitive biochemical marker of HF and cardiac hypertrophy,[23,24] and it is also a marker of asymptomatic ventricular dysfunction and an initial predictor of CVD[25,26] Thus, we conducted a large-scale prospective cohort study in Japanese general population on the association between MT, DM and the longitudinal changes in BNP over 5 years (ΔBNP) while adjusting for various confounders using data of individuals who had no myocardial infarctions or angina pectoris at baseline.

Methods

Study Design and Population

We analyzed a dataset generated by the Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study).[19] The Nagahama Study was a large-scale population-based prospective cohort investigation of a broad range of chronic illnesses conducted in Nagahama City, which is a large suburban city with 125,000 inhabitants in Shiga Prefecture, Japan. The participants in the Nagahama Study were recruited during the baseline period (from 2008 to 2010) from the general population from 30 to 73 years of age, living independently without physical impairment or dysfunction, were eligible. The follow-up data of the participants were collected 5 years after the baseline period.

Inclusion and Exclusion Criteria

Baseline Assessment. Among the 9804 participants, 14 withdrew their consent to participate in the study and 26 were excluded for having different ethnic backgrounds as determined by genetic analysis. Of the 9764 participants, we excluded 133 individuals who lacked clinical information required for this study. Additionally, individuals who reported a history of myocardial infarction or angina pectoris at baseline on their questionnaires ($n = 342$), a forced expiratory volume at 1 s $< 70\%$ ($n = 337$), severe renal functional decline (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) ($n = 10$), and pregnancy ($n = 31$) were excluded from the analysis because these factors are considered causative of an increase in BNP.

Follow-Up Assessment. 8289 of the original 9764 cohort members participated. After excluding 137 individuals who died and 279 individuals who had moved away from Nagahama City, the total follow-up rate was 88.7%. Among the 8911 participants who were assessed at baseline, 1344 did not participate in follow-up assessments. After excluding pregnant women ($n = 9$) as well as individuals who were undergoing hemodialysis ($n = 1$), those who had pacemakers ($n = 7$), those who did not complete the questionnaire on educational attainment level ($n = 10$), and those who lacked information on BNP ($n = 1$), a total of 7539 participants were ultimately included in the longitudinal analysis (Supplementary Fig. S1).

This study was conducted according to the principles of the Declaration of Helsinki and was approved by the ethics committee of Kyoto University Graduate School of Medicine and by the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.

Measurement of Plasma BNP at Baseline and the Follow-Up Period

Plasma for the assay was separated from blood samples collected in EDTA-2Na-treated tubes. Plasma BNP was measured using commercially available enzyme immunoassay kits (E Test TOSOH II "BNP;" Tosoh Corporation, Tokyo, Japan) with an automated analysis device (AIA-1800; Tosoh Corporation, Tokyo, Japan). Measurements were conducted by Shiga Health Research Center (Shiga, Japan); the detection limit was 4.0 (pg/mL). All values less than 4.0 were uniformly considered 4.0 pg/mL at both baseline and follow-up. ΔBNP was calculated by subtracting the value of BNP at baseline from that at the follow-up examination.

History of Myocardial Infarction or Angina Pectoris

The history of myocardial infarction or angina pectoris was assessed based on the response to the question "Do you have a history of myocardial infarction or angina pectoris?" on the structured, self-administered questionnaire.

Menopausal Status

Women were asked about menopausal status on the 2-choice question "Do you still have menstruation?" and were classified as premenopausal (those who answered "yes") or postmenopausal (those who answered "no").

Dental Parameters

Calibrated dentists from the Department of Oral and Maxillofacial Surgery of Kyoto University performed a clinical oral examination of all participants during the baseline period. Healthy, carious, or treated teeth (including dental crowns, dental inlays, and abutment teeth for prostheses) were enumerated to determine the number of present teeth; third molars were excluded. To determine MT owing to infections, such as PD or dental caries by oral bacteria, MT owing to extraction for orthodontic treatment as well as congenitally missing or impacted teeth (for which information was obtained from a clinical interview) were excluded. Previous studies have reported that most of the tooth extractions in adults were due to periodontal disease.[27,28]

Statistical Analyses

Characteristics were determined for all participants, and subgroup analyses were conducted according to sex, age, and menopausal status (for which participants were divided into four categories: men ≤50 years, men >50 years, premenopausal women, and postmenopausal women). The baseline MT were analyzed as either continuous, or categorical variables according to the following categories: MT = 0, 1≤ MT ≤4, and MT ≥5. The categories of MT were characterized by referring to the stage of periodontitis:[29] highest in MT ≥5, followed, respectively, by 1≤ MT ≤4 and MT = 0. Differences in numeric variables between the subgroups were determined using an analysis of variance. The chi-square test was used for categorical variables. Multiple comparisons were performed with Dunnett's method for adjusted means. Subgroup analyses of the association between MT and ΔBNP were conducted according to sex, age, and menopausal status. The association between MT and ΔBNP was analyzed using univariate analysis and a multivariate linear regression model while adjusting for age, body mass index, and educational attainment. Additionally, DM, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, cardio-ankle vascular index (CAVI), eGFR, the Brinkman index, alcohol intake, total protein level, physical activity, and estrogen therapy (only for women) were added to the multivariate model. Furthermore, interaction analyses were conducted to determine the influence of the interactions between MT and DM, and MT and glycosylated hemoglobin (HbA1c) ≥6.0 for a sensitivity analysis, on the ΔBNP. A two-tailed P-value < 0.05 was considered indicative of statistical significance. All statistical analyses were performed using the JMP 14.0 statistical software (SAS Institute).

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for the analysis of observational data were followed in this study.

Additional descriptions of the measurements of other patient characteristics and statistical analyses are provided in the Online Data Supplement.

Results

In total, 9804 participants were recruited in this prospective cohort study. Among them, 7539 participants were included in the longitudinal analysis (Supplementary Fig. S1 and Supplemental Methods). The mean ± SD follow-up interval was 1815 ± 134 days. The mean ± SD ΔBNP of all participants during this period was 4.7 ± 17.3 (pg/mL) (Supplementary Table S1).

Differences in Factors According to Sex, Age, and Postmenopausal Status

Comparisons of factors analyzed as a function of sex, age, and menopausal status are shown in Table 1. The mean ΔBNP and the number of baseline MT were highest in men aged >50, followed by postmenopausal women. Regarding comorbidities and the participants' general condition, the level of HT, brachial-to-ankle pulse wave velocity (baPWV), CAVI, and frequency of DM were highest in men aged >50, followed by postmenopausal women; meanwhile, LDL cholesterol was highest in postmenopausal women followed by men aged ≤50. The follow-up median BNP exceeded the upper normal limit (18.4 pg/mL)[30] in postmenopausal women (Table 1).

Association Between Baseline MT and Baseline Inflammatory Markers

Fig. 1 shows age-, sex-, and BMI-adjusted mean values of log high-sensitive C-reactive protein (hs-CRP), alpha-1 antitrypsin, and monocyte count. These values were higher in the MT ≥5 groups than in the MT = 0 groups. In the multivariate model, MT showed an independent positive association with alpha-1 antitrypsin in women, and in men aged ≤50 after adjustment for TRFs, whereas, MT showed an independent positive association with log hs-CRP in men aged >50 (Supplementary Table S2).

Association Between Baseline MT and ΔBNP as a Function of Sex, Age, and Menopausal Status

In postmenopausal women and men aged >50, the association between MT and ΔBNP, baseline, and follow-up log BNP showed linear correlations, and the difference in ΔBNP between the MT = 0 and MT ≥5 groups was the largest in postmenopausal women (Supplementary Table S3, Supplementary Figs. S2 and S3). A crude analysis of all participants (coefficient, 0.258; 95% confidence interval [CI], 0.189 to 0.328; P <0.001) revealed a positive association between MT and ΔBNP (Table 2, Model 1). Subgroup analyses across sex, age, and menopausal status revealed a significant positive association between MT and ΔBNP in postmenopausal women (coefficient, 0.240; 95% CI, 0.144 to 0.337; P <0.001), but not in men aged >50 (coefficient, 0.057; 95% CI, -0.121 to 0.236; P =0.528) (Table 2, Model 1). Model 1 was progressively adjusted by adding the covariates. Notably, the positive association between MT and ΔBNP among postmenopausal women observed using Model 1 was

TABLE 1. Clinical and demographic characteristics of study participants categorized by sex, age, and menopausal status (n = 7,539)

	Men (age ≤ 50 y) (*n* = 779)	Men (age > 50 y) (*n* = 1,508)	Premenopausal women (*n* = 2,062)	Postmenopausal women (*n* = 3,190)	*P*-value
Number of missing teeth	0.5 ± 1.5	5.3 ± 7.3	0.5 ± 1.2	4.4 ± 6.1	< 0.001
Age (years)	38.5 ± 5.6	63.9 ± 6.0	39.7 ± 6.4	61.1 ± 7.6	< 0.001
Body mass index (kg/m^2)	23.6 ± 3.6	23.4 ± 2.8	21.0 ± 3.2	22.2 ± 3.1	< 0.001
Years of education	13.8 ± 2.3	12.2 ± 2.6	13.4 ± 1.7	11.7 ± 2.1	< 0.001
Physical activities (%)	48.5	59.6	35.7	60.7	< 0.001
Alcohol consumption (Go)	1.2 ± 1.3	1.3 ± 1.1	0.3 ± 0.7	0.2 ± 0.6	< 0.001
Brinkman index	241.3 ± 243.0	489.2 ± 437.7	39.2 ± 101.8	18.5 ± 87.4	< 0.001
Baseline BNP (pg/mL)	6.1 (5.8)	13.9 (14.7)	10.5 (9.6)	15.2 (15.3)	< 0.001
Follow-up BNP (pg/mL)	8.2 (7.8)	18.3 (18.5)	12.9 (11.4)	19.6 (18.6)	< 0.001
ΔBNP (pg/mL)	2.0 ± 7.8	7.5 ± 25.9	2.8 ± 11.1	5.4 ± 16.9	< 0.001
LDL cholesterol (mg/dL)	125.9 ± 32.3	122.7 ± 29.7	110.6 ± 28.1	132.3 ± 29.7	< 0.001
Log hs-CRP (mg/dL)	-1.1 ± 1.2	-0.8 ± 1.1	-1.6 ± 1.2	-1.1 ± 1.1	< 0.001
Alpha-1 antitrypsin (mg/dL)	126.5 ± 17.9	131.3 ± 19.2	132.6 ± 17.8	130.9 ± 17.8	< 0.001
Monocytes (%)	5.3 ± 1.4	5.4 ± 1.4	5.0 ± 1.4	4.7 ± 1.2	< 0.001
Total protein (mg/dL)	7.3 ± 0.4	7.3 ± 0.4	7.3 ± 0.4	7.4 ± 0.4	< 0.001
HbA1c (%)	5.3 ± 0.6	5.6 ± 0.6	5.3 ± 0.3	5.5 ± 0.5	< 0.001
Diabetes mellitus (%)	1.4	8.7	0.4	2.6	< 0.001
HbA1c ≥ 6.0% (%)	3.3	14.9	1.5	7.8	< 0.001
Systolic blood pressure (mmHg)	123.6 ± 12.3	132.6 ± 16.4	111.4 ± 13.2	125.7 ± 17.1	< 0.001
Hypertension (%)	17.3	53.2	6.6	35.1	< 0.001
baPWV (cm/s)	1149.9 ± 111.3	1397.6 ± 379.5	1087.0 ± 111.7	1324.7 ± 200.0	< 0.001
CAVI	6.8 ± 0.7	8.3 ± 1.0	6.4 ± 0.7	7.6 ± 0.9	< 0.001
eGFR (mL/min/1.73 m^2)	85.2 ± 12.5	72.1 ± 13.1	88.7 ± 15.3	75.4 ± 13.6	< 0.001
Antihypertensive drug use (%)	3.1	30.8	1.7	20.9	< 0.001
Lipid-lowering medication use (%)	3.5	13.5	1.3	19.2	< 0.001
Antihyperglycemic drug use (%)	0.6	6.6	0.2	2.2	< 0.001
Estrogen therapy (%)	NA	NA	9.2	8.0	0.147

Note. Values are presented as mean ± standard deviation, median (interquartile range), or frequency. Diabetes mellitus was defined as a glucose level of ≥ 126 mg/dL (fasting: ≥ 6 h) or ≥ 200 mg/dL (nonfasting), HbA1c ≥ 6.5%, or antihyperglycemic treatment. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg or antihypertensive drug use. Alcohol consumption was obtained using Japanese traditional units of alcohol (Go/day), where 1 Go corresponds to 22 g of ethanol. The values at baseline are shown, except ΔBNP and follow-up BNP. BNP, B-type natriuretic peptide; ΔBNP, longitudinal changes in BNP over 5 years; LDL cholesterol, low-density lipoprotein cholesterol; Log hs-CRP, log-transformed high-sensitive C-reactive protein; HbA1c, glycosylated hemoglobin; baPWV, brachial-to-ankle pulse wave velocity; CAVI, cardio-ankle vascular index; eGFR, estimated glomerular filtration rate; NA, not applicable.

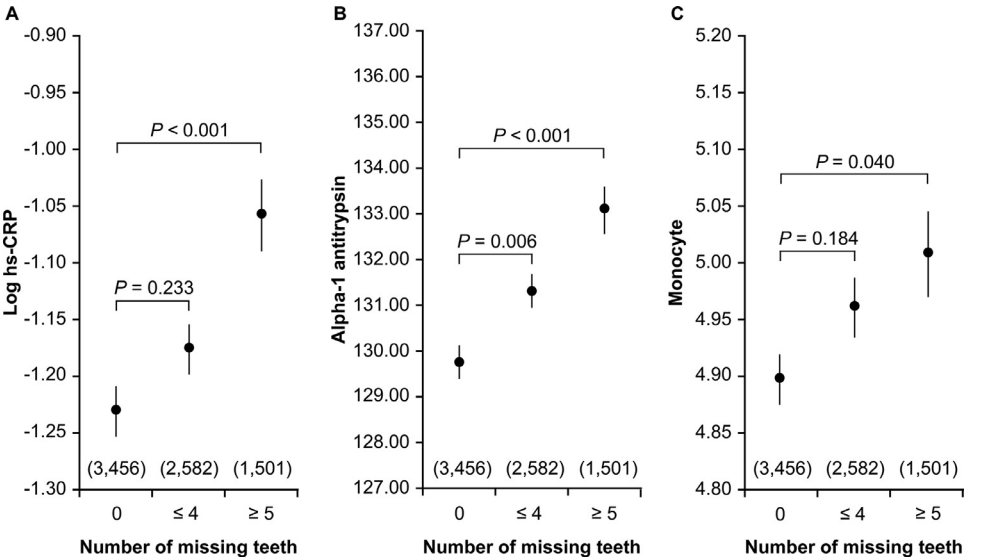

FIG 1. Association between the baseline MT and baseline inflammatory markers.

Values are presented as the adjusted mean ± standard error. Participants were divided into three groups by MT; MT = 0, $1 \leq MT \leq 4$ and $MT \geq 5$ groups. "≤ 4" of the horizontal axis represents $1 \leq MT \leq 4$. Adjusted factors were age, sex, and body mass index. The number of participants in each subgroup is shown in parentheses. A: Association between MT and log hs-CRP. B: Association between MT and alpha-1 antitrypsin. C: Association between MT and monocyte. MT: number of missing teeth; Log hs-CRP: log-transformed high-sensitive C-reactive protein.

TABLE 2. Association between the baseline number of missing teeth and ΔBNP categorized by sex, age, and menopausal status

	Model 1		Model 2		Model 3	
Number of missing teeth	**Coefficient (95% CI)**	***P*-value**	**Coefficient (95% CI)**	***P*-value**	**Coefficient (95% CI)**	***P*-value**
All	0.258 (0.189 to 0.328)	< 0.001	0.139 (0.061 to 0.216)	0.001	0.131 (0.053 to 0.209)	0.001
Men (age ≤ 50 years)	-0.186 (-0.560 to 0.188)	0.330	-0.170 (-0.559 to 0.219)	0.390	-0.207 (-0.605 to 0.192)	0.309
Men (age > 50 years)	0.057 (-0.121 to 0.236)	0.528	0.021 (-0.163 to 0.205)	0.820	< 0.001 (-0.188 to 0.188)	1.000
Premenopausal women	0.100 (-0.299 to 0.498)	0.623	0.055 (-0.361 to 0.471)	0.795	0.025 (-0.396 to 0.446)	0.907
Postmenopausal women	0.240 (0.144 to 0.337)	< 0.001	0.214 (0.112 to 0.317)	< 0.001	0.210 (0.107 to 0.312)	< 0.001

Note. Model 1 was crude analysis. Model 2 added age, body mass index, and years of education, and sex (for only analyses of all) to Model 1. Model 3 added physical activities, alcohol consumption, Brinkman index, diabetes mellitus, systolic blood pressure, cardio-ankle vascular index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, total protein, and estrogen therapy (for only women) to Model 2. The explanatory variable and adjusted variables are all baseline period data. Full results of the Model 3 regression analyses are shown in Supplementary Table S4. Coefficient: unstandardized regression coefficient. CI, confidence interval; BNP, B-type natriuretic peptide; ΔBNP, longitudinal changes in BNP over 5 years.

preserved when using Model 2 (coefficient, 0.214; 95% CI, 0.112 to 0.317; P <0.001) and Model 3 (coefficient, 0.210; 95% CI, 0.107 to 0.312; P <0.001) (Models 2 and 3; Table 2 and Supplementary Table S4). A multivariate analysis among postmenopausal women and men aged >50 revealed an interactive association between sex and MT on ΔBNP (coefficient for interaction, -0.196; 95% CI, -0.380 to -0.013, P for interaction = 0.036 using postmenopausal women as the reference) (Supplementary Table S5).

Effect of the Interaction Between Baseline MT and DM on ΔBNP in Postmenopausal Women

An interaction term (MT × DM) was added to Model 3 (Table 2). This analysis showed a positive interactive association between MT and DM in postmenopausal women (coefficient for interaction, 1.365; 95% CI, 0.902 to 1.827; P for interaction <0.001) (Model 1; Table 3). The interactive association was also seen when an interaction term (MT × HbA1c ≥6.0) was added instead (coefficient for interaction, 1.139; 95% CI, 0.837 to 1.441; P for interaction <0.001) (Model 2; Table 3).

Discussion

Our large-scale, 5-year longitudinal study of the general population was the first report to show an independent positive association between MT and increase in BNP over 5 years, as well as an interactive association between MT and DM among postmenopausal women without a history of myocardial infarction and angina pectoris at baseline. Given that the early detection and prevention of HF are important, these results may be useful for advancing the understanding of the initial adverse effect of inflammation of PD on myocardium wall stress in the ventricles, one of the pathophysiological characteristics of HF.[9,31]

Several previous studies reported that periodontitis or edentulousness is associated with atherosclerotic disease, such as CVD or HT, in postmenopausal women.[22,32] Our finding of an association between MT and an increase in BNP among postmenopausal women may detect more detailed early changes of myocardial wall stress. The present findings added novel evidence of long-term prospective population-based changes in BNP and the corresponding differences according to sex, age, and menopausal status to previous data showing that the greater the extent of periodontal destruction, the higher the levels of N-terminal-pro-BNP in the serum.[33] Our multivariate analyses revealed the sex differences of the

TABLE 3. Multivariable linear regression models including each interaction term (Number of missing teeth × DM or Number of missing teeth × HbA1c ≥ 6.0%) for ΔBNP in women

	Model 1 (Number of missing teeth × DM)		Model 2 (Number of missing teeth × HbA1c ≥ 6.0%)	
	Coefficient for interaction (95% CI)	*P*-value	Coefficient for interaction (95% CI)	*P*-value
All women (n = 5,252)	1.329 (0.931 to 1.726)	< 0.001	1.115 (0.856 to 1.374)	< 0.001
Premenopausal women (n = 2,062)	-0.159 (-4.073 to 3.756)	0.937	-0.889 (-3.458 to 1.679)	0.497
Postmenopausal women (n = 3,190)	1.365 (0.902 to 1.827)	< 0.001	1.139 (0.837 to 1.441)	< 0.001

Note. DM was defined as a glucose level of ≥ 126 mg/dL (fasting: ≥ 6 h) or ≥ 200 mg/dL (nonfasting), HbA1c ≥ 6.5%, or antihyperglycemic treatment. Adjusted factors were age, body mass index, years of education, physical activities, alcohol consumption, Brinkman index, systolic blood pressure, cardio-ankle vascular index, estimated glomerular filtration rate, low-density lipoprotein cholesterol, total protein, and estrogen therapy. Model 1; including an interaction term (Number of missing teeth × DM). Model 2; including an interaction term (Number of missing teeth × HbA1c ≥ 6.0%). DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; Coefficient: unstandardized regression coefficient; CI, confidence interval; ΔBNP, longitudinal changes in BNP over 5 years.

association between MT and ΔBNP after adjusting for confounders and TRFs. The effects of PD inflammation on the myocardium in men may have a mechanism different from the changes that appear as a slight increase in BNP over the passing of several years. In our previous study of the same cohort, we evaluated the sex-based differences in MT and large vessel atherosclerosis using CAVI; PD and large vessel atherosclerosis were found to be positively correlated among men, who had higher rates of arterial stiffness than women did.[19] A key reason for the differences according to sex may be attributable to the predisposition to macrovascular coronary artery disease and myocardial infarction.[3] Meanwhile, coronary microvascular dysfunction/endothelial inflammation resulting in fibrosis of the myocardium are related to cardiac hypertrophy, which raises the risk of future HF;[9,11,34] in particular, the condition has been demonstrated to play a key role in HFpEF among postmenopausal women.[3,4] Furthermore, given that an early subtle elevation in intracardiac pressure can be picked up by BNP before left ventricular abnormalities are either present or detectable on imaging,[26] our study might have detected the sex differences of an early change of the ventricles that resulted from PD inflammation. Our present results indicate a similar tendency to a previous study demonstrating that there is an association between the number of teeth and left ventricular mass by echocardiography in women aged 45−79 years.[35] To further understand the abovementioned sex-based differences, additional studies that confirm clinical diagnoses of HF are needed.

Levels of inflammatory markers including the monocytic proinflammatory cytokines tumor necrosis factor-α and interleukin-6 are reportedly elevated during PD inflammation.[14,36,37] Furthermore, those markers have direct negative effects on the myocardium and increase capillary permeability while inducing endothelial dysfunction, fibrosis, and myocardial hypertrophy.[11,34,38,39] *Porphyromonas gingivalis* produces lipopolysaccharides (LPS) and is one of the most important pathogenic bacterial species implicated in adult periodontitis.[13,36,39] It additionally contains a protease called gingipain that degrades proteins to obtain the peptides and amino acids necessary for the survival of the bacteria, and also enables bacterial suppression of the immune response against LPS.[13,36] A previous study reported that alpha 1-antitrypsin, an antimicrobial peptide and a major inhibitor of serine proteases, was detected in gingival crevicular fluid.[37] In our research, we confirmed that inflammatory markers, especially serum alpha-1 antitrypsin, showed a positive correlation with MT, suggesting that MT is associated with systemic inflammation. Previous study showed the possibilities that oxidized alpha-1 antitrypsin may

contribute to endothelial dysfunction, which it is known to occur in HF.[40] Meanwhile, estrogen maintains vascular protection through mechanisms such as the suppression of LDL cholesterol synthesis, maintenance of endothelial NO activity, inhibition of the renin-angiotensin-aldosterone system, and promotion of other general anti-inflammatory effects.[4,41] MT and ΔBNP showed a significant positive association in postmenopausal women; this might have been associated with a reduction in estrogen secretion,[4] whereas the myocardium was protected by estrogen from inflammation due to PD and other TRFs in premenopausal women. Further long-term follow-up studies are needed to evaluate the differences between pre- and postmenopausal women.

Previous studies showed that DM was more associated with increase in the risk of incident HF in women than in men, even after adjustment for other cardiovascular risk factors.[7,42] The evidence for independent associations between periodontitis and type 2 diabetes is established, with bidirectional influence characterized by systemic inflammation and insulin resistance.[15] Furthermore, the previous study showed the effect of periodontal treatment on the formation of mitochondrial oxidative stress in patients with type 2 diabetes.[43] Diabetic cardiomyopathy is initially characterized by myocardial fibrosis and hypertrophy, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical HF.[44] The present finding of an interactive association between MT and DM with an increase in BNP in postmenopausal women may be partly related to diabetic cardiomyopathy mediated by cardio-myocyte stress, from the viewpoint of the interactive adverse effect of long-term chronic inflammation of PD and DM. A previous study using echocardiography, which provided evidence that nonsurgical periodontal therapy may improve cardiac diastolic function in type 2 diabetic patients with periodontitis,[45] may support our results. The present results emphasize the importance of comprehensive risk management in the collaboration between dental and medical sciences.[17] Furthermore, our results, which identified one of the groups with a high risk of myocardial wall stress in the general population, also provide a direction for future studies including the preventive intervention, which might eventually lead to more personalized care.

Study Limitations

We could not rule out the presence of other diseases that directly affect BNP concentration, such as congenital and valvular heart diseases, cardiomyopathy, or paroxysmal atrial fibrillation. We did not take under

consideration the use of some anti−inflammatory drugs, such as statins. We could not rule out the impact of osteoporosis on our findings. Although this condition is not the main cause of periodontitis, postmenopausal women are likely to have low bone mineral density and bone loss of the jaw.[46] However, the sensitivity analysis adjusting for bone density and for the use of therapeutic drugs to treat osteoporosis, did not materially change the primary findings in our multivariate model (data not shown). To further explore this, additional analyses considering not only bone density but also bone quality (jawbone data are desirable) are required. Our study used some questionnaire-based data; hence, there existed the possibility of self-reporting bias. Furthermore, the generalizability of the present findings to other populations may be limited. The possibility of residual confounders including life-long gender-related non-biological characteristics (attitudes or social roles), such as chronically worse access to medical care, also remains.

Conclusions

Our study showed that tooth loss was associated with an increase in BNP over 5 years, as well as a positive interactive association between MT and DM, among postmenopausal women in the Japanese general population. These findings suggest that chronic inflammation owing to PD might be partly associated with the myocardial wall stress in the ventricles in postmenopausal women, especially those with a history of DM. Further observational and interventional studies are required to clarify the benefits of oral hygiene in preventing HF.

Author's Contributions

Shizuko Fukuhara: Contributed to the conception, design, and data acquisition and interpretation; performed statistical analyses and interpretation; and drafted and critically reviewed the manuscript.

Keita Asai: Contributed to the conception, design, and data acquisition and interpretation; performed statistical analyses and interpretation; and critically reviewed the manuscript.

Takehisa Fukuhara: Contributed to the conception, design, and data interpretation; and critically reviewed the manuscript.

Asumi Kakeno: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Shigeki Yamanaka: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Kazumasa Nakao: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Takuma Watanabe: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Katsu Takahashi: Contributed to conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Toru Yamazaki: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Chisa Umebachi: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Marina Kashiwagi: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Kazuya Setoh: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Takahisa Kawaguchi: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Yasuharu Tabara: Contributed to data acquisition, funding acquisition, conception and design of the Nagahama prospective cohort study.

Satoshi Morita: Contributed to the conception, design, data interpretation, statistical analysis, and data interpretation; and critically reviewed the manuscript.

Takeo Nakayama: Contributed to the conception, design, and data acquisition and interpretation; and critically reviewed the manuscript.

Fumihiko Matsuda: Contributed to data acquisition, funding acquisition, conception and design of the Nagahama prospective cohort study.

Kazuwa Nakao: Contributed to the conception, design, and data interpretation; and critically reviewed the manuscript.

Kazuhisa Bessho: Contributed to the conception, design, and data interpretation; and critically reviewed the manuscript.

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Conflicts of interests for unrelated projects

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100997.

Appendix

The Nagahama Study group executive committee comprises the following individuals: Yasuharu Tabara, Takahisa Kawaguchi, Kazuya Setoh, Yoshimitsu Takahashi, Shinji Kosugi, Takeo Nakayama, and Fumihiko Matsuda from the Center for Genomic Medicine, Kyoto University Graduate School of Medicine (Ya.T, T.K., K.S., F.M.); Department of Health Informatics (Yo.T, T.N.), and Department of Medical Ethics and Medical Genetics (S.K.), Kyoto University School of Public Health.

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