



Association between total type I collagen N-terminal propeptide and coronary artery disease risk score in the general Japanese population

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ABSTRACT

Background: Bone metabolic dysregulation plays an important role in the pathogenesis of atherosclerosis; however, whether its markers contribute to coronary artery disease (CAD) risk in the general population remains unclear. Therefore, this study aimed to analyze the association between bone metabolic markers and CAD risk score in the general Japanese population.

Methods: The Iwate Medical Megabank Organization collected individual participant data during a community-based cohort study in the Iwate prefecture (n = 5,095, age = 58.9 ± 12.4 years). Participants with osteoporosis, chronic kidney disease, malignant disease, or primary wasting disease were excluded from the study. The present study measured the levels of circulating bone metabolic markers, including total type I collagen N-terminal propeptide (TP1NP), bone-type alkaline phosphatase, cross-linked N-telopeptide of type 1 collagen (NTX), and intact parathyroid hormone. CAD risk and atherosclerosis were evaluated using the Suita score and brachial-ankle pulse wave velocity (baPWV) measurement, respectively.

Results: Among the bone metabolic markers, TP1NP was strongly associated with a high Suita score (≥56 points) (OR = 0.77, 95% CI = 0.69–0.82, P < 0.001). When participants were divided into quartiles of TP1NP levels, the subgroup with the lowest TP1NP level was associated with a high Suita score (≥56 points) and high baPWV (>1,400 cm/s).

Conclusions: This study demonstrated that TP1NP levels decreased in participants with high Suita scores and high baPWV, suggesting that TP1NP downregulation may indicate future CAD risk and atherosclerosis progression in the general Japanese population.

1. Introduction

Recently, the prevalence of coronary artery disease (CAD) has been rapidly increasing [1]. In addition, mortality due to CAD was more than twice that due to malignancy [1]. It has been reported that classical CAD risk factors, such as aging, smoking, alcohol consumption, menopause, and lack of exercise, promote bone loss and bone quality deterioration, and induce the progression of atherosclerosis, suggesting that there is a

relationship between abnormal bone metabolism and the development of atherosclerosis [2]. One of the indicators of atherosclerosis is bilateral brachial-ankle pulse wave velocity (baPWV), which has been used to predict cardiovascular disorders (CVDs) and subsequent prognosis [3]. Constituent bone cells, such as osteocytes and osteoblasts, secrete osteocalcin and fibroblast growth factors, which were shown to affect atherosclerosis progression and carbohydrate metabolism [4]. In addition, the increased calcium and phosphorus release from bone associated

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with bone resorption was thought to cause vascular calcification and promote atherosclerosis [5]. These reports suggest that abnormal bone metabolism may play an essential role in the development of atherosclerosis. Bone metabolic turnover could be assessed by measuring bone formation markers (bone-type alkaline phosphatase [BAP], total N-terminal propeptide of type I collagen [TP1NP]), and bone resorption markers (cross-linked N-telopeptide of type 1 collagen [NTX]) in blood [6]. A previous study involving elderly persons reported an increase in mortality as bone metabolic turnover increases [7]. However, it has been uncertain whether circulating bone metabolic markers were associated with CAD risk and atherosclerosis progression in the general Japanese population, particularly among individuals without osteoporosis. Therefore, this study aimed to identify the relationship between bone metabolic markers and CAD risk on the basis of the Suita score in the Tohoku Medical Megabank Organization Community Cohort Study (TMM CommCohort Study).

2. Methods

2.1. Study population

TMM CommCohort Study was a community-based adult cohort study of people living in the Iwate prefecture of East Japan [8,9]. Participants were recruited to the TMM CommCohort Study between May 2013 and March 2016 [8,9]. Details of the study design and protocol were reported previously [8,9]. The present study population comprised participants (over 20 years old) who were living in the Iwate prefecture and recruited by the Iwate Medical University Iwate Tohoku Medical Megabank Organization (IMM). In this cohort, young adult mean (YAM) and bone metabolism markers were measured in 6,997 participants. Among them, 1,902 participants who had osteoporosis, chronic kidney disease (CKD), any malignancy, primary wasting disease, or denta deficiency were excluded from the present analysis. Osteoporosis was defined as a YAM of < 80%, history of fracture, and history of treatment for osteoporosis [10]. CKD was defined as eGFR < 60 ml/min/1.73 m² and the presence of proteinuria [11]. A total of 5,095 participants were finally analyzed (HGH25–2, HG2018-004). The study was approved by the Ethics Committee of Iwate Medical University. Informed consent was obtained from all participants.

2.2. Collection of clinical data

Data on sociodemographic factors and lifestyle, including smoking and medical histories of stroke or CAD, were collected using self-administered questionnaires. Experienced physicians or nurses registered age and gender using participants' insurance cards as well as measured their height, weight, blood pressure, and heart rate and performed physiological tests, such as electrocardiography. Fasting and nonfasting blood samples were collected from participants. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, having been diagnosed with hypertension, and/or using hypotensive drugs [12]. Diabetes mellitus was defined as a glycated hemoglobin (hemoglobin A1c) level of $\geq 6.5\%$, nonfasting blood glucose of ≥ 200 mg/dL, having been diagnosed with diabetes mellitus, and/or being treated with antidiabetic drugs such as insulin [13]. Dyslipidemia was defined as a low-density lipoprotein (LDL) cholesterol level of ≥ 140 mg/dL, having been diagnosed with dyslipidemia, and/or using antidiabetic agents [14].

2.3. Measurements of bone metabolic makers

Samples were centrifuged, and the upper serum phases were collected and frozen at -80 °C before the assays. Serum samples from participants were used to measure TP1NP, BAP, NTX, and intact parathyroid hormone (PTH int) levels. Serum levels of TP1NP were measured by electrochemiluminescence immunoassay using a Cobas

411 analyzer (Roche Diagnostics K.K., Tokyo, Japan). The detectable range of the TP1NP assay was 5 to 1200 ng/ml. Serum BAP level was determined using an enzyme-linked immunosorbent assay kit (Immunodiagnostic Systems, Tyne & Wear, UK) with a detection sensitivity of 1.0 μ g/l. PTH level was measured using an intact assay using a chemiluminescent method (Abbott i2000, TX, USA). The lower detection threshold of the PTH int assay was 1 pg/ml. Serum NTX levels were determined by a fully automated enzyme-linked immunosorbent assay (ELISA) using Osteomark NTx Serum ELISA Test Kits (Alere Inc., Seattle, WA).

2.4. Evaluating the estimated risk of CAD

The estimated CAD risk was calculated using the Suita score. The Suita score includes age, sex, smoking history, blood pressure, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, impaired glucose tolerance, and CKD stage [15]. Participants with a total score of 56 or higher were defined as high risk for CAD because they had a predicted probability of CAD of 9 % or higher at 10 years. It has been reported that the Suita score was more sensitive than the Framingham score in calculating the risk of CAD in the Japanese population [15].

2.5. Physiological examinations

Bilateral brachial–ankle pulse wave velocity (baPWV) was evaluated by utilizing BP-203RPE III (Omron Corporation, Kyoto, Japan). The details of the device and its use were explained, and its clinical relevance and good reproducibility were confirmed. [16]. All examinations were performed by specially trained physicians and nurses. The cutoff value for baPWV was set at $> 1,400$ cm/s. [17]. We measured the YAM using dual-energy X-ray absorptiometry (DXA) [18].

2.6. Statistical analysis

Numerical variables are expressed as mean \pm standard deviation in the case of normal distribution and median (interquartile range) in the case of skewed distribution. Categorical data are indicated in frequencies and percentages. The correlation between the two variables was assessed using Pearson's correlation coefficient. Binomial logistic regression analysis was performed to clarify the association between the Suita score high-risk group and each bone metabolic marker. The distribution of bone metabolic marker was classified by quartiles. The basic attributes were compared among the four groups using analysis of variance in the case of normal distribution and Kruskal–Wallis test in the case of skewed variables. Intergroup differences in demographic parameter proportions were examined using the chi-squared test. We performed a logistic regression analysis to identify the association between quartiles of TP1NP and factors associated with CAD high-risk and baPWV ($> 1,400$ cm/s). All data were analyzed using IBM SPSS Statistics version 25 for Windows (IBM Corp., Armonk, NY, USA). Differences of $p < 0.05$ were considered to be statistically significant.

3. Results

3.1. Baseline characteristics of the study population

The baseline characteristics of the study population are shown in Table 1. The median Suita score was 42 points, and the median baPWV was 1,429 cm/s (Table 1).

3.2. Association of bone metabolic markers with a CAD high-risk group

Association between a CAD high-risk subgroup (Suita score ≥ 56) and bone metabolic markers including TP1NP, BAP, NTX, and PTH int is shown in Table 2. TP1NP level was negatively associated with the CAD high-risk subgroup (Suita score ≥ 56) (odds ratio (OR) = 0.77, 95%

Table 1
Characteristics of analyzed participants.

Number	5,095
Age	58.9 ± 12.4
Female, n (%)	2,939 (57.7)
Smoker, n (%)	2,076 (40.7)
Diabetes mellitus, n (%)	612 (12.0)
Dyslipidemia, n (%)	1,794 (35.2)
Hypertension, n (%)	1,445 (28.4)
Stroke, n (%)	112 (2.2)
Coronary artery disease, n (%)	108 (2.1)
BMI ^a (kg/m ²)	23.8 ± 3.6
Systolic BP ^b (mmHg)	128.3 ± 20.0
Diastolic BP ^b (mmHg)	74.7 ± 11.7
baPWV ^c (cm/s)	1,429 (1,231–1,691)
Suita score, points	42 (30–51)
Total cholesterol (U/L)	208.0 ± 34.7
Triglyceride (U/L)	110.3 ± 71.6
HDL ^d -cholesterol (U/L)	62.9 ± 15.3
LDL ^e -cholesterol (U/L)	116.4 ± 29.3
Creatinine (mg/dl)	0.69 ± 0.15
eGFR ^f (ml/min/1.73 m ²)	79.2 ± 15.1
Uric acid (mg/dl)	5.1 ± 1.3
Corrected calcium (mg/dl)	9.4 ± 0.3
Phosphorus (mg/dl)	3.5 ± 0.6
Hemoglobin (g/dl)	13.9 ± 1.4
Hemoglobin A1c (%)	5.5 ± 0.6
NT-proBNP ^g (pg/mL)	44 (27–73)
TP1NP ^h (ng/mL)	43.9 (33.3–58.1)
BAP ⁱ (μg/L)	12.1 (9.7–15.2)
NTX ^j (nM BCE/L)	13.9 (11.6–16.9)
PTH int ^k (pg/mL)	47 (38–57)

Values are expressed as mean ± SD or median (25%–75%) or number of subjects (percentage).

^a Body mass index; ^b blood pressure; ^c brachial-ankle pulse wave velocity; ^d high-density lipoprotein; ^e low-density lipoprotein; ^f estimated glomerular filtration rate; ^g N-terminal fragment of pro-B-type natriuretic peptide; ^h total procollagen type I intact N-terminal propeptide; ⁱ bone-specific alkaline phosphatase; ^j cross-linked N-telopeptide of type I collagen; ^k parathyroid hormone, intact.

Table 2
Association between Suita score (≥56 points) and bone metabolic markers, as estimated using a binomial logistic regression analysis.

Variable	OR 95%CI	P value
TP1NP ^a (ng/mL)	0.77 (0.69–0.82)	<0.001
BAP ^b (μg/L)	1.12 (1.09–1.14)	<0.001
NTX ^c (nM BCE/L)	0.99 (0.97–1.01)	0.417
PTH int ^d (pg/mL)	0.98 (0.98–0.99)	<0.001

^aTotal procollagen type I intact N-terminal propeptide; ^bbone-specific alkaline phosphatase; ^ccross-linked N-telopeptide of type I collagen; ^dparathyroid hormone, intact.

confidence interval (CI) = 0.69–0.82, P < 0.001).

3.3. Quartiles of bone metabolic markers

The baseline characteristics of the study population in the quartiles of TP1NP (Q1 < 33.3 ng/mL, Q2: 33.3–43.8 ng/mL, Q3: 43.9–58.1 ng/mL, Q4 > 58.1 ng/mL) are shown in Table 3. There were significant differences in age, sex, history of smoking, history of diabetes, history of CAD, body mass index (BMI), SBP, DBP, baPWV, Suita score, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, creatinine, uric acid, corrected calcium, phosphorus, hemoglobin, hemoglobin A1c, and N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP). The quartiles of BAP (Q1: <9.7 μg/L, Q2: 9.7–12.0 μg/L, Q3: 12.1–15.2 μg/L, Q4: >15.2 μg/L) are shown in Table 4. Significant differences were observed in age, sex, smoking history, dyslipidemia history, hypertension history, BMI, SBP, DBP, baPWV, Suita score, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, creatinine, eGFR, uric acid,

corrected calcium, phosphorus, hemoglobin, and hemoglobin A1c. The quartiles of PTH int (Q1: <38.0 pg/mL, Q2: 38.0–46.9 pg/mL, Q3: 47.0–57.0 pg/mL, Q4: >57.0 pg/mL) are shown in Table 5. Significant differences were observed in age, sex, smoking history, diabetes history, hypertension history, CAD history, BMI, SBP, DBP, Suita score, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, creatinine, uric acid, corrected calcium, phosphorus, hemoglobin, and hemoglobin A1c.

3.4. Association between bone metabolic markers and CAD risk

The quartiles of TP1NP levels were calculated and used to examine the association among TP1NP levels, Suita score, and baPWV (Table 6). A univariate logistic regression analysis showed that high risk for CAD (Suita score ≥ 56) and high baPWV (>1,400 cm/s) were associated with the lowest TP1NP subgroup (Q1 vs. Q4: OR = 5.13, 95% CI = 3.93–6.70, P < 0.05). The multivariate logistic regression analysis adjusted for age, sex, smoking history, CAD history, SBP, DBP, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, creatinine, uric acid, hemoglobin, and hemoglobin A1c showed that high risk for CAD (Suita score ≥ 56) was correlated with lower TP1NP (Q1 vs. Q4: OR 5.00, 95% CI: 3.83–6.54, P < 0.05). The multivariate logistic regression analysis also showed that the lowest TP1NP levels were associated with high baPWV (>1,400 cm/s) (Q1 vs. Q4: OR 1.33, 95% CI: 1.05–1.67, P < 0.05). No significant difference was observed between BAP levels and high risk for CAD (Suita score ≥ 56) and between BAP levels and high baPWV (>1,400 cm/s) (Table 7). In additions, the multivariate logistic regression analysis showed that the lowest PTH int levels were associated with high risk for CAD (Suita score ≥ 56) (high risk for CAD: Q1 vs. Q4, OR = 1.87, 95% CI = 1.50–2.33, P < 0.05, Table 8).

4. Discussion

This study compared estimated CAD risk by Suita score and atherosclerosis among bone metabolic markers in 5,095 IMM participants. The number of participants in this study is the largest among previous cohort reports in the general population worldwide. The present study demonstrated that among bone metabolic markers, low TP1NP levels were strongly associated with a high risk for CAD and high baPWV.

The present study represents the most significant cohort report of bone metabolic markers and CAD risk in the Japanese population. Bone metabolic markers were reported to predict bone mineral density loss, suggesting that a decrease in bone mineral density may affect bone metabolic markers [19]. In addition, CKD is associated with abnormal bone mineral metabolism, which affects bone metabolic markers [20]. Therefore, the present study was conducted in the general population without osteoporosis or CKD.

Although the median values of each bone metabolic markers (TP1NP = 43.9 ng/mL, BAP = 12.1 μg/L, NTX = 13.9 nM BCE/L, and PTH int = 43 pg/mL) were within the normal range for bone metabolism, it has been uncertain whether these values induce CAD risk and atherosclerosis [21]. Recently, bone metabolic markers in blood attracted attention as new biomarkers for developing CAD and life prognosis [22]. In this study, we compared the Suita score with bone metabolic markers as a predictive marker for CAD development. Logistic regression analysis showed that, among bone metabolic markers, circulating TP1NP level was negatively associated with Suita score high-risk group (≥56 points) and baPWV (>1,400 cm/s), suggesting that TP1NP levels among bone metabolic markers may be the strongest marker for future CAD risk.

This study showed that low PTH int levels were associated with the Suita score high-risk group (≥56 points). Consistent with this study, a relationship between lower PTH and a high CAD risk has been reported in a previous study [23]. In addition, hypoparathyroidism might affect bone metabolism [24]. These observations speculated that low PTH int levels might be associated with the secretion of bone metabolic markers and may be one of the CAD risk factors.

Table 3
Characteristics of participants according to the quartiles of serum TP1NP^a levels.

Parameter	Q1(<33.3)	Q2(33.3–43.8)	Q3(43.9–58.1)	Q4(58.1 <)	P value
Number	1,263	1,283	1,270	1,279	
Age	61.0 ± 12.6	58.1 ± 13.2	58.2 ± 12.0	58.4 ± 11.6	<0.001
Female, n (%)	524 (41.5)	654 (51.0)	796 (62.7)	964 (75.4)	<0.001
Smoker, n (%)	645 (51.1)	573 (44.7)	488 (38.4)	370 (28.9)	<0.001
Diabetes mellitus, n (%)	247 (19.6)	146 (11.4)	133 (10.5)	86 (6.7)	<0.001
Dyslipidemia, n (%)	444 (35.2)	448 (34.9)	466 (36.7)	435 (34)	0.558
Hypertension, n (%)	370 (29.3)	335 (26.1)	332 (26.1)	315 (24.6)	0.752
Stroke, n (%)	36 (2.9)	32 (2.5)	21 (1.7)	23 (1.8)	0.125
Coronary artery disease, n (%)	41 (3.2)	27 (2.1)	28 (2.2)	12 (0.9)	0.001
BMI ^b (kg/m ²)	24.1 ± 3.4	23.9 ± 3.7	23.9 ± 3.7	23.3 ± 3.5	<0.001
Systolic BP ^c (mmHg)	130.3 ± 19.5	128.0 ± 19.0	128.0 ± 19.0	126.8 ± 18.3	<0.001
Diastolic BP ^c (mmHg)	75.2 ± 11.7	74.9 ± 11.7	75.1 ± 11.7	73.8 ± 11.6	0.004
baPWV ^d (cm/s)	1,520(1,279–1,792)	1,428(1,219–1,709)	1,398(1,220–1,644)	1,386(1,217–1,602)	<0.001
Suita score, points	47 (34–56)	43 (29–52)	40 (30–49)	38 (30–46)	<0.001
Total cholesterol (U/L)	202.9 ± 34.7	206.2 ± 33.6	210.7 ± 34.0	212.2 ± 35.7	<0.001
Triglyceride (U/L)	118.7 ± 80.4	113.4 ± 71.8	109.8 ± 75.2	99.4 ± 55.4	<0.001
HDL ^e -cholesterol (U/L)	62.0 ± 16.5	61.4 ± 14.4	63.2 ± 14.8	65.0 ± 15.1	<0.001
LDL ^f -cholesterol (U/L)	111.0 ± 28.4	116.3 ± 29.3	119.0 ± 28.9	119.3 ± 30.0	<0.001
Creatinine (mg/dl)	0.73 ± 0.16	0.71 ± 0.15	0.69 ± 0.15	0.66 ± 0.13	<0.001
eGFR ^g (ml/min/1.73 m ²)	98.6 ± 22.0	99.3 ± 20.3	98.0 ± 19.3	96.8 ± 17.9	0.194
Uric acid (mg/dl)	5.4 ± 1.3	5.3 ± 1.3	5.1 ± 1.2	4.8 ± 1.2	<0.001
Corrected calcium (mg/dl)	9.3 ± 0.4	9.3 ± 0.4	9.4 ± 0.4	9.4 ± 0.4	0.001
Phosphorus (mg/dl)	3.3 ± 0.4	3.4 ± 0.4	3.5 ± 0.4	3.6 ± 0.5	0.002
Hemoglobin (g/dl)	14.0 ± 1.5	13.9 ± 1.5	13.8 ± 1.4	13.6 ± 1.3	<0.001
Hemoglobin A1c (%)	5.6 ± 0.70	5.5 ± 0.54	5.5 ± 0.51	5.4 ± 0.40	<0.001
NT-proBNP ^h (pg/mL)	47 (27–79)	41 (24–69)	43 (26–70)	50 (29–74)	<0.001

Values are expressed as mean ± SD or median (25%–75%) or number of subjects (percentage).

^aTotal procollagen type I intact N-terminal propeptide; ^bbody mass index; ^cblood pressure; ^dbrachial-ankle pulse wave velocity; ^ehigh-density lipoprotein; ^flow-density lipoprotein; ^gestimated glomerular filtration rate; ^hN-terminal fragment of pro-B-type natriuretic peptide.

Table 4
Characteristics of participants according to the quartiles of serum BAP^a levels.

Parameter	Q1(<9.7)	Q2(9.7–12.0)	Q3(12.1–15.2)	Q4(15.2 <)	P value
Number	1,217	1,304	1,285	1,289	
Age	54.4 ± 13.5	58.7 ± 12.6	60.4 ± 11.7	61.8 ± 10.3	<0.001
Female, n (%)	760 (62.4)	672 (51.5)	673 (52.4)	834 (64.7)	<0.001
Smoker, n (%)	533 (43.8)	556 (42.6)	548 (42.6)	439 (34.1)	<0.001
Diabetes mellitus, n (%)	126 (10.4)	162 (12.4)	160 (12.5)	164 (12.7)	0.238
Dyslipidemia, n (%)	365 (30.0)	468 (35.9)	460 (35.8)	501 (38.9)	<0.001
Hypertension, n (%)	207 (17.0)	343 (26.3)	381 (29.6)	421 (32.7)	<0.001
Stroke, n (%)	16 (1.3)	34 (2.6)	30 (2.3)	32 (2.5)	0.110
Coronary artery disease, n (%)	23 (1.9)	34 (2.6)	27 (2.1)	24 (1.9)	0.528
BMI ^b (kg/m ²)	23.2 ± 3.5	23.9 ± 3.6	24.0 ± 3.6	24.0 ± 3.5	<0.001
Systolic BP ^c (mmHg)	122.8 ± 18.9	128.1 ± 19.0	130.4 ± 18.4	131.7 ± 18.3	<0.001
Diastolic BP ^c (mmHg)	72.2 ± 11.5	74.6 ± 11.1	75.8 ± 11.8	76.3 ± 11.7	<0.001
baPWV ^d (cm/s)	1,319(1,131–1,595)	1,429(1,231–1,685)	1,458(1,277–1,741)	1,484(1,305–1,726)	<0.001
Suita score, points	35 (22–49)	43 (30–52)	43 (34–52)	43 (36–50)	<0.001
Total cholesterol (U/L)	204.7 ± 33.9	207.2 ± 34.6	208.7 ± 34.3	211.3 ± 35.6	<0.001
Triglyceride (U/L)	103.0 ± 72.2	111.3 ± 75.3	110.7 ± 69.2	115.8 ± 69	<0.001
HDL ^e -cholesterol (U/L)	65.2 ± 15.9	62.5 ± 14.7	62.1 ± 15.2	62.0 ± 15.1	<0.001
LDL ^f -cholesterol (U/L)	112.4 ± 28.1	116.3 ± 29.7	117.7 ± 29.4	119.0 ± 29.7	<0.001
Creatinine (mg/dl)	0.69 ± 0.15	0.71 ± 0.15	0.70 ± 0.15	0.67 ± 0.14	<0.001
eGFR ^g (ml/min/1.73 m ²)	105.3 ± 22.4	97.7 ± 19.2	95.7 ± 18.8	94.3 ± 17.5	<0.001
Uric acid (mg/dl)	5.0 ± 1.3	5.3 ± 1.3	5.3 ± 1.3	5.0 ± 1.2	<0.001
Corrected calcium (mg/dl)	9.3 ± 0.4	9.4 ± 0.4	9.4 ± 0.3	9.4 ± 0.4	<0.001
Phosphorus (mg/dl)	3.5 ± 0.4	3.4 ± 0.4	3.4 ± 0.5	3.5 ± 0.5	0.003
Hemoglobin (g/dl)	13.4 ± 1.4	13.9 ± 1.5	14.0 ± 1.4	14.1 ± 1.3	<0.001
Hemoglobin A1c (%)	5.4 ± 0.50	5.5 ± 0.53	5.5 ± 0.57	5.5 ± 0.59	<0.001
NT-proBNP ^h (pg/mL)	45 (27–71)	43.5 (25–75)	43 (26–71)	46 (27–76)	0.300

Values are expressed as mean ± SD or median (25%–75%) or number of subjects (percentage).

^aBone-specific alkaline phosphatase; ^bbody mass index; ^cblood pressure; ^dbrachial-ankle pulse wave velocity; ^ehigh-density lipoprotein; ^flow-density lipoprotein; ^gestimated glomerular filtration rate; ^hN-terminal fragment of pro-B-type natriuretic peptide.

It was reported that mortality increased with an increase in bone metabolic turnover in studies involving elderly persons [6], and that osteoporotic patients in postmenopausal women had higher rates of cardiovascular (CV) events [25]. In addition, reports that examined the association between bone metabolic markers and CVD showed a positive correlation [26,27]. Although these reports showed controversial results

compared to that of the present study, these studies included elderly individuals and participants with osteoporosis. Indeed, circulating bone metabolic markers including TP1NP levels were affected by aging [28–30]. On the other hand, it has been reported that blood TP1NP levels are negatively correlated with traditional CVD risk factors, such as abnormal glucose metabolism and obesity [31,32]. In addition, serum

Table 5
Characteristics of participants according to the quartiles of serum PTH int^a levels.

Parameter	Q1(<38.0)	Q2(38.0–46.9)	Q3(47.0–57.0)	Q4(57.0 <)	P value
Number	1,181	1,317	1,276	1,321	
Age	59.9 ± 13.6	58.9 ± 12.1	58.6 ± 12.1	58.3 ± 11.8	<0.001
Female, n (%)	571 (48.3)	773 (58.7)	776 (60.8)	819 (62.0)	<0.001
Smoker, n (%)	524 (44.4)	526 (39.9)	499 (39.1)	527 (39.9)	0.037
Diabetes mellitus, n (%)	190 (16.1)	154 (11.7)	132 (10.3)	136 (10.3)	<0.001
Dyslipidemia, n (%)	446 (37.8)	457 (34.7)	420 (32.9)	471 (35.7)	0.089
Hypertension, n (%)	290 (24.6)	294 (22.3)	358 (28.0)	410 (31.0)	<0.001
Stroke, n (%)	33 (2.8)	27 (2.1)	30 (2.4)	22 (1.7)	0.265
Coronary artery disease, n (%)	38 (3.2)	23 (1.7)	24 (1.9)	23 (1.7)	0.029
BMI ^b (kg/m ²)	23.6 ± 3.4	23.5 ± 3.4	23.8 ± 3.5	24.3 ± 3.9	<0.001
Systolic BP ^c (mmHg)	127.3 ± 19.2	126.7 ± 18.7	128.4 ± 18.8	130.1 ± 19.0	<0.001
Diastolic BP ^c (mmHg)	72.8 ± 11.6	73.7 ± 11.1	75.2 ± 11.5	77.0 ± 12.1	<0.001
baPWV ^d (cm/s)	1,450(1,217–1,749)	1,411(1,226–1,669)	1,425(1,214–1,684)	1,436(1,258–1,670)	0.140
Suita score, points	43 (30–53)	41 (30–50)	41 (30–50)	41 (30–49)	0.001
Total cholesterol (U/L)	204.9 ± 35.0	207.8 ± 34.1	208.6 ± 34.6	210.4 ± 35.0	0.002
Triglyceride (U/L)	117.1 ± 76.0	107.4 ± 70.6	104.0 ± 66.1	113.2 ± 73.0	<0.001
HDL ^e -cholesterol (U/L)	60.9 ± 15.0	63.3 ± 15.2	63.5 ± 15.4	63.9 ± 15.3	<0.001
LDL ^f -cholesterol (U/L)	114.5 ± 29.1	116.0 ± 28.8	117.2 ± 29.1	117.8 ± 30.3	0.035
Creatinine (mg/dl)	0.71 ± 0.15	0.69 ± 0.15	0.69 ± 0.14	0.69 ± 0.15	<0.001
eGFR ^g (ml/min/1.73 m ²)	96.5 ± 20.0	99.3 ± 20.0	98.6 ± 19.2	98.1 ± 20.5	0.301
Uric acid (mg/dl)	5.2 ± 1.3	5.1 ± 1.3	5.1 ± 1.3	5.2 ± 1.3	0.035
Corrected calcium (mg/dl)	9.5 ± 0.4	9.4 ± 0.3	9.3 ± 0.3	9.3 ± 0.4	<0.001
Phosphorus (mg/dl)	3.5 ± 0.5	3.5 ± 0.4	3.5 ± 0.4	3.3 ± 0.4	<0.001
Hemoglobin (g/dl)	14.0 ± 1.4	13.8 ± 1.4	13.8 ± 1.4	13.8 ± 1.5	0.030
Hemoglobin A1c (%)	5.5 ± 0.62	5.5 ± 0.53	5.5 ± 0.54	5.5 ± 0.51	0.026
NT-proBNP ^h (pg/mL)	43 (25–71)	44 (27–70)	46 (27–76)	45 (26–76)	0.254

Values are expressed as mean ± SD or median (25%–75%) or number of subjects (percentage).

^aParathyroid hormone, intact; ^bbody mass index; ^cblood pressure; ^dbrachial-ankle pulse wave velocity; ^ehigh-density lipoprotein; ^flow-density lipoprotein; ^gestimated glomerular filtration rate; ^hN-terminal fragment of pro-B-type natriuretic peptide.

Table 6
Correlates of elevated TP1NP^a levels (Q1–Q4), as estimated using a multinomial logistic regression analysis.

Variable	Suita score(≥56 points)		[†] Suita score(≥56 points)		baPWV ^b (>1400 cm/s)		^{††} baPWV ^b (>1400 cm/s)	
	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value
Q1(<33.3)	5.13(3.93–6.70)	<0.001	5.00(3.83–6.54)	<0.001	1.75(1.49–2.05)	<0.001	1.33(1.05–1.67)	0.016
Q2(33.3–43.8)	3.00(2.25–3.92)	<0.001	2.93(2.22–3.88)	<0.001	1.22(1.05–1.44)	0.011	1.22(0.98–1.53)	0.08
Q3(43.9–58.1)	2.13(1.60–2.85)	<0.001	2.10(1.57–2.80)	<0.001	1.05(0.90–1.23)	0.524	0.97(0.78–1.21)	0.781
Q4(58.1 <)	Reference		Reference		Reference		Reference	

^aTotal procollagen type I intact N-terminal propeptide; ^bbrachial-ankle pulse wave velocity.

[†]Adjusted for history of coronary artery disease.

^{††}Adjusted for age, sex, history of smoking, history of coronary artery disease, body mass index, systolic blood pressure, diastole blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, uric acid, hemoglobin, and hemoglobin A1c.

Table 7
Correlates of elevated BAP^a levels (Q1–Q4), as estimated using a multinomial logistic regression analysis.

Variable	Suita score(≥56 points)		[†] Suita score(≥56 points)		baPWV ^b (>1400 cm/s)		^{††} baPWV ^b (>1400 cm/s)	
	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value
Q1(<9.7)	1.01(0.86–1.41)	0.43	0.98(0.85–1.33)	0.39	0.83(0.69–1.04)	0.092	0.95(0.83–1.24)	0.39
Q2(9.7–12.0)	0.88(0.75–1.37)	0.35	0.91(0.73–1.42)	0.37	0.93(0.89–1.21)	0.32	0.94(0.91–1.19)	0.41
Q3(12.1–15.2)	0.93(0.62–1.74)	0.48	0.89(0.63–1.73)	0.49	0.92(0.88–1.23)	0.33	0.94(0.95–1.22)	0.45
Q4(15.2 <)	Reference		Reference		Reference		Reference	

^aBone-specific alkaline phosphatase; ^bbrachial-ankle pulse wave velocity.

[†]Adjusted for history of coronary artery disease.

^{††}Adjusted for age, sex, history of smoking, history of coronary artery disease, body mass index, systolic blood pressure, diastole blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, uric acid, hemoglobin, and hemoglobin A1c.

sclerostin was elevated in type 2 diabetic patients [33], and sclerostin was negatively correlated with TP1NP [34]. From these observations, it has been speculated that downregulated TP1NP levels might be associated with CAD risk and atherosclerosis progression.

Although this study investigated the association between bone metabolic markers and CAD risk factors, whether these bone metabolic markers would directly predict CAD has not been shown. This information would be needed for the accurate diagnosis of CAD using

coronary angiogram or computed tomography, and a prospective cohort study investigating cardiovascular events should be conducted.

This study has several limitations that should be taken into consideration. First, only a baseline measurement of bone metabolic markers and other covariates was performed because this was a cross-sectional study. Second, the present study evaluated whether each participant had CAD using self-reported answers rather than clinical examination.

Table 8Correlates of elevated PTH int^a levels (Q1–Q4), as estimated using a multinomial logistic regression analysis.

Variable	Suita score(≥56 points)		Suita score(≥56 points)		baPWV ^b (>1400 cm/s)		baPWV ^b (>1400 cm/s)	
	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value	OR(95% CI)	P value
Q1(<33.3)	1.90(1.52–2.37)	<0.001	1.87(1.50–2.33)	<0.001	1.03(0.88–1.21)	0.704	0.96(0.76–1.20)	0.700
Q2(33.3–43.8)	1.23(0.97–1.54)	0.084	1.23(0.97–1.55)	0.083	0.87(0.75–1.02)	0.084	0.90(0.73–1.12)	0.358
Q3(43.9–58.1)	1.10(0.87–1.40)	0.420	1.10(0.87–1.39)	0.429	0.92(0.79–1.07)	0.289	0.95(0.77–1.19)	0.662
Q4(58.1 <)	Reference		Reference		Reference		Reference	

^aParathyroid hormone; ^bbrachial–ankle pulse wave velocity.[†]Adjusted for history of coronary artery disease.^{††}Adjusted for age, sex, history of smoking, history of coronary artery disease, body mass index, systolic blood pressure, diastole blood pressure, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, uric acid, hemoglobin, and hemoglobin A1c.

5. Conclusion

The present study demonstrated that TP1NP levels decreased in participants with high Suita scores and high baPWV and suggested that downregulated TP1NP might indicate future CAD risk and atherosclerosis progression in the general Japanese population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Footnotes

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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