

**Original**

**Association between Casual Serum Triglyceride Levels and Bone Resorption Activity in Japanese Middle-aged and Elderly Women**

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**Abstract** : High serum triglyceride (TG) levels may lower bone fracture risk, but the association between serum TG and bone resorption activity is unclear. The aim of the present study was to analyze this association using casual serum TG levels in patients with and without accelerated bone resorption. A case-control study was performed in 39 patients with accelerated bone resorption and in 69 controls, treated between April 2011 and March 2016 at the Internal Medicine Clinic. Bone resorption activity was assessed by urinary N-telopeptide of type I collagen (uNTx; a marker of bone resorption), which is routinely measured at the Internal Medicine Clinic. Cases were female outpatients aged  $\geq 40$  years in whom uNTx levels were  $\geq 54.3$  nmol bone collagen equivalent (BCE) / mmol creatinine. Subjects with casual serum TG levels  $> 150$  mg / dl were diagnosed with potential hypertriglyceridemia (PHTG). Propensity score-adjusted multinomial logistic regression was performed to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for PHTG in cases compared with controls. Correlations between uNTX and casual serum TG levels in all patients were evaluated using multivariate regression. The prevalence of PHTG was significantly lower in cases than in controls (OR 0.20; 95% CI 0.05–0.65;  $P = 0.006$ ). uNTx levels were negatively associated with casual serum TG levels in all patients ( $r = -0.07$ ,  $P = 0.046$ ). These results suggest that serum TG levels are negatively associated with bone resorption activity. Reduced bone resorption activity may explain, in part, the reduced fracture risk in Japanese middle-aged and elderly female patients with hypertriglyceridemia.

**Key words** : triglycerides, bone resorption, urinary N-telopeptide of type I collagen, human, osteoporosis, case-control study

**Introduction**

Osteoporosis in elderly women is often underdiagnosed, despite the availability of effective treatment<sup>1)</sup>. To screen for osteoporosis more effectively, there is a need for detailed information regarding the diagnostic and clinical characteristics of patients with osteoporosis, as well as the biological mechanisms underlying the development of the disease<sup>1,2)</sup>. It is noteworthy that

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osteoporosis becomes severe in patients with comorbidities, including lifestyle-related diseases such as diabetes (chiefly type 1), chronic kidney disease (CKD), hypertension, and dyslipidemia<sup>3-5</sup>).

The association between serum lipids and fracture risk has been evaluated in several studies<sup>6-9</sup>. A prospective study showed that plasma low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels are inversely and positively correlated with bone mineral density (BMD), respectively<sup>6</sup>. However, clinical studies<sup>7,8,10</sup> have suggested that high serum triglyceride (TG) levels may lower the risk of vertebral fractures, and that low plasma TG is associated with vertebral fractures in postmenopausal women<sup>7,8</sup>. These clinical findings suggest that plasma lipids may be related to bone fragility and may be the common factor underlying the development of osteoporosis.

Several studies have described the molecular and biological mechanisms underlying the association between plasma LDL-C levels and fracture risk<sup>11-13</sup>. Oxidized LDL suppresses the differentiation of bone marrow stromal cells to osteoblasts, but promotes the differentiation of these cells to adipocytes, which may cause fatty marrow and bone mass reduction<sup>11,14</sup>. Inactivation of LDL receptor-related proteins 5 and 6 (LRP 5/6) is linked to hypercholesterolemia and bone mass reduction, indicating involvement of Wnt signaling in both disorders<sup>14-16</sup>. However, the biological mechanisms underlying the association between low plasma TG and an increased risk of fracture remain unclear<sup>14</sup>. To investigate these mechanisms, the present study examined the association between casual serum TG levels and bone resorption activity in middle-aged and elderly Japanese women.

## Methods

### *Study design and subjects*

A single-center retrospective case-control study was performed in middle-aged and elderly women (i.e. those aged > 40 years). Bone resorption activity was assessed using urinary N-telopeptide of type I collagen (uNTx), a specific marker of bone resorption<sup>17</sup>. uNTx levels are routinely measured in middle-aged and elderly female outpatients at the Internal Medicine Clinic, which manages primary care or internal consultations for all dental clinical departments in Showa University Dental Hospital, a 22-bed dental care center.

In all, 113 Japanese middle-aged or elderly female outpatients aged > 40 years in whom uNTx levels were measured at the Internal Medicine Clinic between April 2011 and March 2016 were potentially eligible for inclusion in the study. The exclusion criteria included serious kidney disorders (serum creatinine [Cr]  $\geq$  2.0 mg/dl), a history of metabolic bone diseases, including thyroid or parathyroid disorders, and cancer bone metastasis<sup>6-8,18</sup>. Five patients were excluded based on these criteria, leaving 108 patients in the study.

The Research Ethics Committee of Showa University approved this study (Research No. DH2016-007). All data were analyzed anonymously, and thus the requirement for informed consent was waived.

### *Case definition*

The 108 patients were divided into cases ( $n = 39$ ; accelerated bone resorption) and controls ( $n = 69$ ) based on uNTx levels of  $> 54.3$  and  $< 54.3$  nmol bone collagen equivalent (BCE) / mmol Cr, respectively, because patients with uNTX levels of  $\geq 54.3$  BCE / mmol Cr have an increased risk of fracture regardless of age<sup>19, 20</sup>.

### *Data collection*

Medical records of patients were analyzed retrospectively. Data were collected for age, body mass index (BMI), systolic and diastolic blood pressure (SBP and DBP, respectively), smoking and drinking habits, medications (including antihypertensive drugs, lipid-lowering drugs, and anti-osteoporotic drugs taken on the same day as uNTX measurement), the cardio-ankle vascular index (CAVI) within 1 year of measurement of uNTX, and comorbidities before measurement. Laboratory data included casual serum TG and LDL-C levels. Casual serum TG levels were measured with an enzymatic method. Patients with casual serum TG levels  $\geq 150$  mg / dl were categorized as having potential hypertriglyceridemia (PHTG), whereas those with casual serum LDL-C levels  $\geq 120$  mg / dl were categorized as having potential hyper-LDL cholesterolemia (PH-LDL-C)<sup>21, 22</sup>. TG and LDL-C were measured on the same day as uNTX.

The prevalence of PHTG and PH-LDL-C was determined in cases and controls. To adjust for confounding factors, given the use of observational data, propensity scores for estimated probabilities for PHTG and PH-LDL-C were derived from logistic regression models that predicted PHTG and PH-LDL-C based on age, BMI, drinking and smoking habits, casual serum TG, LDL-C, and HDL-C levels, the use of lipid-lowering drugs, and the use of anti-osteoporotic drugs.

### *Statistical analyses*

Age, BMI, SBP, DBP, mean CAVI, and laboratory data retrieved from medical records are presented as the mean  $\pm$  SD. These data were compared between cases (subjects with accelerated bone resorption) and controls using the Mann-Whitney *U*-test. Data regarding age group, comorbidities, and medications are shown as the number of subjects in each group with percentages in parentheses. These data were compared between cases and controls using the Chi-squared test or Fisher's exact test. A multinomial logistic regression model including the propensity score was used to estimate prevalence odds ratios (ORs) and 95% confidence intervals (CIs) for PHTG and PH-LDL-C for cases compared with controls. Correlations of uNTX levels with casual serum TG and LDL-C levels were evaluated using multivariate regression adjusted for age, BMI, estimated glomerular filtration rate (eGFR), casual serum TG, casual serum LDL-C, the use of lipid-lowering drugs, and the use of anti-osteoporotic drugs<sup>6, 7, 23</sup>.  $P < 0.05$  was considered significant in all analyses. All calculations were performed using JMP (SAS Institute Inc., Cary, NC, USA).

## **Results**

### *Study population*

The characteristics of the study subjects are given in Table 1. There were 39 subjects in the case group and 69 in the control group. There was no significant difference in mean age between the cases and controls ( $71.1 \pm 13.1$  vs.  $70.7 \pm 12.1$  years, respectively; Table 1). Casual serum TG and serum Cr were lower, whereas urine albumin was higher, in the cases than in the controls (Table 1;  $P = 0.041$ ,  $0.016$ , and  $0.002$ , respectively, Mann–Whitney  $U$ -test).

#### *PHTG and PH-LDL-C*

Propensity score-adjusted multinomial logistic regression analysis showed that the prevalence of PHTG was significantly lower in cases than in controls (OR 0.20; 95% CI 0.05–0.65;  $P = 0.006$ ). The prevalence of PH-LDL-C did not differ significantly between the cases and controls (OR 1.07; 95% CI 0.45–2.57;  $P = 0.86$ ; Table 2).

#### *Correlation between uNTx and casual serum TG and LDL-C levels*

Associations of uNTx with casual serum TG and LDL-C levels in all patients are shown in Figure 1. Multivariate regression showed that there was a significant negative correlation between uNTx and serum TG levels ( $r = -0.07$ ,  $P = 0.046$ ), but no significant correlation between uNTx and LDL-C levels ( $r = 0.07$ ,  $P = 0.31$ ).

### **Discussion**

This study investigated the prevalence ORs of PHTG and PH-LDL-C in patients with accelerated bone resorption compared with controls, and assessed the correlation between bone resorption activity and plasma lipid concentrations. The prevalence of PHTG was significantly lower in patients with accelerated bone resorption than in the control group. Bone state is closely related to the balance between bone formation and bone resorption. Accelerated bone resorption can lead to bone fragility and an increased risk of fracture due to loss of bone mineral density (BMD) and deterioration of bone quality<sup>24</sup>. Based on the results of the present study, we propose the hypothesis that reduced bone resorption activity may contribute, in part, to reduced fracture risk in Japanese middle-aged and elderly female patients with hypertriglyceridemia, and that acceleration of bone resorption may be linked to bone fragility and an increased risk of fractures in patients with lower plasma TG. Furthermore, the results suggest that lower plasma TG may be valuable as a potential biomarker for osteoporosis in Japanese middle-aged and elderly women.

There was a weak but significant negative correlation between uNTx and casual serum TG levels in the present study. The molecular and biological mechanisms underlying the association between plasma TG and bone resorption activity remain unclear. Low plasma TG levels have been found to be associated with the presence of vertebral fracture in postmenopausal women, but are not correlated with BMD levels at any skeletal site<sup>7</sup>. An observational study found a significant difference in serum TG between women with and without vertebral fracture, but no lipid components (including TG) were independent contributors to variation in spine or hip BMD<sup>8</sup>. These results support the hypothesis that bone fragility in patients with lower plasma

Table 1. Characteristics of patients with accelerated bone resorption (cases) and controls

	All subjects (n = 108)	Cases (n = 39)	Controls (n = 69)	P-value
Age (years) <sup>a</sup>	70.8 ± 12.4	71.1 ± 13.1	70.7 ± 12.1	0.97
Age group <sup>b</sup>				0.42
40-64 years	29 (26.8)	12 (30.7)	17 (24.6)	
65-84 years	64 (59.2)	20 (51.2)	44 (63.7)	
≥ 85 years	15 (13.8)	7 (17.9)	8 (11.5)	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	23.0 ± 3.9	22.6 ± 4.1	23.2 ± 3.8	0.52
SBP (mmHg) <sup>a</sup>	142.4 ± 24.8	144.3 ± 26.3	141.3 ± 24.1	0.46
DBP (mmHg) <sup>a</sup>	84.9 ± 14.4	87.1 ± 14.5	83.7 ± 14.3	0.23
Mean CAVI (m/s) <sup>a</sup>	8.5 ± 1.1	8.4 ± 1.2	8.5 ± 1.0	0.62
Current or former smoker <sup>b</sup>	6 (5.5)	1 (2.5)	5 (7.2)	0.30
Current or occasional drinker <sup>b</sup>	35 (32.4)	11 (28.2)	24 (34.7)	0.48
Laboratory findings <sup>a</sup>				
Total protein (g/dl)	71 ± 0.5	71 ± 0.6	71 ± 0.4	0.87
Albumin (g/dl)	4.2 ± 0.2	4.20 ± 0.38	4.21 ± 0.19	0.84
Creatinine (mg/dl)	0.64 ± 0.17	0.62 ± 0.21	0.65 ± 0.14	0.016*
eGFR (mL/min per 1.73 m <sup>2</sup> )	71.8 ± 17.0	75.0 ± 21.1	70.0 ± 14.2	0.07
Uric acid (mg/dl)	4.8 ± 1.0	4.7 ± 1.0	4.9 ± 1.1	0.46
Calcium (mg/dl)	9.3 ± 0.4	9.3 ± 0.5	9.2 ± 0.3	0.91
HbA1c (%)	5.7 ± 1.0	5.7 ± 1.1	5.7 ± 0.9	0.14
Total cholesterol (mg/dl)	212 ± 36	212.9 ± 46.7	212.1 ± 29.3	0.47
LDL-C (mg/dl)	125.7 ± 32.8	133.2 ± 39.3	121.8 ± 28.5	0.24
HDL-C (mg/dl)	65.6 ± 13.8	66.4 ± 15.6	65.1 ± 12.8	0.96
Triglyceride (mg/dl)	128.0 ± 68.2	110.3 ± 59.4	137.3 ± 71.1	0.041*
BNP (pg/ml)	45.5 ± 116.1	76.7 ± 186.9	27.2 ± 28.04	0.25
Urine albumin (mg/l)	84.9 ± 623.8	203.5 ± 1043.5	19.4 ± 33.2	0.002*
uNTx (nmol BCE/mmol Cr)	44.7 ± 25.5	73.0 ± 16.7	28.8 ± 12.3	<0.001*
Comorbidities before index date				
Hypertension <sup>b</sup>	60 (55.6)	21 (53.8)	39 (56.5)	0.78
Diabetes mellitus <sup>c</sup>	6 (5.5)	3 (7.6)	3 (4.3)	0.66
Chronic kidney disease <sup>b</sup>	33 (30.5)	15 (38.4)	18 (26.0)	0.17
Pulmonary disease <sup>c</sup>	2 (1.8)	0 (0.0)	2 (2.9)	0.53
Chronic heart disease <sup>b</sup>	18 (16.6)	6 (15.3)	12 (17.3)	0.78
Depression <sup>b</sup>	13 (12.0)	5 (12.8)	8 (11.5)	0.85
Medications				
Antihypertensive drugs <sup>b</sup>	54 (50.0)	16 (41.0)	38 (55.0)	0.16
ARB or renin inhibitors <sup>b</sup>	44 (40.7)	12 (30.7)	32 (46.3)	0.11
Calcium blocker <sup>b</sup>	34 (31.4)	11 (28.2)	23 (33.3)	0.58
Osteoporosis drugs <sup>b</sup>	21 (19.4)	8 (20.5)	13 (18.8)	0.78
Activated vitamin D3 <sup>b</sup>	20 (18.5)	8 (20.5)	12 (17.3)	0.68
Bisphosphonate <sup>c</sup>	4 (3.7)	0 (0.0)	4 (5.8)	0.29
SERM <sup>c</sup>	1 (0.9)	0 (0.0)	1 (1.4)	1.00
Lipid-lowering drugs <sup>b</sup>	27 (25.0)	8 (20.5)	19 (27.5)	0.41
Statin <sup>b</sup>	26 (24.0)	8 (20.5)	18 (26.0)	0.51
Fibrate <sup>c</sup>	1 (0.9)	0 (0.0)	1 (1.4)	1.00
Antidepressant drugs <sup>b</sup>	24 (22.2)	10 (25.6)	14 (20.2)	0.52

Data are presented as the mean ± SD, or as the number of subjects in each group with percentages in parenthesis.

<sup>a</sup>Statistical analyses were conducted using the Mann-Whitney *U*-test.

<sup>b</sup>Statistical analyses were conducted using the Chi-square test.

<sup>c</sup>Statistical analyses were conducted using Fisher's exact test.

\**P* < 0.05.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAVI, cardio-ankle vascular index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; uNTx, urinary N-telopeptide of type I collagen; BCE, bone collagen equivalent; Cr, creatinine; ARB, angiotensin AT<sub>2</sub> receptor blocker; SERM, selective estrogen receptor modulator.

Table 2. Crude and adjusted odds ratios for hyper-low-density lipoprotein cholesterolemia and hypertriglyceridemia in cases and controls

	Crude		Adjusted <sup>a</sup>	
	OR (95% CI)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value
PH-LDL-C	1.08 (0.48, 2.42)	0.83	1.07 (0.45, 2.57)	0.86
PHTG	0.21 (0.05, 0.61)	0.003*	0.20 (0.05, 0.65)	0.006*

<sup>a</sup>A logistic regression model that included propensity scores was used to adjust for remaining differences between the groups.

\**P* < 0.05.

OR, odds ratio; CI, confidence interval; PH-LDL-C, potential hyper-low-density lipoprotein cholesterolemia; PHTG, potential hypertriglyceridemia.

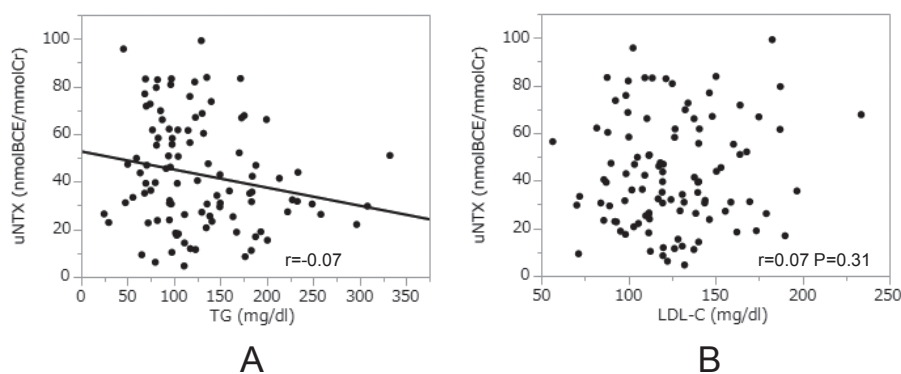


Fig. 1. Associations of urinary N-telopeptide of type I collagen (uNTx) with (A) casual serum triglyceride (TG) and (B) low-density lipoprotein cholesterol (LDL-C) levels. uNTx levels were negatively correlated with casual serum TG levels (A), but there was no significant correlation between uNTx and serum LDL-C levels (B).

TG depends on deterioration of bone quality, rather than on bone mass reduction. Similarly, accelerated bone resorption may contribute to bone fragility and the increased risk of fractures in middle-aged and elderly women with lower plasma TG through deterioration of bone quality. To confirm these hypotheses, there is an urgent need for further research to assess the associations between plasma TG and bone mass or bone formation. A case-control study has recently been launched by our research group to assess these associations.

Several previous studies have assessed the association between saturated fatty acids (SFA) and osteoclast (OC) differentiation and reported that OC differentiation is controlled by SFA<sup>25-27</sup>. An experimental study reported that lipoprotein lipase (LPL) is associated with higher osteoclastogenesis and that osteoporotic bone tissue exhibits higher osteoclastogenesis and lower TG metabolism than normal bone<sup>28</sup>. These results may explain, in part, the mechanisms underlying the association between lower plasma TG concentrations and accelerated bone resorption, and support our hypothesis that lower plasma TG concentrations due to a downregulation in the capacity to synthesize TG may contribute to acceleration of bone resorption through activation

of OC differentiation. On the basis of the results of the present and previous studies, we propose that measurement of plasma TG concentrations is clinically meaningful in predicting those at high risk of osteoporosis.

In the present study there was no significant difference in the prevalence of PH-LDL-C between patients with accelerated bone resorption and controls, and no significant association between casual serum LDL-C levels and bone resorption activity. These results are biologically plausible because several studies have suggested that bone fragility in patients with higher plasma LDL-C depends on reduced bone formation, rather than accelerated bone resorption<sup>11, 14, 15, 29</sup>. However, the association between plasma LDL-C and bone metabolism is contentious<sup>7, 11, 12, 15, 29, 30</sup> and there is a need for further evaluation of this relationship.

Several limitations of the present study need to be acknowledged. First, the results of multinomial logistic regression analysis using propensity scores are generalizable only among those in the range of propensity scores included in the analysis. Propensity score methods can reduce bias in causal estimates due to observed differences among subjects, but are still subject to bias from unobserved differences. Second, bone resorption activity may not be fully explained by measurements of bone turnover markers, including uNTx, although uNTx is a typical biomarker for bone resorption activity. Third, we evaluated the association between bone resorption and casual serum TG levels, rather than fasting levels. There is a significant positive correlation between casual and fasting serum TG levels<sup>22</sup>), but diurnal variations may have affected outcomes. Fourth, bone fragility and increased risk of fracture are not fully explained by accelerated bone resorption, but the bone formation rate and other factors that may contribute to bone fragility and the risk of fracture were not assessed. Finally, patients taking medications for osteoporosis and dyslipidemia were included in the analysis. This may have affected the final conclusions, despite the adjustment for each medication used.

In summary, the present case-control study compared the prevalence ORs of PHTG between cases, namely middle-aged and elderly female patients with accelerated bone resorption, and controls. In addition, we investigated the correlation between uNTx levels and casual serum TG levels. The prevalence of PHTG was significantly lower in patients with accelerated bone resorption than in controls, and uNTx levels were negatively associated with casual serum TG levels. These results support our hypothesis that reduced bone resorption activity may contribute, in part, to the reduced fracture risk in Japanese middle-aged and elderly women with hypertriglyceridemia. Further analyses are needed to determine the mechanisms underlying the association between serum TG and bone resorption activity.

#### **Conflict of interest disclosure**

The authors state that they have no conflict of interest to declare.

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