Serum γ-Glutamyl Transferase Is Inversely Associated with Bone Mineral Density Independently of Alcohol Consumption

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Background: γ-Glutamyl transferase (GGT) is a well-known marker of chronic alcohol consumption or hepatobiliary diseases. A number of studies have demonstrated that serum levels of GGT are independently associated with cardiovascular and metabolic disorders. The purpose of this study was to test if serum GGT levels are associated with bone mineral density (BMD) in Korean adults.

Methods: A total of 462 subjects (289 men and 173 women), who visited Severance Hospital for medical checkup, were included in this study. BMD was measured using dual energy X-ray absorptiometry. Cross-sectional association between serum GGT and BMD was evaluated.

Results: As serum GGT levels increased from the lowest tertile (tertile 1) to the highest tertile (tertile 3), BMD decreased after adjusting for confounders such as age, body mass index, amount of alcohol consumed, smoking, regular exercise, postmenopausal state (in women), hypertension, diabetes mellitus, and hypercholesterolemia. A multiple linear regression analysis showed a negative association between log-transformed serum GGT levels and BMD. In a multiple logistic regression analysis, tertile 3 of serum GGT level was associated with an increased risk for low bone mass compared to tertile 1 (odds ratio, 2.271; 95% confidence interval, 1.340 to 3.850; $P=0.002$).

Conclusion: Serum GGT level was inversely associated with BMD in Korean adults. Further study is necessary to fully elucidate the mechanism of the inverse relationship.

Keywords: Gamma-glutamyltransferase; Metabolic disorders; Bone density

INTRODUCTION

γ-Glutamyl transferase (GGT), a well-known marker of chronic alcohol consumption and hepatobiliary disease, is abundantly expressed in several tissues, particularly those with secretory or absorptive functions, such as the kidneys, pancreas, seminal vesicles, small intestine, and bile duct [1,2]. A number of studies have demonstrated that serum levels of GGT are independently

associated with cardiovascular and metabolic disorders such as obesity, metabolic syndrome, type 2 diabetes mellitus, coronary heart disease, and stroke [3-14], although the mechanism of these associations has not been fully elucidated. GGT plays a key role in glutathione homeostasis. GGT is located on the outer surface of the plasma membrane with its active site exposed to the extracellular space [1,2]. As an ectopeptidase, it catalyzes degradation of extracellular glutathione to generate its constituent amino acids including cysteine. These amino acids are taken up by the cells and reutilized for *de novo* synthesis of glutathione, which participates in many biological functions, including antioxidant defense, maintenance of intracellular redox status, signal transduction, and nutrient metabolism [1,2,15].

Bone is an active metabolizing tissue, as both bone formation and resorption occur throughout life. This bone remodeling process, which determines bone mass, is regulated by many systemic and local factors such as estrogens, vitamin D, parathyroid hormone, bone morphogenetic proteins, receptor activator for NF-κB-ligand (RANKL), and osteoprotegerin [16]. Several *in vitro* and *in vivo* studies have demonstrated that GGT affects bone metabolism through systemic and local mechanisms [17-20]. Both deficiency and excess GGT are involved in the abnormal bone remodeling processes, which result in decreased bone mass. However, only a few clinical studies have demonstrated a significant relationship between GGT and bone [20]. In the present study, we performed a cross-sectional analysis to investigate whether serum levels of GGT are associated with bone mineral density (BMD) in Korean adults.

METHODS

Subjects and data collection

A total of 462 subjects (289 men and 173 women) aged 21 to 83 years were recruited from the Healthcare Center at the Severance Hospital, Yonsei University College of Medicine in Seoul, Korea, and were included in analyses. All adult Koreans were included if they did not meet any of the exclusion criteria, including a history of a medical condition known to be associated with abnormal bone metabolism or to alter bone mass such as hyperparathyroidism, rheumatoid arthritis, and chronic renal failure; history of hepatobiliary diseases such as liver cirrhosis, primary biliary cirrhosis, or viral hepatitis (including positivity for serum hepatitis B surface antigen or serum hepatitis C antibody); and current use of medications capable of affecting bone and mineral metabolism such as glucocorticosteroid, thyroid hormones, sex hormones, selective estrogen re-

ceptor modulators, or bisphosphonates. All subjects completed standardized questionnaires about their medical history, including past illnesses, family history, current medication, smoking, alcohol consumption, exercise, and menopausal status (in women). Height, weight, and waist and hip circumference were measured while subjects wore light clothing and no shoes. Waist circumference was measured midway between the lowest rib and the iliac crest, and hip circumference was taken over the widest part of the gluteal region. Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Smokers were defined as those who smoked at the time of the study or who had smoked within 5 years. Those who had stopped smoking in the last 5 years or more were regarded as nonsmokers. Questions about alcohol intake included the type of alcoholic beverage and the frequency and amount of alcohol consumed on a weekly basis. Based on their answers, amount of alcohol consumed per day was calculated in g/day. Regular exercisers were defined as those who exercised at least three times per week. Women who had not had a menstrual cycle for 1 year were considered postmenopausal. Hypertension was defined as systolic blood pressure (BP) $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg or current use of BP lowering agent. Diabetes mellitus was defined as fasting glucose $\geq$126 mg/dL or hemoglobin A1c $\geq$6.5% or current use of a glucose lowering agent. Hypercholesterolemia was defined as total cholesterol $\geq$200 mg/dL or use of a cholesterol lowering agent. The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine.

BMD measurement

BMD (g/cm²) measures of the lumbar spine (L1 to L4), femoral neck, and total hip were assessed using dual energy X-ray absorptiometry (QDR-4500W, Hologic, Bedford, MA, USA). Three subjects (two males, one female) could not be assessed for lumbar spine BMD due to prior vertebroplasty. In these subjects, only the femoral neck and total hip BMD were used as data. The coefficients of variation for these measurements were <1.1%. Osteoporosis was defined as BMD of the lumbar spine, total hip, or femoral neck that was 2.5 standard deviations (SDs) or more below the mean of a young Korean reference population (T-score <−2.5), and osteopenia was defined as a T-score between −1 and −2.5.

Biochemical values

Blood samples were collected from each subject after an overnight fast. The concentrations of plasma glucose, serum calci-

Table 1. Demographic and Clinical Characteristics of Participants according to Tertiles of Serum GGT Levels

Variable	Men				Women			
	Tertile 1 (*n*=100)	Tertile 2 (*n*=93)	Tertile 3 (*n*=96)	*P* for trend	Tertile 1 (*n*=57)	Tertile 2 (*n*=58)	Tertile 3 (*n*=58)	*P* for trend
Age, yr	57.2±8.3	55.5±9.0	54.7±7.9	0.037	51.1±10.1	55.7±9.4	58.0±8.8	<0.001
BMI, kg/m^2	24.4±2.3	25.4±2.7	25.6±2.9	0.002	21.9±2.7	22.4±3.0	23.6±3.7	0.005
Waist, cm	87.9±7.1	89.6±11.1	91.1±6.9	0.017	77.4±8.4	79.8±8.9	82.8±10.4	0.004
Alcohol, g/day	15.4±21.6	22.2±27.9	38.5±53.5	<0.001	0.2±0.8	1.6±5.6	2.0±8.7	0.122
Smoking	23 (23.0)	45 (48.4)	51 (53.1)	<0.001	2 (3.5)	3 (5.2)	5 (8.6)	0.241
Regular exercise	47 (47.0)	28 (30.1)	35 (36.5)	0.124	19 (33.3)	23 (39.7)	13 (22.4)	0.207
Hypertension	40 (40.0)	43 (46.2)	53 (55.2)	0.033	11 (19.3)	18 (31.0)	23 (39.7)	0.018
Diabetes mellitus	22 (22.0)	17 (18.3)	22 (22.9)	0.883	4 (7.0)	5 (8.6)	6 (10.3)	0.527
Hypercholesterolemia	41 (41.0)	43 (46.2)	64 (66.7)	<0.001	22 (38.6)	19 (32.8)	34 (58.6)	0.030
SBP, mm Hg	127±14	126±13	128±14	0.557	115±15	118±15	124±15	0.003
DBP, mm Hg	77±10	77±9	80±10	0.056	71±9	73±10	73±8	0.166
FPG, mg/dL	103±22	106±27	107±20	0.296	95±27	94±13	99±22	0.404
HbA1c, %	5.9±0.8	5.8±0.7	5.9±0.5	0.987	5.5±0.4	5.7±0.6	5.8±0.8	0.009
Triglyceride, mg/dL	119±56	142±58	180±95	<0.001	95±49	104±49	146±78	<0.001
HDL-C, mg/dL	47±9	46±11	49±12	0.282	57±12	56±13	55±14	0.410
LDL-C, mg/dL	119±35	114±28	122±37	0.628	115±25	124±23	128±35	0.017
TC, mg/dL	179±33	179±30	193±37	0.004	186±32	191±29	203±39	0.007
AST, mg/dL	22.8±19.0	22.1±6.4	25.6±11.9	0.147	19.4±6.2	21.2±4.8	26.5±9.5	<0.001
ALT, mg/dL	22.2±15.6	26.8±13.7	33.5±20.2	<0.001	15.7±5.6	18.6±6.5	27.8±14.6	<0.001
Creatinine, mg/dL	1.0±0.1	1.0±0.2	1.0±0.2	0.672	0.8±0.1	0.8±0.1	0.8±0.2	0.053

Values are expressed as mean±SD or number (%). Tertiles of serum GGT levels in men: tertile 1, ≤24 IU/L; tertile 2, 25–38 IU/L; tertile 3, ≥39 IU/L. Tertiles of serum GGT levels in women: tertile 1, ≤13 IU/L; tertile 2, 14–20 IU/L; tertile 3 ≥21 IU/L.

GGT, γ-glutamyl transferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

um, phosphorus, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total cholesterol, triglycerides, high density lipoprotein cholesterol, and low density lipoprotein cholesterol were measured using standard laboratory techniques. Serum GGT levels were measured by an enzymatic method using a Hitachi 7600-110 automated chemistry analyzer (Hitachi, Tokyo, Japan).

Statistical analyses

Statistical analyses were carried out using SPSS version 20.0 (IBM Co., Armonk, NY, USA). Male and female participants were divided into tertiles based on serum GGT level. The GGT levels in men were higher than those in women. Thus, sex-specific tertiles of serum GGT were used for analyses. In men, the cut-off points were <24 IU/L (tertile 1), 25 to 38 IU/L (tertile 2), and >39 IU/L (tertile 3). In women, the cut-off points were

<13 IU/L (tertile 1), 14 to 20 IU/L (tertile 2), and >21 IU/L (tertile 3). Demographic and clinical characteristics were analyzed according to tertiles of serum GGT levels (Table 1). A general linear model for a linear trend analysis was used in continuous data analyses. The chi-square test for a linear trend was used for the categorical data analyses. BMD at the lumbar spine, femoral neck, total hip, and BMD T-scores were analyzed according to tertiles of serum GGT levels (Table 2). Analysis of covariance was used to adjust for confounding variables. Variables for adjustment included age (years), BMI (kg/m^2), amount of alcohol consumed (g/day), smoking (yes or no), regular exercise (yes or no), hypertension (yes or no), diabetes mellitus (yes or no), hypercholesterolemia (yes or no), and postmenopausal state (in women; yes or no). Multiple linear regression analyses for BMD were performed after adjusting for confounding variables (Table 3). The distribution of

Table 2. Comparison of BMD among Tertiles of Serum GGT Levels

Variable	Men				Women			
	Tertile 1 (*n*=100)	Tertile 2 (*n*=93)	Tertile 3 (*n*=96)	*P* for trend	Tertile 1 (*n*=57)	Tertile 2 (*n*=58)	Tertile 3 (*n*=58)	*P* for trend
LS BMD, g/cm²	1.066±0.013	1.063±0.013	1.022±0.012	0.018	0.986±0.017	0.970±0.017	0.915±0.017	0.004
LS BMD (T-score)								
Model 1[a]	0.4±0.1	0.3±0.1	0.0±0.1	0.011	–0.2±0.1	–0.3±0.1	–0.8±0.1	0.004
Model 2[b]	0.4±0.1	0.3±0.1	0.0±0.1	0.006	–0.2±0.1	–0.3±0.1	–0.8±0.1	0.006
Model 3[c]	0.3±0.1	0.4±0.1	0.0±0.1	0.047	–0.3±0.1	–0.3±0.1	–0.7±0.1	0.022
Model 4[d]	0.3±0.1	0.4±0.1	0.0±0.1	0.050	–0.3±0.1	–0.3±0.1	–0.7±0.1	0.025
FN BMD, g/cm²	0.814±0.011	0.816±0.011	0.811±0.011	0.826	0.748±0.013	0.718±0.013	0.692±0.013	0.003
FN BMD (T-score)								
Model 1[a]	–0.3±0.1	–0.2±0.1	–0.3±0.1	0.793	–0.5±0.1	–0.8±0.1	–1.0±0.1	0.003
Model 2[b]	–0.2±0.1	–0.3±0.1	–0.3±0.1	0.117	–0.6±0.1	–0.7±0.1	–1.0±0.1	0.009
Model 3[c]	–0.2±0.1	–0.2±0.1	–0.4±0.1	0.163	–0.6±0.1	–0.8±0.1	–1.0±0.1	0.020
Model 4[d]	–0.2±0.1	–0.2±0.1	–0.4±0.1	0.188	–0.6±0.1	–0.8±0.1	–1.0±0.1	0.021
TH BMD, g/cm²	0.963±0.012	0.970±0.013	0.952±0.012	0.542	0.858±0.016	0.816±0.015	0.796±0.015	0.005
TH BMD (T-score)								
Model 1[a]	0.2±0.1	0.2±0.1	0.1±0.1	0.468	0.1±0.1	–0.3±0.1	–0.5±0.1	0.006
Model 2[b]	0.3±0.1	0.2±0.1	0.0±0.1	0.042	0.0±0.1	–0.3±0.1	–0.5±0.1	0.007
Model 3[c]	0.3±0.1	0.2±0.1	0.0±0.1	0.038	0.0±0.1	–0.3±0.1	–0.4±0.1	0.023
Model 4[d]	0.3±0.1	0.2±0.1	0.0±0.1	0.056	0.0±0.1	–0.3±0.1	–0.4±0.1	0.026

Values are expressed as mean±SE. Tertiles of serum GGT level in men: tertile 1, ≤24 IU/L; tertile 2, 25–38 IU/L; tertile 3, ≥39 IU/L. Tertiles of serum GGT level in women: tertile 1, ≤13 IU/L; tertile 2, 14–20 IU/L; tertile 3 ≥21 IU/L.
BMD, bone mineral density; GGT, γ-glutamyl transferase; LS, lumbar spine; FN, femoral neck; TH, total hip.
[a]Model 1: no adjustment; [b]Model 2: adjusted for age and body mass index; [c]Model 3: adjusted as in model 2 plus amount of alcohol consumed, smoking, regular exercise, and postmenopausal state (in women); [d]Model 4: adjusted as in model 3 plus hypertension, diabetes mellitus, and hypercholesterolemia.

GGT values was right-skewed; therefore, natural log-transformation was applied. Multiple logistic regression analysis was used to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) of having low bone mass including osteopenia and osteoporosis (Table 4). The OR (95% CI) for having low bone mass in those who belonged to tertiles 2 and 3 was evaluated compared to those who belonged to tertile 1. All tests were two-sided, and $P<0.05$ was considered significant.

RESULTS

Demographics and clinical characteristics of the participants
The mean±SD age of the participants was 55.8±8.4 years for men and 55.0±9.8 for women. The mean±SD BMI was 25.1±2.7 for men and 22.7±3.2 for women. The mean±SD serum level of GGT was 40.5±31.4 IU/L in men and 21.4±19.0 IU/L in women. The demographic and clinical character-

istics of the participants were compared among the tertiles of serum GGT levels in men and women (Table 1). The average age of men decreased with increasing serum GGT level from tertile 1 to tertile 3, whereas the average age of women increased. In both sexes, the mean values of BMI and waist circumference increased with serum GGT level from tertile 1 to tertile 3. The average amount of alcohol consumed and the percentage of participants smoking increased with increasing serum GGT level in men. The prevalence of hypertension and hypercholesterolemia also increased with elevating serum GGT level in both sexes. Other clinical and biochemical parameters are presented in Table 1.

Associations between serum GGT levels and BMD
Mean BMD values measured at the lumbar spine, femoral neck, and total hip were compared among tertiles of serum GGT levels (Table 2). Mean BMD values at the lumbar spine

Table 3. Multiple Linear Regression Analyses between Serum GGT Levels and BMD

	Ln GGT			
	Men		Women	
	β	*P* value	β	*P* value
LS BMD				
Model 1[a]	−0.163	0.006	−0.306	<0.001
Model 2[b]	−0.184	0.002	−0.316	<0.001
Model 3[c]	−0.146	0.016	−0.314	<0.001
Model 4[d]	−0.147	0.017	−0.311	<0.001
FN BMD				
Model 1[a]	−0.034	0.569	−0.271	<0.001
Model 2[b]	−0.119	0.037	−0.269	<0.001
Model 3[c]	−0.113	0.052	−0.276	<0.001
Model 4[d]	−0.111	0.061	−0.278	<0.001
TH BMD				
Model 1[a]	−0.065	0.268	−0.287	<0.001
Model 2[b]	−0.148	0.009	−0.306	<0.001
Model 3[c]	−0.152	0.008	−0.307	<0.001
Model 4[d]	−0.149	0.011	−0.307	<0.001

GGT, γ-glutamyl transferase; BMD, bone mineral density; Ln GGT, log-transformed value of serum GGT level; LS, lumbar spine; FN, femoral neck; TH, total hip.
[a]Model 1: no adjustment; [b]Model 2: adjusted for age and body mass index; [c]Model 3: adjusted as in model 2 plus amount of alcohol consumed, smoking, regular exercise, and postmenopausal state (in women); [d]Model 4: adjusted as in model 3 plus hypertension, diabetes mellitus, and hypercholesterolemia.

Table 4. Multiple Logistic Regression Analysis for Low Bone Mass

Variable	OR (95% CI)	*P* value
Age	1.053 (1.027–1.079)	<0.001
Women	2.210 (1.326–3.683)	0.002
Body mass index	0.850 (0.788–0.918)	<0.001
Amount of alcohol consumed	0.992 (0.982–1.001)	0.086
Smoking	1.386 (0.804–2.391)	0.241
Regular exercise	0.745 (0.481–1.152)	0.185
Serum GGT level		
Tertile 1	Reference	
Tertile 2	0.981 (0.584–1.651)	0.944
Tertile 3	2.271 (1.340–3.850)	0.002

Low bone mass: the lowest bone mineral density T-score among those measured at lumbar spine, femoral neck, and total hip ≤−1.0. Tertiles of serum GGT levels in men: tertile 1, ≤24 IU/L; tertile 2, 25–38 IU/L; tertile 3, ≥39 IU/L. Tertiles of serum GGT level in women: tertile 1, ≤13 IU/L; tertile 2, 14–20 IU/L; tertile 3 ≥21 IU/L.
OR, odds ratio; CI, confidence interval; GGT, γ-glutamyl transferase.

decreased as serum GGT level increased from tertile 1 to 3 in both sexes. Mean BMD values at the femoral neck and total hip also decreased with increasing serum GGT level in women. The BMD T-scores were compared between the different tertiles in men and women. As shown in Table 2, the BMD T-scores at all sites decreased with increasing GGT level from tertile 1 to tertile 3 in women, which remained statistically significant even after adjusting for confounders (model 1 to 4). In men, the BMD T-scores at lumbar spine significantly decreased with increasing serum GGT level (model 1). Adjustment for possible predictors of BMD such as age, BMI, amount of alcohol consumed, smoking, and regular exercise made the associations between serum GGT levels and BMD T-scores at the lumbar spine and total hip statistically significant (model 2, 3). Even after further adjustment for hypertension, diabetes mellitus, and hypercholesterolemia, the associations between serum GGT levels and BMD T-scores at the lumbar spine and total

hip showed a tendency toward inverse association (model 4). Multiple linear regression analysis for BMD was performed with log-transformed serum GGT level as covariates. In this model, log-transformed serum GGT level was inversely associated with BMD (Table 3).

Multiple logistic regression analysis for low bone mass
The multiple logistic regression analysis results for low bone mass including osteopenia and osteoporosis are presented in Table 4. Age, sex, BMI, amount of alcohol consumed, smoking, regular exercise, and tertile of serum GGT level were included as covariates. In this analysis, age, sex, BMI, and serum GGT level were associated with low bone mass. Age and BMI were independently associated with low bone mass with ORs (95% CI) of 1.053 (1.027 to 1.079) and 0.850 (0.788 to 0.918), respectively. Compared to men, the OR (95% CI) for low bone mass was 2.210 (1.326 to 3.683) for women. Tertile 3 of the serum GGT level was associated with increased risk for low bone mass compared to tertile 1 (OR, 2.271; 95% CI, 1.340 to 3.850; *P*=0.002), but tertile 2 of serum GGT level was not associated with low bone mass in this analysis.

DISCUSSION

In the present study, we showed that serum GGT level was inversely associated with BMD in Korean adults after adjusting

for confounders such as alcohol consumption, which is a well-known factor associated with both elevated serum GGT level and low bone mass. Furthermore, we also demonstrated that the highest tertile of serum GGT level ($\geq$39 IU/L in men and $\geq$21 IU/L in women) was associated with an increased risk for low bone mass including osteopenia and osteoporosis. These results suggest that GGT might negatively affect bone metabolism.

Several *in vitro* and *in vivo* studies have demonstrated that GGT can affect bone metabolism through systemic and local mechanisms [17-20]. It was shown that the GGT protein purified from rat kidney effectively stimulates osteoclast formation in mouse bone marrow culture possibly via expression of RANKL in marrow stromal cells [17]. In addition, transgenic mice overexpressing GGT either systemically or locally in skeletal tissue exhibit osteopenia and microstructural deterioration, which was attributable to both increased bone resorption and decreased bone formation as evidenced by histomorphometry [18]. Bone marrow cells from these mice exhibited significantly higher expression of transcription factors essential for osteoclastogenesis such as c-*fos*, c-*jun*, and NFATc1. In that study, mutated GGT devoid of enzyme activity was also as potent as the wild-type molecule for inducing osteoclast formation, suggesting that GGT acts not as an enzyme but as a cytokine. GGT-deficient mice also exhibit a marked decrease in bone density along with other abnormalities including growth retardation, early mortality, and cataracts [19,21]. Osteopenia in GGT-deficient mice was attributable to both increased bone resorption and decreased bone formation. In these mice, restoration of cysteine deficiency by *N*-acetylcysteine supplementation ameliorated skeletal abnormalities, suggesting that abnormal cysteine metabolism in GGT-deficient mice might have caused the abnormal skeletal phenotype [19]. A clinical study also suggested GGT as a marker of bone resorption in human subjects. It showed that urinary GGT excretion was highly correlated with deoxypyridinoline, an established biochemical marker of bone resorption, in a survey of postmenopausal women [20].

Taken together, both deficiency and excess GGT seem to be involved in abnormal bone metabolism, which results in decreased bone mass. GGT seems to affect bone formation mainly through its enzymatic activity on glutathione metabolism, and also affects bone resorption as a cytokine independent of enzymatic activity. However, GGT deficiency is a very rare autosomal recessive disease in a clinical setting, and only a few patients with this disease have been reported worldwide [22-26]. In contrast, patients with excess GGT can easily be found, particularly among those who chronically consume alcohol or

those with hepatobiliary diseases. Therefore, excess GGT rather than deficiency is clinically relevant to the general health condition. In the present study, we also think excess GGT may explain the inverse relationship between serum GGT and BMD.

As stated above, GGT also plays an important role in the intracellular antioxidant defense by maintaining glutathione homeostasis [27]. Cells increase expression of glutathione in response to oxidative stress, as this tripeptide removes oxidants [28,29]. Expression of several enzymes involved in glutathione homeostasis including GGT must be modulated to upregulate glutathione synthesis. Several experimental studies have demonstrated that GGT expression is increased in response to oxidative stress [30-32]. This result suggests that increased GGT concentration could be a marker of oxidative stress that is known to play a role in the development of many pathological conditions such as cancer, diabetes mellitus, atherosclerosis, neurodegenerative diseases, and rheumatoid arthritis [33,34]. Oxidative stress is also known to affect bone metabolism and have an inverse association with bone mass [35,36]. Several experimental studies have shown that oxidative stress enhances osteoclastic activity [37], while inhibiting osteoblastic differentiation [38]. Therefore, serum GGT level as a marker of oxidative stress may have an inverse relationship with bone mass, as found in the present study. Abnormal bone metabolism associated with liver diseases may also explain the association between bone and GGT in this study. Serum level of GGT is a well-known marker of hepatobiliary disease. In the present study, serum levels of AST and ALT also increased with elevating serum GGT level. There have been studies that demonstrated chronic liver diseases may have negative effects on bone [39].

The present study had several limitations. First, because it was a cross-sectional observational study, the associations found are not proof of causal relationships and might be confounded by many unmeasured and unaccounted for variables even after multiple adjustments. Second, we did not measure estrogen levels, which may play a role in the relationship between serum GGT and BMD, particularly in women. In a previous study, oral contraceptive use and menopause were associated with increased serum GGT levels [40], suggesting that estrogens, a well-known determinant of bone mass, might also be a factor that affects serum GGT levels. Third, we did not measure bone turnover markers. Therefore, we could not determine how serum GGT is clinically associated with bone turnover.

In conclusion, we showed that serum GGT level was inversely associated with BMD in Korean adults and that excess GGT level was associated with increased risk for low bone

mass. Further studies are necessary to investigate the effect of GGT on bone among those with increased serum GGT level such as individuals with chronic alcoholism or hepatobiliary diseases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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