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ORIGINAL ARTICLE

Association between bone mineral density and nonalcoholic fatty liver disease in Korean adults

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Abstract
Purpose Nonalcoholic fatty liver disease (NAFLD) is associated with various metabolic abnormalities that can increase the risk of an osteoporotic fracture. Across the few previous studies of the association between NAFLD and bone mineral density (BMD), the association was not consistent. We examined the association between BMD and NAFLD in generally healthy adults.
Methods The subjects who visited the Seoul National University Hospital for health checkup between 2005 and 2015 were included. Men aged more than 40 and postmenopausal women were included. Lumbar spine and femoral neck (FN) BMD were measured using dual-energy X-ray absorptiometry. Liver ultrasonography was conducted to evaluate the extent of fatty changes. After excluding subjects with a secondary cause of liver disease such as heavy drinking or viral hepatitis, multivariable linear regression analysis adjusted for possible cofactors was performed to investigate the association between BMD and NAFLD.
Results A total of 6634 subjects was included in this study (men:women = 3306:3328). Multivariate regression analysis revealed a significant negative association between FN BMD and NAFLD in men ($\beta = -0.013$, $p = 0.029$). However, there was a positive correlation between lumbar spine BMD and NAFLD in postmenopausal women ($\beta = 0.022$, $p = 0.005$).
Conclusions Moderate or severe NAFLD exerted a detrimental effect on FN BMD in men. However, moderate or severe NAFLD had a positive effect on lumbar spine BMD in postmenopausal women. Potential sex-specific differences of the effect of NAFLD on BMD need to be elucidated further.

Keywords Nonalcoholic fatty liver disease · Osteoporosis · Bone mineral density · Metabolic syndrome

Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common clinical disorders of the liver that can manifest as mild steatosis or nonalcoholic steatohepatitis and progress to end-stage liver disease with cirrhosis and hepatocellular carcinoma [1, 2]. Some studies indicated a possible association between NAFLD and clinical diseases, such as diabetes, cardiovascular disease, and chronic kidney disease [3–5]. Moreover, NAFLD is associated with central obesity, which is a component of metabolic syndrome (MetS) [6, 7]. These findings provide evidence that NAFLD is a hepatic manifestation of MetS, which is a cluster of risk factors for cardiovascular diseases, including central obesity, dyslipidemia, hypertension, and impaired glucose tolerance [8]. Recently, studies have determined that the risk of osteoporosis, characterized by decreased

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bone mineral density (BMD), is higher in subjects with MetS [9–12].

These associations have led to a concern about the relationship between NAFLD and osteoporosis. However, the association has not been consistent across studies [13–17]. In addition, the results of these studies might not be generalizable because of critical limitations, such as the small sample sizes [13, 14, 18–20], insufficient consideration of cofactors that could affect BMD (e.g., waist circumference, physical activity, inflammatory markers), and inclusion of a single sex [13, 14]. Moreover, as BMDs were not measured in multiple sites, the associations between NAFLD and BMDs of the femoral neck (FN) and lumbar spine could not be compared between studies [13]. Because most of these studies used ultrasonography to diagnose NAFLD, which does not provide information regarding the severity of liver steatosis, we evaluated the severity of fatty change in the present study using a four-point scale: normal (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3).

In this study, we aimed to investigate the association between NAFLD, with consideration of the level of steatosis, and lumbar spine and FN BMDs, using data from generally healthy adults and including various possible cofactors.

Methods

Subjects

In this study, 19,993 subjects who visited Seoul National University Hospital to undergo a health checkup, dual-energy X-ray absorptiometry (DXA), and abdominal ultrasonography between December 1, 2005, and March 31, 2015, were included. We initially chose to include adults aged >40 years. However, we considered that menopause is a major determinant of BMD [20, 22]. As a questionnaire for the assessment of menopause was not available for all women, we substituted being menopausal for age ≥55 years in defining subjects at the postmenopausal stage, by considering the trend of the ages at menopause in the general population [23, 24]. Finally, 3306 male and 3328 female subjects were included in this study (Fig. 1).

The subjects without high-sensitivity C-reactive protein (HSCRP) data were excluded. Those who did not answer questions about their current drinking and smoking statuses or physical activities were also excluded. In particular, those who did not provide a response for alcohol consumption were excluded, because NAFLD and non-NAFLD could not be distinguished in these subjects. Subjects with any evidence of chronic viral liver disease, cholestasis, cirrhosis, or malignancy were excluded. In addition, we

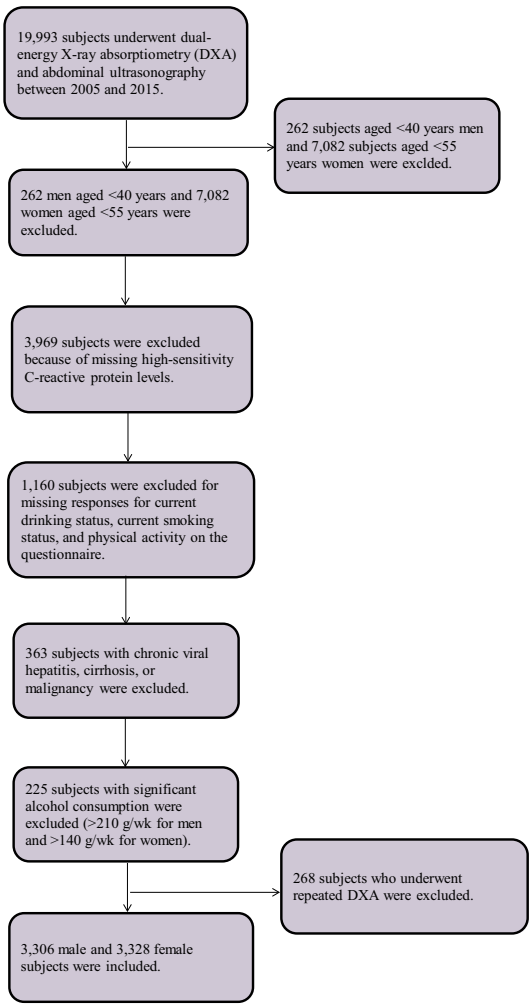

Fig. 1 Flowchart of the study subject inclusion

decided to use the latest BMD results in the examinees who underwent repeated DXA.

Smoking habit was divided into two categories as follows: (1) current smoker and (2) nonsmoker or ex-smoker. Information on the type, amount, and frequency of alcohol consumption was collected. Based on the alcohol content of the beverages reported, the mean daily alcohol consumption was calculated and expressed in grams per week. Physical activity at leisure time was estimated using the short form of the International Physical Activity Questionnaire, by adding questions on the frequency and duration of moderate and vigorous activities and walking. The subjects were divided into either the exercise or nonexercise group. The exercise group included subjects who exercised moderately for >150 min/week or those who exercised intensively for >75 min/week [25].

This study was approved by the Seoul National University Hospital Institutional Review Board. It was designed

as a retrospective, cross-sectional study, and data were obtained by reviewing hospital records.

Anthropometric measurements

Body mass index (BMI) was calculated by dividing weight by the square of height (kg/m^2). Waist circumference (WC) was measured horizontally at the level of the umbilicus. Prior to measuring blood pressure (BP), the subjects were asked to rest for 5 min.

Serum biomarkers

After overnight fasting, serum was collected for measurement of biochemical markers, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and fasting plasma glucose (FPG) levels. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltranspeptidase (γ-GTP) were measured using standard biochemical methods. Patients were divided into low-, moderate-, and high-risk groups according to HSCRP levels on the basis of the following cutoff points: >1, 1–3, and >3.0 mg/L, respectively. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula: GFR = 186 × serum creatinine$^{-1.154}$ × age$^{-0.203}$ × 0.742 (for females). Using the chronic kidney function categorization of the US National Kidney Foundation, renal function was classified according to estimated GFR (eGFR) as follows: normal renal function (≥90 mL/min/1.73 m^2), mild renal dysfunction (60–89.9 mL/min/1.73 m^2), moderate renal dysfunction (30–59.9 mL/min/1.73 m^2), severe renal dysfunction (15–29.9 mL/min/1.73 m^2), and kidney failure (<15 mL/min/1.73 m^2) [26].

Definition of MetS

MetS was defined according to the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLBI) criteria for Asians [21]. For the diagnosis of MetS, three or more of the following criteria must be fulfilled: WC ≥90 cm in men and ≥80 cm in women, fasting TG ≥150 mg/dL or use of lipid-lowering medication, HDL <40 mg/dL in men and <50 mg/dL in women or use of medication, BP ≥130/85 mmHg or use of antihypertensive medication, and FPG ≥100 mg/dL or current use of anti-diabetes medication.

DXA for lumbar spine and FN BMDs

BMDs (g/cm^2) at the lumbar spine and FN were measured using DXA (Lunar Prodigy Advance; General Electric Medical Systems, Milwaukee, WI, USA).

Liver ultrasonography and criteria for NAFLD

NAFLD was diagnosed based on ultrasonographic evidence of hepatic steatosis, such as a bright hepatic echo pattern, loss of intrahepatic architecture, and increased echo attenuation. According to ultrasonographic appearance, grades 0, 1, 2, and 3 indicated normal, mild, moderate, and severe changes, respectively. The subjects were divided into two groups as follows: group 1 included grades 0 (normal) and 1 (mild), and group 2 included grades 2 (moderate) and 3 (severe).

NAFLD was defined as definite hepatic steatosis on ultrasonography without a secondary cause including significant alcohol abuse (>210 g/week for men and >140 g/week for women) [26], any evidence of chronic viral liver disease, and other metabolic liver diseases. Liver ultrasonography was conducted with a 4-MHz probe and evaluated by board certified radiologists.

Statistical analysis

All analyses were performed using Stata version 14.0 (StataCorp., College Station, TX) For each baseline variable, according to sex, we performed the *t* test for continuous variables and the Chi-square test for categorical variables. To evaluate the association between NAFLD and BMD, factors with *p* values <0.05 in the univariate analysis were included in the subsequent linear regression analysis. First, unadjusted linear regression analyses were conducted to assess the association between each factor and the lumbar spine and FN BMDs. Then, multivariate linear regression analysis was conducted to assess the association between NAFLD and BMD after adjusting for the significant factors. Multiple regression analysis was performed with the mean lumbar spine and FN BMDs as dependent variables and two groups of NAFLD (groups 1 and 2) as the independent variables. Group 1 consisted of patients with a normal or mildly fatty liver on ultrasonography, and group 2 consisted of patients with advanced fatty liver on ultrasonography.

The analyses were adjusted for age, BMI, smoking status, alcohol consumption status, and ALT level, which were considered in light of the findings of previous studies (model 1). In addition, model 2 was adjusted for WC, HSCRP, and physical activity. Finally, model 3 was adjusted for diastolic blood pressure (DBP), FPG, HDL level, and MDRD-GFR, which were statistically significant variables in the univariate regression analysis. The BMD trend according to NAFLD was evaluated using the p values from the trend test.

Results

The general characteristics of the subjects are presented in Table 1. In both sexes, the NAFLD group had higher mean

Table 1 General characteristics of the study population

	Male ($n = 3306$)		p	Female ($n = 3328$)		p
	Without NAFLD ($n = 2018$) mean ± SD	With NAFLD ($n = 1288$) mean ± SD		Without NAFLD ($n = 2112$) mean ± SD	With NAFLD ($n = 1217$) mean ± SD	
Age (years)	57.118 ± 9.078	55.511 ± 8.236	<0.001*	62.764 ± 6.421	62.933 ± 6.211	0.461
Weight (kg)	65.862 ± 8.920	73.402 ± 8.877	<0.001*	54.602 ± 7.029	60.513 ± 7.677	<0.001*
Height (cm)	168.608 ± 6.030	169.236 ± 5.994	0.004*	154.525 ± 5.672	154.541 ± 5.359	0.936
BMI (kg/m^2)	23.131 ± 2.593	25.607 ± 2.594	<0.001*	22.877 ± 2.788	25.339 ± 2.984	<0.001*
WC (cm)	84.785 ± 7.807	92.045 ± 6.891	<0.001*	81.766 ± 8.135	88.555 ± 8.078	<0.001*
SBP (mmHg)	126.084 ± 15.320	129.790 ± 15.124	<0.001*	125.006 ± 16.544	129.274 ± 15.503	<0.001*
DBP (mmHg)	76.391 ± 10.677	78.994 ± 10.738	<0.001*	74.542 ± 18.589	75.956 ± 10.168	0.014*
FPG (mg/dL)	95.447 ± 22.078	104.385 ± 26.372	<0.001*	92.815 ± 17.415	103.638 ± 24.681	<0.001*
TC (mg/dL)	193.848 ± 35.115	202.710 ± 39.573	<0.001*	205.195 ± 37.198	208.117 ± 40.062	0.034*
TG (mg/dL)	111.215 ± 67.230	155.052 ± 102.001	<0.001*	98.503 ± 50.408	132.125 ± 74.671	<0.001*
HDL (mg/dL)	54.283 ± 14.080	47.104 ± 10.801	<0.001*	60.905 ± 15.449	55.271 ± 12.872	<0.001*
LDL (mg/dL)	117.349 ± 32.573	124.785 ± 37.783	<0.001*	124.616 ± 34.365	126.524 ± 38.638	0.143
AST (IU/L)	26.036 ± 13.622	29.311 ± 14.850	<0.001*	24.591 ± 10.366	26.885 ± 12.399	<0.001*
ALT (IU/L)	26.691 ± 18.159	36.571 ± 22.066	<0.001*	21.105 ± 13.979	27.861 ± 17.136	<0.001*
γ-GTP (IU/L)	43.846 ± 61.872	51.737 ± 51.899	<0.001*	25.379 ± 130.801	30.916 ± 39.579	0.151
Mean lumbar BMD (L1-L4) (g/cm^2)	1.183 ± 0.185	1.234 ± 0.173	<0.001*	0.993 ± 0.153	1.031 ± 0.152	<0.001*
Femoral neck BMD (g/cm^2)	0.935 ± 0.135	0.960 ± 0.127	<0.001*	0.794 ± 0.111	0.811 ± 0.107	<0.001*
Osteoporosis			<0.001*			<0.001*
Normal	1303 (64.57)	965 (74.92)		706 (33.44)	473 (38.87)	
Osteopenia	648 (32.11)	312 (24.22)		1185 (56.13)	688 (56.53)	
Osteoporosis	67 (3.32)	11 (0.85)		220 (10.42)	56 (4.60)	
eGFR (mL/min/1.73 m^2)			0.969			0.172
≥90	604 (30.12)	382 (29.75)		698 (33.41)	442 (36.710)	
60–89	1308 (65.24)	842 (65.58)		1280 (61.27)	712 (59.140)	
30–59	91 (4.54)	58 (4.52)		103 (4.93)	48 (3.990)	
15–29	2 (0.10)	2 (0.16)		5 (0.24)	2 (0.170)	
≤15	0 0.00	0 0.00		3 (0.14)	0 0.000	
HSCRP			<0.001*			<0.001*
<1 mg/L	1322 (65.51)	672 (52.17)		1507 (71.39)	598 (49.14)	
1–3 mg/L	466 (23.09)	434 (33.70)		416 (19.71)	436 (35.83)	
≥3 mg/L	230 (11.40)	182 (14.13)		188 (8.91)	183 (15.04)	
Obesity			<0.001*			<0.001*
No (BMI < 25 kg/m^2)	1560 (77.30)	553 (42.93)		1675 (79.35)	588 (48.32)	
Yes (BMI ≥ 25 kg/m^2)	458 (22.70)	735 (57.07)		436 (20.65)	629 (51.68)	
Metabolic syndrome			<0.001*			<0.001*
No	1723 (85.38)	781 (60.64)		1646 (77.97)	646 (53.08)	
Yes	295 (14.62)	507 (39.36)		465 (22.03)	571 (46.92)	
Type 2 diabetes mellitus			<0.001*			<0.001*
No	1315 (88.14)	626 (77.86)		1393 (89.76)	658 (79.28)	
Yes	177 (11.86)	178 (22.14)		159 (10.24)	172 (20.72)	
Current smoking status			0.612			0.871
No	1419 (70.32)	895 (69.49)		2061 (97.63)	1187 (97.53)	
Yes	599 (29.68)	393 (30.51)		50 (2.37)	30 (2.47)	

Table 1 continued

	Male ($n = 3306$)		p	Female ($n = 3328$)		p
	Without NAFLD ($n = 2018$) mean ± SD	With NAFLD ($n = 1288$) mean ± SD		Without NAFLD ($n = 2112$) mean ± SD	With NAFLD ($n = 1217$) mean ± SD	
Current alcohol consumption status			0.586			0.594
No	990 (48.99)	605 (44.62)		1767 (83.70)	1010 (82.99)	
Yes	1031 (51.01)	751 (55.38)		344 (16.30)	207 (17.01)	
Physically active			<0.001*			0.001*
No	1441 (71.41)	1009 (78.34)		1674 (79.30)	1024 (84.14)	
Yes	577 (28.59)	279 (21.66)		437 (20.70)	193 (15.86)	

NAFLD nonalcoholic fatty liver disease, *BMI* body mass index, *WC* waist circumference, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *FPG* fasting plasma glucose, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyltranspeptidase, *BMD* bone mineral density, *HSCRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate

* $p < 0.05$

Table 2 Summary of the regression analysis of the correlations between BMD and NAFLD in groups 1 and 2

	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
Men						
Lumbar spine BMD	−0.013	0.122	−0.012	0.144	−0.012	0.163
Femoral neck BMD	−0.015	0.012	−0.012	0.036	−0.013	0.029
Postmenopausal women						
Lumbar spine BMD	0.020	0.008	0.020	0.009	0.022	0.005
Femoral neck BMD	0.006	0.241	0.006	0.220	0.007	0.206

Model 1 included age, body mass index (BMI), alanine aminotransferase (ALT) level, smoking status, alcohol consumption status. Model 2 included age, BMI, waist circumference, ALT level, high-sensitivity C-reactive protein level, smoking status, alcohol consumption status, physical activity. Model 3 included the same as model 2 plus diastolic blood pressure, fasting plasma glucose, triglyceride level, high-density lipoprotein level, eGFR

BMD bone mineral density, *NAFLD* nonalcoholic fatty liver disease

body weight, BMI, WC, SBP, DBP, FPG level, TC level, TG level, AST level, ALT level, and lumbar spine and FN BMDs than the non-NAFLD group ($p < 0.05$), but the non-NAFLD group had significantly higher HDL levels than the NAFLD group ($p < 0.05$, Table 1). Among the subjects, the men were younger and had significantly higher weight, height, BMI, WC, systolic blood pressure (SBP), DBP, TG level, FPG level, AST level, ALT level, γ-GTP level, and BMD in the lumbar spine and FN, but lower serum TC, HDL, and LDL levels and eGFR. Ultrasonographic results, serum HSCRP level, smoking and alcohol consumption statuses, and physical activity significantly differed between the men and women (Table S1).

The results of the univariate regression analyses are listed in Table S2. In both men and women, NAFLD was significantly correlated with lumbar spine BMD ($\beta = 0.05$; 95 % confidence interval [CI], 0.041–0.060; $p < 0.001$) and FN BMD (β coefficient = 0.03; 95 % CI, 0.020–0.032; $p < 0.001$). Age, body weight, height, BMI, WC, DBP, and FPG, TC, TG, γ-GTP, AST, and ALT levels were also associated with BMD.

Subgroup analyses according to both sex and severity of fatty liver were performed in group 1 (grades 0 and 1). BMD did not differ significantly between the patients with and without mild NAFLD (Table S3). However, among the patients with NAFLD in group 2 (moderate and severe steatosis), the men had lower FN BMDs ($\beta = -0.013$; 95 % CI, −0.024 to −0.001; $p = 0.029$), and the women had higher mean lumbar spine BMDs ($\beta = 0.022$; 95 % CI, 0.007–0.037; $p = 0.005$) than the patients in group 1 (Table 2). The result of the subgroup analysis performed for women who responded as being menopausal was consistent with the results of the analysis for the postmenopausal women (aged ≥55 years; Table S4).

Discussion

The results of the present analyses show a significant difference in the FN BMDs of men between groups 1 and 2 group after controlling for additional variables ($\beta = -0.013$, $p = 0.029$). In contrast, a positive correlation was found between lumbar spine BMD and NAFLD in postmenopausal women ($\beta = 0.022$, $p = 0.005$), which is not consistent with previous findings [13, 14].

We can conclude that mild liver steatosis on ultrasonography does not affect BMD. However, advanced NAFLD was associated with BMD. Purnak et al. [18] showed that, although simple steatosis was not associated with decreased BMD, the presence of elevated serum ALT and HSCRP levels, which are indicators of nonalcoholic steatohepatitis, was associated with lower BMD.

Furthermore, although ultrasonography is an established technique for screening patients at risk of NAFLD, it has low accuracy and operator dependency in detecting mild steatosis but has acceptable sensitivity and specificity in detecting moderate-to-severe hepatic steatosis [22]. For patients without chronic liver disease, ultrasonography offers a reasonably accurate diagnosis of moderate-to-severe liver steatosis, with a reported sensitivity ranging from 81.8 to 100.0 % and a specificity as high as 98 % [22].

In our study, we found a negative association between NAFLD and FN BMD in men, consistent with previously reported results, but a positive association between NAFLD and lumbar spine BMD. Previous studies observed a sex-related difference in the association between NAFLD and BMD [14, 23, 24]. Potential explanations for this sex-related difference include features of age-related osteoporosis [25, 26], body fat deposition [27], a tendency to fall, and sex hormone levels.

In the present study, although NAFLD in women did not appear to have any effect on FN BMD, the results showed a positive correlation between NAFLD and lumbar spine BMD. According to the results of previous studies, central body fat distribution was associated with spinal BMD, but not with FN BMD [28, 29]. Saarelainen et al. [28] suggested that irrespective of the use of hormone replacement therapy (HRT), higher trunk fat mass is positively associated with spinal BMD but not with hip BMD in postmenopausal women. Kirchengast et al. [30] found that central or upper body fat distribution did not affect hip BMD. These findings suggest that upper body fat can hinder spinal bone loss and is mainly associated with higher lumbar spine BMD irrespective of HRT. In addition, the lumbar spine had a much higher relative proportion (60–95 %) of metabolically active and hormonally more sensitive trabecular bone than the FN (25 %) [31, 32].

Although many preceding studies have been conducted, the pathophysiological associations between NAFLD and BMD have not been completely clarified. However, identification of the molecular pathways and mechanisms that link these two disorders is of great importance because the development of preventive and pharmacological approaches for these disorders may be warranted [15].

The precise mechanisms that have been identified include insulin resistance and inflammation. Excess accumulation of adipose tissue in the liver increases the release of free fatty acids from adipocytes, which may be a main factor in the modulation of insulin sensitivity [33]. Insulin resistance and an inflammatory response are of critical importance for inducing NAFLD [34]. Prior studies indicate that insulin levels and/or insulin resistance is associated with BMD [35, 36]. Many factors promote inflammation, including the presence of pro-inflammatory cytokines, adipokines, mitochondrial dysfunction, oxidative stress, and subsequent lipid peroxidation. When accumulated in the mitochondria, free fatty acids and cholesterol are considered the "aggressive" lipids that lead to tumor necrosis factor alpha (TNF-α)-mediated liver damage and reactive oxygen species formation. These lipids could also exist in a nonsteatotic liver and act as early "inflammatory" hits that lead to NAFLD pathologies [37]. Furthermore, TNF-α increases the expression levels of genes that amplify osteoclastogenesis and decrease the expression levels of genes that are involved in bone formation [38]. In addition, recent evidence indicates that an elevated serum HSCRP level is an independent risk factor for NAFLD [34, 39], and the ALT level has been used as a marker of NAFLD [40]. Many previous studies showed that these pro-inflammatory chemokines and cytokines contribute to bone metabolism [14]. However, in the present study, the correlation analysis did not reveal a significant relationship between BMD and inflammatory markers such as HSCRP and ALT levels. Future studies are needed to clarify the underlying mechanism.

In this study, the associations observed differed from those demonstrated by previous research, likely because previous studies did not adjust for many of the confounding factors that were included in the present study and consisted of healthy old people who underwent health screening. While the sample size of most previous studies was relatively small, the present study had a large sample size of a generally healthy population with normal biochemical and metabolic profiles, which might allow for generalization to the Korean population.

This study had some limitations. First, hepatic biopsy data were not available for our participants, and NAFLD was diagnosed according to the presence of hepatic steatosis on ultrasonography. However, although liver biopsy is the gold standard for confirming NAFLD, ultrasonographic examination is the most widely used modality to detect hepatic steatosis. Moreover, it has been suggested to have high sensitivity (89 %) and specificity (93 %) for the prediction of liver histology [41]. Second, bone metabolism

could be influenced by many undetected confounding factors. Although the present study considered many additional factors that were not evaluated in previous studies, including physical activity, inflammatory markers, and eGFR, undetected confounding factors that contribute to osteoporosis such as the use of corticosteroids, calcium/vitamin D intake, and use of HRT could not be ruled out [42, 43]. Finally, owing to the cross-sectional nature of the present study, incidental correlations could not be completely excluded. Longitudinal studies are needed to clarify their precise interrelationships.

In conclusion, the results of this analysis showed a significant difference in BMD between patients with moderate or severe NAFLD and those with normal or mild NAFLD, after adjusting for possible confounding factors. Potential sex-specific differences in the effect of NAFLD on BMD need to be elucidated further, and additional studies are needed to clarify the correlation between NAFLD and BMD.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants (that were performed by any of the authors of this article) were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent No informed consent.

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