Endocrine (2012) 42:423–429
DOI 10.1007/s12020-012-9639-6

ORIGINAL ARTICLE

Association of nonalcoholic fatty liver disease with low bone mass in postmenopausal women

Seong-Su Moon · Young-Sil Lee · Sung Woo Kim

Received: 1 December 2011 / Accepted: 16 February 2012 / Published online: 11 March 2012

Abstract Osteoporosis is a disease associated with insulin resistant states such as central obesity, diabetes, and metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is also increased in such conditions. However, little is known about whether osteoporosis and nonalcoholic fatty liver disease are etiologically related to each other or not. We examined whether bone mineral density (BMD) is associated with NAFLD in pre- and postmenopausal women. Four hundred eighty-one female subjects (216 premenopausal and 265 postmenopausal) were enrolled. Lumbar BMD was measured using dual-energy X-ray absorptiometry. Liver ultrasonography was done to check the severity of fatty liver. We excluded subjects with a secondary cause of liver disease. Blood pressure, lipid profile, fasting plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase, and body mass index were measured in every subject. Mean lumbar BMD was lower in subjects with NAFLD than those without NAFLD in postmenopausal women (0.98 ± 0.01 vs. 1.01 ± 0.02 g/cm^2, $P = 0.046$). Multiple correlation analysis revealed a significant association between mean lumbar BMD and NAFLD in postmenopausal subjects after adjusting for age, body mass index, ALT, smoking status, and alcohol consumption (β coefficient -0.066, 95% CI -0.105 to -0.027, $P = 0.001$). Even after adjusting the presence of metabolic syndrome, the significance was maintained (β coefficient -0.043, 95% CI -0.082 to -0.004, $P = 0.031$). Lumbar BMD is related with NAFLD in postmenopausal females. We suggest that postmenopausal women with NAFLD may have a higher risk of osteoporosis than those without.

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

S.-S. Moon (✉) · Y.-S. Lee
Department of Internal Medicine, Dongguk University School of Medicine, Dongdae-ro 87, Gyeongju, Gyeongbuk province 780-350, South Korea
e-mail: drmoonss@hanmail.net

S. W. Kim
Department of Radiology, Dongguk University School of Medicine, Gyeongju, South Korea

Introduction

Osteoporosis is a skeletal disease characterized by reduced bone mass and quality with a consequent increased risk of fracture [1], which is considered as a major cause of morbidity and mortality in old age [2]. It is not confined to the bone but is also associated with systemic metabolic derangements such as central obesity, type 2 diabetes, and metabolic syndrome [3–6].

It has been reported that osteoporosis is increased in subjects with metabolic syndrome, which is a cluster of risk factors of cardiovascular disease, including central obesity, dyslipidemia, hypertension, and impaired glucose tolerance [7–9]. Incidence of osteoporotic fractures was also higher in patients with metabolic syndrome. Thus, metabolic syndrome is suggested as a risk factor for osteoporosis [6]. However, the associations between osteoporosis and individual components of metabolic syndrome are still controversial.

Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome [10, 11] and is also strongly associated with obesity, type 2 diabetes, and metabolic syndrome [12, 13]. Up to 75% of obese patients and 70% of patients with type 2

diabetes are affected by NAFLD [14, 15]. NAFLD is defined as hepatic steatosis in the absence of a secondary cause and is the most common form of chronic liver disease [16, 17]. Although simple steatosis is considered benign, hepatic steatosis can progress to a severe form of the disease such as nonalcoholic steatohepatitis and liver cirrhosis. Therefore, NAFLD is recognized as an emerging health problem worldwide [12, 18, 19].

So far, there has been no study about whether osteoporosis and nonalcoholic fatty liver disease are etiologically related to each other or not. Therefore in this study, we examined the association between BMD and NAFLD in Korean women.

Subjects and methods

In this retrospective cross-sectional study, 481 subjects (216 premenopausal and 265 postmenopausal) who visited the Kyungpook National University Hospital for health check-up were enrolled between October 1, 2009 and December 31, 2009. All subjects enrolled in this study were of Korean ethnicity. The subjects with significant alcohol abuse (>20 g of ethanol per week), previous use of steatogenic medications, any evidence of chronic viral liver disease, cholestasis, and other metabolic liver diseases were excluded. The subjects were asked about medications, hypertension, and other important medical history. In the physical examinations, height, body weight, and blood pressure were measured by standard methods. Prior to measuring blood pressure, the subjects were asked to rest for 10 min and, while seated, the systolic and diastolic pressures in the upper arm were measured twice.

Blood was drawn from all patients the morning after an overnight fast. Fasting blood glucose (FBG) levels were measured by the hexokinase method using Modular Analytics SWA (Roche Diagnostics GmbH, Mannheim, Germany). Total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltranspeptidase (γ-GTP) levels were determined using a Hitachi Modular Analytics D2400 apparatus (Roche, Tokyo, Japan) assay.

Subjects were classified as having metabolic syndrome if they had any three of the following five characteristics: obesity [body mass index (BMI) $\geq$ 25 kg/m^2], hypertriglyceridemia (triglycerides $\geq$ 150 mg/dl or triglyceride-lowering medication), HDL-C $<$ 50 mg/dl in females, hypertension ($\geq$130 mmHg systolic or $\geq$85 mmHg diastolic pressure, or use of anti-hypertensive medication), and hyperglycemia (FPG $\geq$ 100 mg/dl or use of anti-hyperglycemic medication, or previously diagnosed type 2 diabetes). Because waist circumference measurements were not available for all subjects, we substituted overall adiposity (i.e., BMI $\geq$ 25 kg/m^2, which has been proposed as a cutoff for the diagnosis of obesity in Asians) for abdominal obesity [20]. This study was approved by the Kyungpook National University Hospital Institutional Review Board. This study was designed as a retrospective, cross-sectional study. Actually the data were obtained by reviewing records. Therefore, we could be exempted from obtaining informed consent from each subject by the Institutional Review Board (KNUH-2012-01-006).

Dual X-ray absorptiometry for lumbar BMD

BMD at the lumbar spines (L1-4) were measured by dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy; General Electric Medical Systems, Milwaukee, WI, USA).

Ultrasonography for liver and criteria of NAFLD

NAFLD was defined as the presence of definite hepatic steatosis on ultrasonography such as a bright hepatic echo pattern, increased attenuation of the echo beam, and loss of intrahepatic architectural detail [21, 22] without a secondary cause including significant alcohol abuse (>20 g of ethanol per week), previous use of steatogenic medications, any evidence of chronic viral liver disease, and other metabolic liver diseases. Ultrasonography for liver conducted using a 4 MHz probe (Acuson Sequoia, CA, USA) was performed by grading by an experienced radiologist.

Statistical analyses

All analyses were performed using Statistical Package for Social Science 15.0 software (SPSS, Chicago, IL, USA). Nominal variables are presented as the number of cases with the percentage and continuous variables as the mean $\pm$ standard of error. The significance of the mean differences between the two groups was evaluated by Student's t test. The categorical variables of the groups were compared by χ^2 analysis. Univariate regression analysis was performed using mean lumbar BMD as a dependent variable and with other variable as covariates to identify factors associated with mean lumbar BMD. The association between mean lumbar BMD and NAFLD was investigated by multivariate regression analyses, with NAFLD serving as the independent variable and mean lumbar BMD serving as the dependent variable. These analyses were adjusted for age, body mass index, and ALT, which were statistically significant variables ($P < 0.05$) in the univariate regression analysis (model 1). Age, body mass index, ALT, smoking status, and alcohol consumption status were adjusted in model 2. In model 3, age, ALT, smoking status, alcohol consumption status, and presence of metabolic syndrome were adjusted. $P < 0.05$ was considered significant.

Results

Characteristics of the subjects after their classification according to menopausal state

General characteristics of the subjects with and without NAFLD according to menopausal state are shown in Table 1. In postmenopausal group, the NAFLD group had higher mean body weight, BMI, systolic blood pressure, diastolic blood pressure, FPG, total cholesterol, triglyceride, LDL-C, AST, ALT, γ-GTP, prevalence of metabolic syndrome, and history of type 2 diabetes and dyslipidemia than the non-NAFLD group ($P < 0.05$). Height, mean BMD, and HDL-C were significantly higher in the non-NAFLD group than in the NAFLD group ($P < 0.05$). After adjustment for age, body mass index, ALT, smoking status, and alcohol consumption, each lumbar spine BMD (L1-L3) as well as mean lumbar spine BMD were significantly higher in the non-NAFLD group than in the NAFLD group ($P < 0.05$) (Fig. 1).

Table 1 General characteristics of the study population without and with NAFLD after their classification according to menopause

	Premenopausal Without NAFLD ($n = 162$)	With NAFLD ($n = 54$)	*P*	Postmenopausal Without NAFLD ($n = 102$)	With NAFLD ($n = 163$)	*P*
Age (years)	38.8 ± 0.6	43.3 ± 0.7	<0.001*	58.2 ± 0.7	59.5 ± 0.5	0.112
Body weight (kg)	55.1 ± 0.5	62.1 ± 1.1	<0.001*	56.2 ± 0.7	60.3 ± 0.5	<0.001*
Height (cm)	159.6 ± 0.7	160.0 ± 0.9	0.794	157.2 ± 0.5	155.6 ± 0.4	0.012*
BMI (kg/cm^2)	22.2 ± 0.8	24.2 ± 0.4	0.134	22.7 ± 0.2	24.9 ± 0.2	<0.001*
SBP (mmHg)	114.3 ± 1.5	126.6 ± 3.5	<0.001*	125.3 ± 2.3	137.8 ± 2.0	<0.001*
DBP (mmHg)	70.7 ± 0.8	74.0 ± 1.6	0.042*	71.4 ± 0.9	77.6 ± 0.7	<0.001*
FPG (mg/dl)	90.9 ± 0.7	108.1 ± 5.3	<0.001*	93.7 ± 1.0	104.9 ± 2.4	<0.001*
T-chol (mg/dl)	179.0 ± 2.3	196.8 ± 4.1	<0.001*	200.2 ± 3.5	208.6 ± 3.3	0.099
Triglyceride (mg/dl)	78.1 ± 2.5	133.8 ± 10.7	<0.001*	101.0 ± 4.6	142.3 ± 5.7	<0.001*
HDL-C (mg/dl)	63.4 ± 1.1	53.9 ± 1.7	<0.001*	60.2 ± 1.5	54.3 ± 1.0	0.001*
LDL-C (mg/dl)	102.9 ± 2.0	122.0 ± 3.6	<0.001*	125.3 ± 3.0	133.0 ± 2.9	0.078
AST (U/l)	17.6 ± 0.3	19.6 ± 0.9	0.011*	20.9 ± 0.4	23.5 ± 0.7	0.003*
ALT (U/l)	14.5 ± 0.5	21.9 ± 1.6	<0.001*	16.9 ± 0.6	23.1 ± 1.0	<0.001*
γ-GTP (U/l)	15.4 ± 0.7	23.5 ± 2.9	<0.001*	21.4 ± 2.8	24.7 ± 1.7	<0.001*
T-bilirubin (mg/dl)	0.67 ± 0.02	0.68 ± 0.05	0.793	0.61 ± 0.02	0.62 ± 0.02	0.607
Creatinine (mg/dl)	0.66 ± 0.01	0.64 ± 0.01	0.452	0.72 ± 0.05	0.71 ± 0.06	0.954
MeanBMD (g/cm^2)	1.15 ± 0.01	1.18 ± 0.02	0.132	1.01 ± 0.02	0.98 ± 0.01	0.046*
Metabolic syndrome	1 (0.6)	11 (20.4)	<0.001*	9 (8.8)	71 (43.6)	<0.001*
Smoking status			0.674			0.289
Ex-smoker	2 (1.2)	0 (0)		1 (1.0)	5 (3.1)	
Nonsmoker	149 (92.0)	51 (94.4)		100 (98.0)	153 (93.9)	
Smoker	11 (6.8)	3 (5.6)		1 (1.0)	5 (3.1)	
Alcohol consumption status			0.094			0.378
Ex-drinker	1 (0.6)	0 (0)		0 (0)	3 (1.8)	
Non-drinker	98 (60.5)	41 (75.9)		86 (84.3)	132 (81.0)	
Drinker	63 (38.9)	13 (24.1)		16 (15.7)	28 (17.2)	
Type 2 diabetes	8 (4.9)	3 (5.6)	0.858	16 (15.7)	44 (27.0)	0.032*
Hypertension	1 (0.6)	2 (3.7)	0.093	4 (3.9)	12 (7.4)	0.253
Dyslipidemia	2 (1.2)	3 (5.6)	0.067	7 (6.9)	26 (16.0)	0.029*

Data are mean ± standard of error, number, and percentage for metabolic syndrome, smoking, alcohol drinking, diabetes, hypertension dylipidemia

n number of patients, *NAFLD* non-alcoholic fatty liver disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *T-chol* total cholesterol, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyltranspeptidase, *T-bilirubin* total-bilirubin, *MeanBMD* mean lumbar spine bone mineral density

* $P < 0.05$

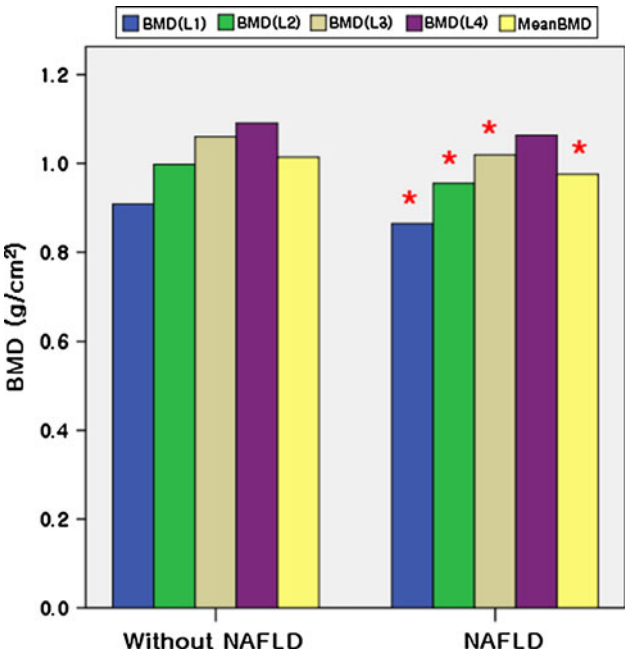

Fig. 1 Mean values of lumbar BMD (L1-L4) in postmenopausal women after classification to NAFLD. *L* lumbar spine, *MeanBMD* mean lumbar spine bone mineral density, *NAFLD* non-alcoholic fatty liver disease. *$P < 0.05$ versus without NAFLD, adjusted for age, body mass index, ALT, smoking status, and alcohol consumption

Univariate regression analysis: effect of variables on BMD

As shown in Table 2, univariate regression analysis was performed to examine the association between BMD and the other variables listed in Table 1. In postmenopausal group, NAFLD (β coefficient -0.039, 95% CI -0.076 to -0.001, $P = 0.046$) was identified as variable that correlated significantly with BMD. Age, body weight, height, BMI, and ALT were also associated with BMD. However, in premenopausal women, NAFLD was not associated with BMD.

Multiple regression analysis: adjusted effect of NAFLD on BMD

In postmenopausal women, multiple regression analysis was performed with BMD as a dependent variable and NAFLD as an independent variable (Table 3). After adjustment for age, BMI, and ALT (model 1), BMD was found to associate with NAFLD (β coefficient -0.069, 95% CI -0.107 to -0.030, $P = 0.001$). This association remained statistically significant after adjustment for other additional variables that were known as risk factors for osteoporosis, namely smoking status and alcohol consumption (β coefficient -0.066, 95% *CI* -0.105 to -0.027, $P = 0.001$) (model 2). Moreover, this association remained statistically significant after adjustment for the metabolic syndrome (β coefficient -0.043, 95% *CI* -0.082 to -0.004, $P = 0.031$) (model 3).

Discussion

This study revealed that NAFLD is significantly associated with low lumbar BMD in postmenopausal women and this significance was maintained after adjusting for the concerned variables including age, body mass index, ALT, smoking status, and alcohol consumption, and even after taking the presence of metabolic syndrome into account. In premenopausal women, there was no such relationship. The discrepancy between pre- and postmenopausal women may be due to the effect of estrogen. As well as osteoporosis, NAFLD increases after menopause [23] and the prevalence of NAFLD is lower in postmenopausal women taking hormone replacement therapy than those taking no hormone therapy [24]. Declined estrogen, which is suggested as a powerful antioxidant, may reduce fatty acid oxidation and increase lipogenesis within the liver [25].

Although contentious, metabolic syndrome is a reported risk factor for osteoporosis [7]. Metabolic syndrome is characterized as insulin resistance and a constellation of risk factors for a cardiovascular disease including central obesity, dyslipidemia, hypertension, and impaired glucose tolerance [8]. Conventionally, body mass index is known to be positively associated with bone mass. However, after taking body weight into account, fat mass or central obesity was associated with low bone mass [26, 27]. This suggests that the association between osteoporosis and body weight is complex beyond just weight bearing effect. Inflammation caused by central adiposity is suggested as one of mediators between osteoporosis and metabolic syndrome. Metabolic syndrome is associated with low-grade inflammation [28], which is known to stimulate bone resorption through several molecular mechanisms [29, 30].

NAFLD, which is characterized as hepatic steatosis in the absence of a secondary cause and the most common form of chronic liver disease [16, 17], is considered as the hepatic manifestation of metabolic syndrome. The pathogenesis of NAFLD is also related with insulin resistance and inflammation [31]. Increased visceral adiposity, such as that seen in obesity, results in production of inflammatory adipokines and hormones including tumor necrosis factor-α, interlukin-6, interlukin-1, and resistin, and increased lipolysis and influx of free fatty acid to the liver, which eventually leads to triglyceride synthesis. Macrophage infiltration of visceral adipose tissue follows the release of the adipokines and contributes to the chronic low-grade inflammatory status [32, 33].

Osteoporosis and fracture are highly prevalent in patients with chronic liver disease such as primary biliary

Table 2 Univariate regression analysis: the effect of the study variables on BMD

	Premenopausal β (95% CI)	*P*	Postmenopausal β (95% CI)	*P*
Age (years	−0.001 (−0.004–0.002)	0.539	−0.008 (−0.011 to −0.005)	<0.001*
Body weight (kg)	0.005 (0.003–0.008)	<0.001*	0.006 (0.004–0.009)	<0.001*
Height (cm)	0.002 (0.000–0.004)	0.100	0.009 (0.005–0.012)	<0.001*
BMI (kg/cm^2)	0.001 (−0.002–0.003)	0.651	0.009 (0.002–0.016)	<0.001*
SBP (mmHg)	0.000 (−0.001–0.001)	0.431	0.000 (−0.001–0.000)	0.459
DBP (mmHg)	0.000 (−0.002–0.002)	0.765	−0.001 (10.003–0.001)	0.316
FPG (mg/dl)	0.000 (−0.001–0.001)	0.514	0.000 (−0.001–0.000)	0.283
T-chol (mg/dl)	0.000 (−0.001–0.000)	0.411	0.000 (0.000–0.000)	0.930
Triglyceride (mg/dl)	0.000 (0.000–0.001)	0.269	0.000 (0.000–0.000)	0.570
HDL-C (mg/dl)	−0.001 (−0.002–0.001)	0.320	0.000 (−0.002–0.001)	0.603
LDL-C (mg/dl)	0.000 (−0.001–0.001)	0.581	0.000 (−0.001–0.000)	0.519
AST (U/l)	−0.002 (−0.006–0.002)	0.298	0.002 (−0.001–0.004)	0.151
ALT (U/l)	−0.001 (−0.003–0.002)	0.642	0.002 (0.000–0.004)	0.020*
γ-GTP (U/l)	0.001 (−0.001–0.002)	0.466	0.000 (−0.001–0.001)	0.540
T-bilirubin (mg/dl)	0.014 (−0.048–0.077)	0.449	0.004 (−0.073–0.080)	0.927
Creatinine (mg/dl)	0.129 (−0.064–0.323)	0.190	−0.010 (−0.036–0.016)	0.444
NAFLD	0.035 (−0.011–0.081)	0.132	−0.039 (−0.076 to −0.001)	0.046*
Metabolic syndrome	0.076 (−0.011–0.162)	0.086	−0.001 (−0.042–0.039)	0.943
Smoking status	0.004 (−0.070–0.079)	0.910	0.082 (−0.004–0.169)	0.063
Alcohol consumption status	−0.018 (−0.059–0.023)	0.387	−0.047 (−0.094–0.000)	0.050
Type 2 diabetes	0.057 (−0.033–0.147)	0.217	−0.038 (−0.083–0.006)	0.087
Hypertension	0.086 (−0.083–0.256)	0.317	0.001 (−0.077–0.079)	0.975
Dyslipidemia	0.104 (−0.028–0.235)	0.121	0.008 (−0.048–0.064)	0.783

n number of patients, *NAFLD* non-alcoholic fatty liver disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *T-chol* total cholesterol, *HDL-C* high density lipoprotein cholesterol, *LDL-C* low density lipoprotein cholesterol, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *γ-GTP* γ-glutamyltranspeptidase, *T-bilirubin* total-bilirubin, *MeanBMD* mean lumbar spine bone mineral density

* $P < 0.05$

Table 3 Summary of the regression analysis of the correlation between BMD and NAFLD, adjusted for multiple variables in postmenopausal women

	R square	β coefficient	95% CI	*P* value
Model 1	0.196	−0.069	−0.107 to –0.030	0.001*
Model 2	0.216	−0.066	−0.105 to −0.027	0.001*
Model 3	0.174	−0.043	−0.082 to −0.004	0.031*

Model 1: adjusted for age, body mass index, ALT, and NAFLD

Model 2: adjusted for age, body mass index, ALT, smoking status, alcohol consumption status, and NAFLD

Model 3: adjusted for age, the presence of metabolic syndrome, ALT, smoking status, alcohol consumption status, and NAFLD

CI confidence interval

* $P < 0.05$

cirrhosis and sclerosing cholangitis [34–37]. There have been several hypotheses regarding pathogenesis of osteoporosis in liver disease. Depressed bone formation and increased bone resorption may contribute to osteoporosis [38]. Bilirubin decreases the proliferative capacity of osteoblasts [39]. The reduced level of insulin-like growth factor (IGF-1) was also suggested to be related to the osteoporosis in liver disease [40]. An increased bone resorption was observed in histomorphometrical studies in patients with chronic cholestasis [41].

However, there has been no study specifically regarding the association between the mild fatty liver without cholestasis and osteoporosis. In this study, even after adjustment for metabolic syndrome, NAFLD was an independent risk factor for lower BMD in postmenopausal women. This suggests that there might be an etiologic relationship between NAFLD and osteoporosis in addition to metabolic syndrome and obesity.

This study has several limitations. First, the cross-sectional design prevents an affirmation that NAFLD causes development of osteoporosis. There is also a possible discrepancy between BMD and bone fractures particularly in insulin resistant states [42, 43]. The relationship between NAFLD and osteoporosis or fracture should be verified in future longitudinal studies. Second, although this study shows that NAFLD is an independent risk factor for lower BMD in addition to metabolic syndrome, we did not measure any inflammatory marker like C-reactive protein or biochemical marker for bone metabolism. Therefore, we could not confirm any mechanism for the development of low BMD in NAFLD. Third, because waist circumference measurements were not available for all subjects, we substituted overall adiposity for abdominal obesity in defining subjects with metabolic syndrome. That also must have been a limitation. Finally, we did not perform a biopsy to define NAFLD and we categorized the study subjects into two groups according to the presence of hepatic steatosis on ultrasonography, which may constitute a selection bias and may underestimate the true prevalence of NAFLD.

Despite these limitations, this study shows that lumbar BMD is related with NAFLD in postmenopausal females. We suggest that postmenopausal women with NAFLD may have a higher risk of osteoporosis than those without. Further research is needed to confirm this finding and to understand its implication.

Acknowledgment The authors appreciate the help of Professor Jong-Sup Kim of Kyungpook National University Hospital for collecting data.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am. J. Med. **94**(6), 646–650 (1993)
2. C. Cooper, E.J. Atkinson, S.J. Jacobsen, W.M. O'Fallon, L.J. Melton 3rd, Population-based study of survival after osteoporotic fractures. Am. J. Epidemiol. **137**(9), 1001–1005 (1993)
3. M.A. Petit, M.L. Paudel, B.C. Taylor, J.M. Hughes, E.S. Strotmeyer, A.V. Schwartz, J.A. Cauley, J.M. Zmuda, A.R. Hoffman, K.E. Ensrud, Bone mass and strength in older men with type 2 diabetes: the Osteoporotic Fractures in Men Study. J. Bone Miner. Res. **25**(2), 285–291 (2010)
4. D. von Muhlen, S. Safii, S.K. Jassal, J. Svartberg, E. Barrett-Connor, Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. Osteoporos. Int. **18**(10), 1337–1344 (2007)
5. D.K. Hwang, H.J. Choi, The relationship between low bone mass and metabolic syndrome in Korean women. Osteoporos. Int. **21**(3), 425–431 (2010)
6. Kim, K.C., Shin, D.H., Lee, S.Y., Im, J.A., Lee, D.C.: Relation between obesity and bone mineral density and vertebral fractures in Korean postmenopausal women. Yonsei Med J **51**(6), 857–863 (2010)
7. Y.K. Jeon, J.G. Lee, S.S. Kim, B.H. Kim, S.J. Kim, Y.K. Kim, I.J. Kim, Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocr. J. **58**(2), 87–93 (2011)
8. M.A. Cornier, D. Dabelea, T.L. Hernandez, R.C. Lindstrom, A.J. Steig, N.R. Stob, R.E. Van Pelt, H. Wang, R.H. Eckel, The metabolic syndrome. Endocr. Rev. **29**(7), 777–822 (2008)
9. G.A. Bray, T. Bellanger, Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. Endocrine **29**(1), 109–117 (2006)
10. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation **106**(25), 3143–3421 (2002)
11. A.I. Shulman, D.J. Mangelsdorf, Retinoid x receptor heterodimers in the metabolic syndrome. N. Engl. J. Med. **353**(6), 604–615 (2005)
12. E. Scorletti, P.C. Calder, C.D. Byrne, Non-alcoholic fatty liver disease and cardiovascular risk: metabolic aspects and novel treatments. Endocrine **40**(3), 332–343 (2011)
13. S.M. Grundy, Metabolic complications of obesity. Endocrine **13**(2), 155–165 (2000)
14. G. Targher, L. Bertolini, R. Padovani, S. Rodella, R. Tessari, L. Zenari, C. Day, G. Arcaro, Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care **30**(5), 1212–1218 (2007)
15. S. Bellentani, G. Saccoccio, F. Masutti, L.S. Croce, G. Brandi, F. Sasso, G. Cristanini, C. Tiribelli, Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann. Intern. Med. **132**(2), 112–117 (2000)
16. J.R. Lewis, S.R. Mohanty, Nonalcoholic fatty liver disease: a review and update. Dig. Dis. Sci. **55**(3), 560–578 (2010)
17. M. Lazo, J.M. Clark, The epidemiology of nonalcoholic fatty liver disease: a global perspective. Semin. Liver Dis. **28**(4), 339–350 (2008)
18. C. Loguercio, T. De Simone, M.V. D'Auria, I. de Sio, A. Federico, C. Tuccillo, A.M. Abbatecola, C. Del Vecchio Blanco, Non-alcoholic fatty liver disease: a multicentre clinical study by the Italian Association for the Study of the Liver. Dig. Liver Dis. **36**(6), 398–405 (2004). doi:10.1016/j.dld.2004.01.022
19. C. Loguercio, V. De Girolamo, I. de Sio, C. Tuccillo, A. Ascione, F. Baldi, G. Budillon, L. Cimino, A. Di Carlo, M.P. Di Marino, F. Morisco, F. Picciotto, L. Terracciano, R. Vecchione, V. Verde, C. Del Vecchio Blanco, Non-alcoholic fatty liver disease in an area of southern Italy: main clinical, histological, and pathophysiological aspects. J. Hepatol. **35**(5), 568–574 (2001)
20. World Health Organization. The Asia-Pacific perspective: redefining obesity and its treatment. Health Communication, Sydney (2000)
21. A.J. Sanyal, AGA technical review on nonalcoholic fatty liver disease. Gastroenterology **123**(5), 1705–1725 (2002)
22. D. Joy, V.R. Thava, B.B. Scott, Diagnosis of fatty liver disease: Is biopsy necessary? Eur. J. Gastroenterol. Hepatol. **15**(5), 539–543 (2003)

23. S.H. Park, W.K. Jeon, S.H. Kim, H.J. Kim, D.I. Park, Y.K. Cho, I.K. Sung, C.I. Sohn, D.K. Keum, B.I. Kim, Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. J. Gastroenterol. Hepatol. **21**(1 Pt 1), 138–143 (2006)
24. J.M. Clark, F.L. Brancati, A.M. Diehl, Nonalcoholic fatty liver disease. Gastroenterology **122**(6), 1649–1657 (2002)
25. A. Suzuki, M.F. Abdelmalek, Nonalcoholic fatty liver disease in women. Womens Health (Lond. Engl.) **5**(2), 191–203 (2009)
26. Y.H. Hsu, S.A. Venners, H.A. Terwedow, Y. Feng, T. Niu, Z. Li, N. Laird, J.D. Brain, S.R. Cummings, M.L. Bouxsein, C.J. Rosen, X. Xu, Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am. J. Clin. Nutr. **83**(1), 146–154 (2006)
27. L.J. Zhao, Y.J. Liu, P.Y. Liu, J. Hamilton, R.R. Recker, H.W. Deng, Relationship of obesity with osteoporosis. J. Clin. Endocrinol. Metab. **92**(5), 1640–1646 (2007). doi:10.1210/jc.2006-0572
28. W.Y. Lee, J.S. Park, S.Y. Noh, E.J. Rhee, K.C. Sung, B.S. Kim, J.H. Kang, S.W. Kim, M.H. Lee, J.R. Park, C-reactive protein concentrations are related to insulin resistance and metabolic syndrome as defined by the ATP III report. Int. J. Cardiol. **97**(1), 101–106 (2004)
29. D.H. Jones, Y.Y. Kong, J.M. Penninger, Role of RANKL and RANK in bone loss and arthritis. Ann. Rheum. Dis. **61**(Suppl 2), ii32–39 (2002)
30. L.C. Hofbauer, M. Schoppet, Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA **292**(4), 490–495 (2004)
31. M. Krawczyk, L. Bonfrate, P. Portincasa, Nonalcoholic fatty liver disease. Best Pract. Res. Clin. Gastroenterol. **24**(5), 695–708 (2010)
32. P. Trayhurn, I.S. Wood, Signalling role of adipose tissue: adipokines and inflammation in obesity. Biochem. Soc. Trans. **33**(Pt 5), 1078–1081 (2005)
33. P. Trayhurn, Adipose tissue in obesity—an inflammatory issue. Endocrinology **146**(3), 1003–1005 (2005)
34. T. Diamond, D. Stiel, M. Lunzer, M. Wilkinson, J. Roche, S. Posen, Osteoporosis and skeletal fractures in chronic liver disease. Gut **31**(1), 82–87 (1990)
35. P. Angulo, T.M. Therneau, A. Jorgensen, C.K. DeSotel, K.S. Egan, E.R. Dickson, J.E. Hay, K.D. Lindor, Bone disease in patients with primary sclerosing cholangitis: prevalence, severity and prediction of progression. J. Hepatol. **29**(5), 729–735 (1998)
36. S.P. Pereira, G.P. Bray, P.I. Pitt, F. Li, C. Moniz, R. Williams, Non-invasive assessment of bone density in primary biliary cirrhosis. Eur. J. Gastroenterol. Hepatol. **11**(3), 323–328 (1999)
37. J. Newton, R. Francis, M. Prince, O. James, M. Bassendine, D. Rawlings, D. Jones, Osteoporosis in primary biliary cirrhosis revisited. Gut **49**(2), 282–287 (2001)
38. G.W. McCaughan, R.B. Feller, Osteoporosis in chronic liver disease: pathogenesis, risk factors, and management. Dig. Dis. **12**(4), 223–231 (1994)
39. C.H. Janes, E.R. Dickson, R. Okazaki, S. Bonde, A.F. McDonagh, B.L. Riggs, Role of hyperbilirubinemia in the impairment of osteoblast proliferation associated with cholestatic jaundice. J Clin Invest **95**(6), 2581–2586 (1995)
40. F.J. Gallego-Rojo, J.L. Gonzalez-Calvin, M. Munoz-Torres, J.L. Mundi, R. Fernandez-Perez, D. Rodrigo-Moreno, Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. Hepatology **28**(3), 695–699 (1998)
41. J.A. Cuthbert, C.Y. Pak, J.E. Zerwekh, K.D. Glass, B. Combes, Bone disease in primary biliary cirrhosis: increased bone resorption and turnover in the absence of osteoporosis or osteomalacia. Hepatology **4**(1), 1–8 (1984)
42. G. Mazziotti, M. Gola, A. Bianchi, T. Porcelli, A. Giampietro, V. Cimino, M. Doga, C. Gazzaruso, L. De Marinis, A. Giustina, Influence of diabetes mellitus on vertebral fractures in men with acromegaly. Endocrine **40**(1), 102–108 (2011)
43. G. Mazziotti, J. Bilezikian, E. Canalis, D. Cocchi, A. Giustina, New understanding and treatments for osteoporosis. Endocrine **41**(1), 58–69 (2012)