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Original Article

Association of osteoporosis with non-alcoholic fatty liver disease in adults

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ABSTRACT

Background: osteoporosis is defined by decrease in bone strength and is not confined to bone but is also associated with systemic disorders such as obesity, diabetes mellitus and metabolic syndrome. Non alcoholic fatty liver is the manifestation of metabolic syndrome in liver and may be related to poor bone mineralization by inducing systemic inflammation. Objectives: The aim of this study is evaluation of relationship between non-alcoholic fatty liver disease and osteoporosis in adults for the first time in Iran. Materials and Methods: 235 individuals who were referred to the bone densitometry centre of Imam Khomeiny Hospital of Urumia from October, 2012 to May, 2013 were evaluated. Blood pressure, height, weight, Body mass index, waist circumference and laboratory tests including lipid profile, FBS, AST and ALT was measured in all subjects. All the individuals underwent ultrasonography for diagnosis of non-alcoholic fatty liver disease and determination of the grade of fatty liver. Results: in this study non-alcoholic fatty liver disease increased the risk of developing osteoporosis (odds ratio: 1.17) but there was no statistically significant association between nonalcoholic fatty liver disease and osteoporosis (P value= 0.66). This result was obtained after adjusting for age and LDL level in the subjects. Conclusion: Our study demonstrates that the association between non-alcoholic fatty liver disease and osteoporosis is not statistically significant; however non-alcoholic fatty liver disease increases the risk of developing osteoporosis. Further studies are necessary for evaluating this relationship and to determine the clinical importance of surveying bone densitometry in patients with non-alcoholic fatty liver disease.

Keywords: Non- alcoholic fatty liver disease, osteoporosis, bone mineral density.

Introduction

Osteoporosis is characterized by decrease in bone strength and is common in post menopause women. The main manifestations of osteoporosis are vertebra and hip fractures; however, fracture could occur in any bone site. The frequency of osteoporosis increases with growing age because bone loss happens progressively with increasing age. Different genetic and acquired disorders increase the risk of osteoporosis. [1]

Osteoporosis is not confined to bone but also associated with systemic disorders like central obesity, type 2 diabetes mellitus and metabolic syndrome. Studies show that osteoporosis increases in individuals with metabolic syndrome. [2]. Non-alcoholic fatty liver is the manifestation of metabolic syndrome in liver and may be associated with poor bone mineralization. The pathogenesis is assumed to be systemic inflammation caused by NAFLD. The loss of balance in cytokines especially increased ratio of tumor necrosis factor to adiponektin may play an important role in development of non-alcoholic osteohepatitis [3, 4].

Non-alcoholic fatty liver disease is nowadays the most common hepatic disorder worldwide [5]. The hypothesis of association between NAFLD and osteoporosis was proposed according to the previous studies showing relationship between osteoporosis and metabolic syndrome. Systemic inflammation is on the other hand a known factor of decreasing bone mass densitometry (BMD). The inflammatory cytokines that are important in osteoporosis play role in pathogenesis of NAFLD as well [6, 7]. As a result, inflammatory background in NAFLD may be the cause of association between NAFLD and low bone density.

The frequency of non-alcoholic fatty liver is 14-20% in the United States and Europ. The spectrum of NAFLD includes simple liver steatosis, non-alcoholic steatohepatitis and

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progression to cirrhosis subsequently [8]. ALT level has a low predicting value for development or progression of NAFLD. It seems that ALT is an insensitive criterion for liver steatosis and non-alcoholic steatohepatitis [9-12].

Imaging studies could be used to show characteristic features of fatty liver, but the ultimate diagnosis of liver steatosis or NASH requires liver biopsy. Liver biopsy is an invasive procedure and there is the possibility of error in sampling and interpretation of the samples [13-15]. Liver biopsy is therefore limited to epidemiologic studies. Ultrasonography is the preferred method in screening of the asymptomatic patients with raised liver enzymes and the possibility of NAFLD [16]. On ultrasonography (US) fatty liver can be visualized as an increase in parenchymal echogenicity on gray-scale images and can be graded as mild, moderate, and severe [17].

Materials and Methods:

235 individuals, who were referred to the bone densitometry centre from October 2012 to May, 2013 were evaluated in our study. The subjects with consumption of more than 20 grams of alcohol in the week, usage of steatogenic medications or corticosteroids were not enrolled in the study.

The previous history of hypertension, hyperlipidemia, diabetes, smoking, important illness and medications was questioned and recorded. In all precipitants systolic and diastolic blood pressure, height, weight, body mass index (BMI) and waist circumference were measured by standard methods.

Bone density was measured in lumbar (L1- L4) and femoral sites by dual-energy X-ray absorptiometry (DXA) and the results were recorded. T-score bellow -2.5 was considered as having osteoporosis [1].

Ultrasonography of liver was performed on all the subjects to determine the presence of fatty liver. Diagnosis of fatty liver was on the basis of sonographic characteristics in the patients without previous hepatic disease. The sonographic criterion was bright hepatic echo pattern, increased attenuation of the echo beam, and loss of intrahepatic architectural detail [18, 19]. Grading of fatty liver was then determined in the patients with non-alcoholic fatty liver disease based on sonographic characteristics. Grade 0 of fatty infiltration was considered to be the normal liver echogenicity. In grade 1 (mild) fatty infiltration, echogenicity was slightly increased, with normal visualization of the diaphragm and the intrahepatic vessel borders. The grade 2 (moderate) of fatty infiltration was established when echogenicity was moderately increased, with slightly impaired visualization of the diaphragm or intrahepatic vessels. In grade 3 (severe) of fatty infiltration, echogenicity was markedly increased with poor or visualization of the diaphragm, the intrahepatic vessels, and the posterior portion of the right lobe [17]. All the sonographis in this study was performed by one expert radiologist. We did not perform liver biopsy for demonstrating diagnosis of NAFLD in this study.

Total cholesterol, triglyceride, HDL, LDL, AST, ALT and FBS were measured in all subjects. The participants were considered to have metabolic syndrome if any three of the following criterion were positive: HDL-C< 50 mg/dl in women and < 40 mg/dl in men or using medication; hypertriglyceridemia (triglyceride ≥ 150 mg/dl or using lowering triglyceride agent); waist circumference more than 102 centimeters in men and more than 88 centimeters in women; hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure≥ 85mmHg or using antihypertensive drug); Fasting plasma glucose ≥100 mg/dL or using specific medication [20].

The results were analyzed with SPSS, release 20; statistical software. The Pearson chi-square test and fisher exact test (whenever the expected values in two of the cells of a contingency table were below 5) was applied to evaluate the association between Non alcoholic fatty liver and osteoporosis. Independent sample t- test (Mannwhitney in non-normal distribution) was used to study the association between osteoporosis and numerical Variables. We fitted regression models with statistically significant confounding variables including age, metabolic syndrome, Body Mass index , Impaired fasting glucose, Systolic and Diastolic blood pressure ,LDL and triglyceride levels, ALT level and smoking , all being reported as confounding factors in previous studies [21-23] fasting glucose ≥ 100 mg/dL, systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, LDL level ≥ 130 mg/dL, HDL level < 40 for men and < 50 for women, triglyceride ≥ 150 mg/dL and ALT level ≥ 40 U/L were the cut off points for abnormal values in this analysis.

The multiple logistic regression was also applied to calculate adjusted ORs and 95 % confidence intervals for odds of osteoporosis development.

Results:

235 individuals were evaluated in this study. 23 were male and 212 were female. Mean age was 53 year of old with the least age of 20 year of old and most age of 84 year of old.

53 subjects (22.6%) were osteoporotic according to bone densitometry with T score less than 2.5 in either femoral or vertebral site. 182 subjects (77.4%) had no osteoporosis. The two groups were compared in confounding factors. The characteristics of studied population in each of osteoporotic and non- osteoporotic group are shown in table 1.

Table 1: characteristics of study population in osteoporotic and non-osteoporotic groups.

Variables		with osteoporosis	without osteoporosis	P value
		Mean ± SD		
Age		61.07 ± 10.58	50.73 ± 9.93	< 0.001
Body mass index(kg/cm2)		29.36 ± 5.80	30.43 ± 6.96	0.5
		N(%)		
Metabolic syndrome	yes	24 (45.3)	60 (33)	<0.03
	No	29 (54.7)	122 (67)	
Impaired fasting glucose≥ 100 mg/dl	yes	12 (23)	122 (67)	0.66
	No	41 (77)	60 (33)	
Systolic blood pressure ≥ 140 mmHg	yes	13 (24.5)	39 (21.4)	0.63
	No	40 (75.5)	143 (78.6)	
Diastolic blood pressure ≥	yes	12 (22.6)	40 (22)	0.91

90 mmHg	No	41 (77.4)	142(78)	
LDL ≥ 130 mg/dl	yes	7 (13.2)	49 (26.9)	0.03
	No	46 (86.8)	133 (73.1)	
Triglyceride ≥150 mg/dl	yes	20 (37.7)	68 (37.4)	0.96
	No	33 (62.3)	114 (62.9)	
HDL level < 40 mg/dL in men; < 50mg/dL in women	yes	10 (18.9)	19 (10.4)	0.1
	No	43 (81.1)	163 (89.6)	
ALT level > 40 U/l	yes	5 (22.7)	17 (77.3)	0.69
	No	48 (22.5)	165 (77.5)	
smoking	yes	6 (11.3)	7 (3.8)	0.38
	No	47 (88.7)	175 (96.2)	

There were no differences in BMI, impaired fasting glucose or smoking between two osteoporotic and non-osteoporotic groups (P value =0.5; P value= 0.66 and P value = 0.38 respectively) nor any association between osteoporosis and triglyceride level, HDL, systolic blood pressure, diastolic blood pressure and ALT level was found in our study by comparing the abnormal values between two groups. (P value= 0.96; P value = 0.1; P value = 0.63 and P value = 0.91 respectively). However, there was statistically significant association between osteoporosis and LDL level (P value = 0.03) and between age and osteoporosis (as was expected since increasing age is associated with osteoporosis) (p value< 0.001). There were no statistically significant difference in prevalence of metabolic syndrome between osteoporotic and non osteoporotic group (P value = 0.1)

Association between osteoporosis and non-alcoholic fatty liver disease was evaluated by regression analysis after adjustment for age and LDL level as the only two factors statistically associated with osteoporosis. We found no statically significant association between osteoporosis and NAFLD in logistic regression model. (P value= 0.66). However, NAFLD increased the risk of developing osteoporosis (odds ratio= 1.17). The results of logistic regression are shown in table 2.

Table 2: logistic regression analysis: the effect of the established confounding variables on osteoporosis.

Variables	Adjusted odds ratio		P value
	OR	95%CI	
non alcoholic fatty liver	1.17	0.57-2.39	0.66
Age	1.10	1.06-1.15	<0.001
LDL	2.49	0.99-6.27	0.03

Discussion

Non- alcoholic fatty liver disease is the most common hepatic disorder worldwide [5]. NAFLD was associated with increasing risk of development of osteoporosis by 17% in our study but the relationship was not statistically significant. This relationship was evaluated after adjustment for age and LDL level, the only two factors that were statically associated with osteoporosis in our survey.

Osteoporosis and fracture are common in individuals with chronic liver disease such as primary biliary cirrhosis and sclerosing cholangitis [24-27]. Frequency of osteoporosis in chronic liver disease reaches 50% in patients awaiting liver transplantation. There are several hypotheses about the cause of this correlation. Bilirubin decreases the ability of osteoblasts for proliferation [28]; it may be the reason of relationship between osteoporosis and cholestatic liver disease. More ever reduced level of insulin-like growth factor (IGF1) in liver disease is known to be related to development of osteoporosis. Increased bone resorption is observed in chronic liver cholestasis [29]. Relationship between NAFLD and osteoporosis when cholestasis or cirrhosis does not persist has been studied in very limited investigations [23]. Despite many of chronic liver diseases that are associated with low BMI, non-alcoholic fatty liver is associated with obesity. Though we found no statically significant association between NAFLD and osteoporosis, NAFLD increased the risk of osteoporosis in our observation.

Seong-Su Moon and *et al* found association between nonalcoholic fatty liver disease and osteoporosis in postmenopausal women after adjustment for age, ALT level and BMI. However, they did not find association between NAFLD and osteoporosis in premenopausal women. [23]. Association between non-alcoholic fatty liver disease and developing osteoporosis has been shown in few similar studies available [21, 22] Age limitation in these studies may be the reason of the discrepancy in results with our investigation. More ever the number of subjects evaluated in our survey is more than the other similar studies except for the Seong-Su Moon's study with 481 subjects [21-23].

Systemic inflammation is the well known factor of decreased BMD in different disorders [30-32]. Inflammatory cytokines like tumor necrosis factor-alpha, interleukin 6 and interleukin 1 increase osteoclastic activity by up-regulating receptor activator of nuclear factor *kB* ligand (RANKL). TNF-a inhibits osteoblastic differentiation and promotes osteoblastic apoptosis. This cytokines have well known role in NAFLD [33-35]. Thus inflammatory process in NAFLD may be the leading cause of association between NAFLD and low bone density that has been found as statistically significant relationship in few other studies and as increased risk of development of osteoporosis with non-alcoholic fatty liver disease in our study [21-23].

Obesity leads to a chronic inflammation with negative effect on bone health. Central obesity on the other hand is one of the causes of macrovesicular steatosis which is the characteristic histologic feature of non-alcoholic fatty liver disease [8]. Thus obesity may be another factor linking the two disorders either by producing inflammatory state or by some other unknown mechanisms. However, association between BMI and osteoporosis has been inconsistent in previous investigations [36, 37]. We did not find significant association between BMI and osteoporosis. It is deduced in some previous investigations that bone mineralization may increase in obese children as a result of increased mechanical loading on weight bearing bones and thus obesity negatively correlates with osteoporosis [38, 39]. It is suggested that obesity does not affect bone mineralization solely and other factors including resistance to insulin, cytokines and adipokines are the effective factors on bone health in patients with NAFLD [21].

NAFLD is frequently seen in conjunction with other components of the metabolic syndrome (hypertension, diabetes mellitus, elevated lipids, and obesity), with NAFLD being considered the hepatic manifestation of this syndrome [8]. Metabolic syndrome causes low grade inflammation and resultant bone resorbtion [40, 41]. This inflammation may be the associating factor between metabolic syndrome, non-alcoholic liver disease and osteoporosis. However, a survey taken place in America has shown that after adjustment for age, sex and other variants, bone density in femoral head is more in patients with metabolic syndrome compared to patients without [42]. Other study showed that metabolic syndrome lowered risk of fracture in non- vertebral sites [43]. Contradictory results were obtained in some other studies, finding no association between metabolic syndrome and lower bone density [6, 7]. No statistically significant association between metabolic syndrome and osteoporosis was observed in our survey. Difference in demographic elements such as age, sex, obesity and ethnic may be the cause of discrepancy of the results of these studies.

We found no association between high triglyceride level and developing osteoporosis. There was no association between systolic and diastolic blood pressure with osteoporosis either. There was negative association between triglyceride level and femoral neck density in Ha Young Kim and *et al* study and they found no correlation between blood pressure, blood glucose and HDL with BMD [44]. These results are in consistent with our study. Hypertension was associated with both increased and decreased bone density in previous studies [45-47]. Systolic hypertension was higher in obese adolescence with NAFLD compared to adolescence without NAFLD and adolescence with lean body in Ozgur Pigron and *et al*'s study but they did not find any correlation between hypertension and osteoporosis [21].

Hyperglycemia is a predictor of bone loss and osteoporotic fracture but the association between hyperglycemia and bone densitometry is not apparent [48]. We did not observe any significant association between hyperglycemia and osteoporosis.

The use of cigarettes over a long period has detrimental effects on bone mass. These effects may be mediated directly by toxic effects on osteoblasts or indirectly by modifying estrogen metabolism [1]. In our study the number of participants who smoked was low compared to nonsmokers (only two smoked) this may be the reason we found no association between osteoporosis and smoking.

According to previous studies ALT has a low predictive value for development of NAFLD, it seems that ALT is an insensitive criterion for diagnosis of hepatic steatosis and non-alcoholic steatohepatitis [49, 50]. This explains why there was no association between ALT and osteoporosis in our survey. It seems that abnormality of liver enzymes only occurs in severe disease and measuring liver enzymes solely is not enough for screening non-alcoholic fatty liver disease [21].

Our study had few limitations. First we used sonographic features to diagnose NAFLD and determine the grading of it. The only present survey that used liver biopsy for diagnosis of NAFLD was P.E. Padree and *et al* study that compared 38 children with biopsy proven NAFLD with healthy children [22]. For practical purposes most studies define NAFLD according to laboratory and imaging characteristics like elevated liver enzymes and presence of steatosis in ultrasonography or CT scan in patients with negative serologic tests for viral hepatitis, autoimmune liver disease and congenital cause of chronic hepatitis [5]. However, biopsy is necessary to determine the severity of NAFLD. In patients with abnormal liver enzymes and normal serology, ultrasonography has positive predictive value of 96% in diagnosing NAFLD [51]. Many experts believe that this level of accuracy is adequate [52]. Although the sensitivity and specificity of ultrasonography in diagnosis of NAFLD is high, this technique has limitations including dependency to operator [53], no ability to give quantative information of the degree of lipid accumulation and decreased sensitivity if the fat infiltration is 30% or less [54]. Sensitivity of ultrasonography lessens in patients with morbid obesity as well [55]. Despite the limitations of sonography, it is preferred to liver biopsy. Thus we used ultrasonography that is noninvasive and has high sensitivity for diagnosis of NAFLD.

Second, bone densitometry was performed in individuals that were referred by their physician with clinical indication of measuring bone density. Thus occurrence of selection bias seems probable. Further studies on healthy individuals are suggested.

Last, in order to lessen the expenses of the study, we first performed ultrasonography on the subjects and then they underwent bone densitometry. In other similar studies bone densitometry was performed first and ultrasonography was done afterwards to determine the presence of NAFLD and subjects were then divided to NAFLD and non-NFLD groups. However, the difference between our methods of study compared with other surveys does not seem to have effect on ultimate results.

In spite of these limitations our study shows that non-alcoholic fatty liver disease increases the risk of osteoporosis however this association was not statistically significant. Further studies are mandatory to confirm this association and to determine if a higher grade of NAFLD is associated with more sever osteoporosis as well. If such correlation is definitely confirmed, in the future NAFLD may be considered as an indication to evaluate bone density. It could also be assumed that weight loss and exercise as treatment of NAFLD could have therapeutic effect on osteoporosis as well. Confirmation of this hypothesis needs further studies.

Conclusion

Our study demonstrates that the association between non-alcoholic fatty liver disease and osteoporosis is not statistically significant; however non-alcoholic fatty liver disease increases the risk of developing osteoporosis by 17%. More investigations are necessary for evaluating this relationship. If such correlation exists, it would be useful to evaluate bone density in patients with NAFLD. Further studies seem mandatory to determine the interventions that may improve bone density in patients with NAFLD.

Conflict of interest:

none declared.

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