Original Article

Bone mineral density loss in patients with cirrhosis

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Abstract

Background/Aims: Evidence of increased risk of osteoporosis and osteopenia in chronic liver disease and cirrhosis is inconsistent. This study aims to investigate this relationship and to identify the predictors of increased loss of bone mineral density in Saudi patients.

Patients and Methods: One hundred and sixty-four patients and controls who are age and gender matched, were included in this study with 1:1 ratio. Patients' included in this study were adults with confirmed liver cirrhosis. Bone mineral densitometry (BMD) at both lumbar spine (LS) and femoral neck (FN) were collected for both groups. Univariate and multivariate regression analyses were performed to identify predictors of BMD loss.

Results: Results showed that cirrhotic patients are at higher risk of developing osteoporosis or osteopenia at LS (OR 2.23, 95% CI [1.19–4.19], $P = 0.01$) but not at FN, when compared to control sample. Patients with cirrhosis were found to have lower vitamin D and PTH levels ($P = 0.0005$) and ($P = 0.006$), respectively. Of the possible predictors tested (gender, age, body mass index [BMI], phosphorus, calcium, parathyroid hormone (PTH), vitamin D, and Model for End Stage Liver Disease [MELD] score), female gender was the main predictor of loss of BMD at LS only (OR 4.80, 95% CI [1.47–15.73], $P = 0.01$).

Conclusions: The study showed that cirrhotic patients are at increased susceptibility of having decreased BMD, particularly at the LS and it highlights the need for preventive measures, especially for female patients.

Keywords: Bone mineral densitometry, chronic liver disease, cirrhosis, osteopenia, osteoporosis

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INTRODUCTION

Chronic liver disease (CLD) and cirrhosis are highly prevalent entities that cause significant morbidity and mortality.[1,2] In Saudi Arabia, the general prevalence of CLD is unknown; however, different studies have demonstrated the huge burden that is imposed on the health-care system by different CLD etiologies. For instance, viral hepatitis is still contributing to a significant morbidity and mortality and the prevalence of non-alcoholic fatty liver diseases (NAFLD) is increasing, reaching up to 16%.[3,4]

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Patients with CLD are at increased risk of many hepatic and extrahepatic complications.[1] Several studies have shown an increased susceptibility for metabolic bone diseases mainly osteoporosis and rarely osteomalacia.[5,6] The pathogenesis of such "hepatic osteodystrophy" is not well understood; however, it has been attributed to many proteins and cytokines that are influenced by the changes in function of liver parenchyma, including insulin like growth factor-1 (IGF-1), fibronectin, and sex hormones.[2] There is variability between the different studies regarding the prevalence of osteoporosis in CLD patients. This could be attributed to differences in patients' characteristics among the different studies.[7] Many factors have been reported to increase the risk of osteoporosis in CLD, including; age, gender, type of CLD as well severity of cirrhosis.[5,8] Furthermore, guidelines are inconsistent on the indications to perform BMD testing for CLD patients.[5]

Osteoporosis is a silent disease that can increase risk of fractures, which confers both morbidity and mortality for such patients with increased risk for hospitalization, surgical procedures, and limitations in daily life activities.[9] Thus, early diagnosis of osteoporosis in cirrhotic patients is crucial in the prevention of fractures and improving their quality of life. Up to this date, no studies have evaluated the risk of bone mineral loss in patients with cirrhosis in Saudi Arabia. Thus, our primary aim in this study was to investigate the association between cirrhosis and abnormal BMD. We also aimed to understand the biochemical changes that occur to different bone profile variables and to identify different predictors among patients with cirrhosis that will increase their risk of abnormal BMD in comparison to a control group.

PATIENTS AND METHODS

Study design

This is a controlled cross-sectional study. Patients who underwent pretransplant assessment in years 2014–2015 at King Faisal Specialist Hospital & Research Center (KFSH & RC), Riyadh, Saudi Arabia were reviewed for eligibility of enrollment. Eighty-two patients were eligible for enrollment and their electronic files were reviewed retrospectively. Another group of 82 age and gender matched controls from family medicine clinics in the same institution were recruited. The study was conducted according to the principles of the Declaration of Helsinki of the World Medical Association and the local responsible committee on human experimentation. The study was granted approval by the institutional review board (IRB) of King Faisal Specialist Hospital and Research Center (Research Advisory Council-RAC# 2151202).

Patient selection

Patients' included in this study are adults (age >18 years old) confirmed to have cirrhosis for a minimum duration of 5 years. We excluded all patients having primary bone disease or evidence of secondary causes of osteoporosis other than CLD, solid or hematological malignancies, significant cardiopulmonary disease, end stage renal failure or systemic use of corticosteroids (≥5 mg prednisone per day for 3 months over 2 years prior to enrolment). Moreover, patients with autoimmune hepatitis, alcoholic liver disease, and metabolic liver diseases such as Wilson disease were excluded due to their known risk of osteoporosis because of disease manifestation, medication used or related habits (i.e., alcohol intake). Control sample satisfied the inclusion and exclusion criteria. Cirrhosis was confirmed by minimum of two of the following: imaging; Computed tomography or ultrasound of the abdomen showing classical features of cirrhotic liver, liver biopsy showing evidence of cirrhosis with Metavir score of 4 or fibroscan showing stage F4 disease.

Specifications of data collected

A retrospective chart review for both patients and control groups was performed. Charts were reviewed to confirm meeting inclusion and exclusion criteria. To decrease confounding variables, age, and gender were used to match the control sample. Age matching was done using preset 5 years age groups (i.e., [15–19.9], [20–24.9], etc.). Based on age and gender, each patient was randomly assigned a control in a ratio of 1:1. Then, it was classified into one of four groups (underweight: <18.50, normal: 18.50–24.99, overweight: 25.00–29.99, and obese: ≥30). Laboratory values including measurements of plasma levels of calcium (in mmol/L), phosphorus (in mmol/L), 25-hydroxy vitamin D level (measured using elecrochemiluminescence binding assay in ng/mL), and PTH level (measured by elecrochemiluminescence immunoassay in pg/mL). Bone mineral densitometry (BMD) was collected for both lumbar spine (LS, L1–L4) and femoral neck (FN). Dual energy x-ray absorptiometry (DXA) scan was used in measuring BMD (Lunar iDXA, General Electric). The results were then classified according to T-score into: normal: <–1 SD, osteopenia: between –1 and <–2.5 SD, and osteoporosis: >–2.5 SD at both LS and FN.[10] MELD score was calculated for patients with cirrhosis and patients were classified into the following groups: group 1: 10–19, group 2: 20–29, and group 3: ≥30. This classification was based on the stratification by mortality used in Wiesner *et al.*[11]

Statistical analysis

Statistical analysis was performed by using the software package SAS version 9.4 (SAS Institute Inc., Cary, NC,

USA). Descriptive statistics for the continuous variables was reported as mean and categorical variables were summarized as frequencies and percentages. Continuous variables were compared by Student's *t*-test, whereas categorical variables were compared by Chi-square test. Univariate and multivariate regression analysis was used to establish which characteristics were independently associated with osteoporosis (age, BMI, 25-hydroxy vitamin D, PTH). The level of statistical significance was set at $P < 0.05$.

RESULTS

A total of 164 patients and controls were enrolled in this study with a ratio of 1:1 and they were matched for age and gender. The median age of the patients group was 56.5 yrs (range 34-74), whereas the median age of the control group was 57 yrs (range 33-72). Males constituted 66% of the sample. Most of the patients group (72%) had higher than normal BMI, which was similar in the controls (74%). No significant difference was found between the two groups in any of the listed variables [Table 1]. Patients with CLD had diverse underlying etiologies including hepatitis B (32%), hepatitis C (28%), cryptogenic (27%), and NAFLD (13%). The results showed that 38%, 48%, and 15% of patients had MELD score of 10-19, 20-29, and ≥30, respectively.

The differences between patients with CLD and controls in the plasma levels of 25-hydroxy vitamin D, calcium, phosphorus, and parathyroid hormone are presented in Table 2. No significant difference was found between both groups in the levels of calcium and phosphorus. Cirrhotic patients had significantly decreased levels of 25-hydroxy vitamin D in comparison to the controls (mean [95% CI] = 40.58 ng/mL [34.31–46.85] vs 55.57 ng/mL [50.18–60.95], $P = 0.0005$). Further analysis was done to investigate the changes on laboratory values for specific etiologies of cirrhosis. This analysis showed that patients with hepatitis B had significantly lower levels of 25-hydroxy vitamin D in comparison to the controls (36.58 ng/mL [26.16–46.99] vs 59.36 ng/mL [49.53–69.19], $P = 0.002$). However, no statistically significant differences were found for other etiologies.

Table 1: Baseline demographic characteristics

	Patients	Controls
Age median (range)	56.5 (34-74)	57 (33-72)
Gender (%)		
Male	54 (66)	54 (66)
Female	28 (34)	28 (34)
BMI (%)		
Underweight	1 (1)	0 (0)
Normal	21 (26)	19 (25)
Overweight	26 (32)	30 (39)
Obese	32 (40)	27 (35)
Type of CLD (%)		
Hepatitis B	26 (32)	
Hepatitis C	23 (28)	
NAFLD	11 (13)	
Cryptogenic	22 (27)	
MELD score		
10-19	31 (38)	
20-29	39 (48)	
>30	12 (15)	

BMI: Body mass index; CLD: Chronic liver disease; NAFLD: Non-alcoholic fatty liver disease; MELD: Model for end stage liver disease

The parathyroid hormone levels in cirrhotic patients was significantly different when compared to the control group (43.20 pg/mL [37.32–49.08] vs 56.23 pg/mL [49.15–63.31], $P = 0.006$). In terms of etiological background of CLD, hepatitis C and NAFLD exhibited significantly lower PTH when compared to controls ($P = 0.001$ and 0.04, respectively).

Bone mineral density loss in cirrhotic patients

Cirrhotic patients were found to have higher prevalence of osteoporosis at both LS (23% vs 11%) and FN (12% vs 4%) [Table 3]. A higher prevalence was present in all etiologies of liver diseases except for hepatitis B at LS and NAFLD at FN. The ratio of abnormal BMD values (osteopenia and osteoporosis) in both groups is shown in Table 4. In addition, cirrhotic patients exhibited around double the risk of osteoporosis or osteopenia (BMD less than –1) at the LS (66% vs 46%, OR 2.23, 95%, CI [1.19–4.19], $P = 0.01$). Conversely, FN studies showed no significant increase in the risk of having abnormal BMD value (63% vs 60%, OR 1.17, 95% CI [0.62–6.00], $P = 0.63$). When results for individual etiologies of CLD were analyzed, there was no significant difference, although a tendency toward significance was noted at the LS in hepatitis C (74% vs 48%, OR 3.09, 95% CI [0.89–10.67], $P = 0.07$) and cryptogenic liver disease (68% vs 41%, OR 3.09, 95% CI [0.89–10.65], $P = 0.07$). The results of individual etiologies at the FN had no significance in any of them.

Predictors of decreased bone mineral density in chronic liver disease patients

The relationship between different factors and BMD levels were studied using univariate and multivariate analyses [Table 5]. Female gender (OR 4.80, 95% CI [1.47–15.73], $P = 0.01$) and lower vitamin D (OR 0.96, 95% CI [0.94–0.99], $P = 0.01$) levels were predictors of BMD levels at the LS in CLD patients, this was further supported by multivariate analysis. Similar relationships were not demonstrated at FN. Other factors such as low BMI and low calcium had tendency toward significance as predictors of BMD at the LS, with *P* values of 0.06 and

Table 2: Serum levels of calcium, phosphorus, vitamin D, and PTH in cirrhotic patients and controls

	All patients	Hepatitis B	Hepatitis C	NAFLD	Cryptogenic
Calcium (mmol/L)					
Patient group mean (95% CI)	2.35 (2.32-2.38)	2.32 (2.28-2.37)	2.34 (2.31-2.38)	2.30 (2.19-2.41)	2.38 (2.27-2.48)
Control group mean (95% CI)	2.31 (2.28-2.35)	2.33 (2.27-2.39)	2.31 (2.26-2.36)	2.36 (2.29-2.43)	2.31 (2.23-2.39)
P	NS	NS	NS	NS	NS
Phosphorus (mmol/L)					
Patient group mean (95% CI)	1.05 (1.00-1.09)	1.03 (0.91-1.14)	1.04 (0.97-1.11)	1.01 (0.89-1.13)	1.03 (0.93-1.12)
Control group mean (95% CI)	1.06 (1.02-1.10)	1.11 (1.03-1.18)	1.07 (1-1.15)	1.12 (1-1.25)	1.01 (0.91-1.10)
P	NS	NS	NS	NS	NS
Vitamin D (pg/mL)					
Patient group mean (95% CI)	40.58 (34.31-46.85)	36.58 (26.16-46.99)	44.29 (30.73-57.86)	50.82 (35.47-66.17)	41.38 (27.41-55.36)
Control group mean (95% CI)	55.57 (50.18-60.95)	59.36 (49.53-69.19)	50.13 (39.86-60.39)	41.00 (17.49-64.51)	59.32 (47.62-71.01)
P	0.0005	0.002	NS	NS	0.05
Parathyroid hormone (pg/ml)					
Patient group mean (95% CI)	43.20 (37.32-49.08)	42.36 (32.14-52.59)	39.20 (34.11-44.29)	42.60 (29.57-55.62)	42.96 (32.46-53.45)
Control group mean (95% CI)	56.23 (49.15-63.31)	53.20 (40.03-66.37)	59.50 (46.05-72.95)	59.13 (6.42-111.8)	62.05 (44.77-79.32)
P	0.006	NS	0.001	NS	0.04

NAFLD: non-alcoholic fatty liver disease; NS: Not significant

Table 3: Ratio of osteoporosis in patients and controls

	Patient *n* (%)	Control *n* (%)
Ratio of osteoporosis-lumber spine		
All (*n*=82)	19 (23)	9 (11)
Hepatitis B (*n*=26)	3 (11)	3 (11)
Hepatitis C (*n*=23)	7 (30)	2 (9)
NAFLD (*n*=11)	3 (27)	1 (9)
Cryptogenic (*n*=23)	6 (26)	3 (13)
Ratio of osteoporosis-femoral neck		
All (*n*=82)	10 (12)	3 (4)
Hepatitis B (*n*=26)	2 (8)	0 (0)
Hepatitis C (*n*=23)	4 (17)	1 (4)
NAFLD (*n*=11)	0 (0)	1 (9)
Cryptogenic (*n*=23)	4 (17)	1 (4)

Table 4: Ratio of abnormal BMD results in patients and controls

	Patient *n* (%)	Control *n* (%)	OR (95% CI)	*P*
Ratio of osteoporosis and osteopenia-lumber spine				
All (*n*=82)	54 (66)	38 (46)	2.23 (1.19-4.19)	0.01
Hepatitis B (*n*=26)	18 (69)	14 (54)	1.93 (0.62-6.00)	NS
Hepatitis C (*n*=23)	17 (74)	11 (48)	3.09 (0.89-10.67)	0.07
NAFLD (*n*=11)	4 (36)	4 (36)	1.00 (0.18-5.68)	NS
Cryptogenic (*n*=23)	15 (68)	9 (41)	3.09 (0.89-10.65)	0.07
Ratio of osteoporosis and osteopenia-femoral neck				
All (*n*=82)	52 (63)	49 (60)	1.17 (0.62-2.19)	NS
Hepatitis B (*n*=26)	14 (54)	17 (65)	0.62 (0.20-1.89)	NS
Hepatitis C (*n*=23)	16 (70)	1.1 (48)	2.49 (0.74-8.34)	NS
NAFLD (*n*=11)	8 (73)	8 (73)	1.00 (0.15-6.53)	NS
Cryptogenic (*n*=23)	14 (64)	13 (59)	1.21 (0.36-4.08)	NS

NAFLD: Non-alcoholic fatty liver disease; NS: Not significant

0.05, respectively, however, MELD score was not found to be a significant predictor at both LS and FN studies.

DISCUSSION

Different controlled and uncontrolled studies have shown high prevalence of metabolic bone diseases in patients with CLD and cirrhosis. Results, however, are inconsistent and often exaggerated by uncontrolled studies.[7,8] Moreover, certain types of CLD impose patients to increased risk of osteoporosis due to other associated risk factors (e.g., alcohol use, corticosteroids use in autoimmune liver disease, etc.).[5,7,8] Many studies have investigated the pathophysiological links between CLD and osteoporosis, which is most probably related to remodeling imbalance involving both increased bone resorption and decreased bone formation.[12-14] This process is caused by different factors, in which many of them are common to all liver diseases, whereas others are specific to certain liver etiologies. Liver plays a major role in vitamin D metabolism and affects many different cytokines and hormones, including the IGF-1, IL-6, fibronectin, receptor-activator of nuclear factor kappa ligand/osteoprotegerin system, and others.[2,15] The American Gastroenterology Association (AGA) has concluded in its technical review in 2003 that BMD loss is mild in CLD patients and it is similar to the expected bone mass loss in patients without history of corticosteroids use.[8] Following the AGA conclusion, more data had accumulated; however, seldom evidence was from the Middle East in general and Saudi Arabia, in particular.

When compared to control sample, patients who have cirrhosis are at about double the risk of having an abnormal BMD reading at the LS but not at the FN. The increased loss of BMD at LS compared to that at the FN was seen in many other studies.[16,17] Moreover, the ratio of patients with a BMD T-score of lower than 2.5 SD was 23% at LS and 11% at FN. In general, studies have shown an increased risk of osteoporosis in liver disease patients, with a prevalence reaching up to 12–55% in patients with cirrhosis.[5]

Despite the general increase in risk of abnormal BMD in cirrhotic patients, no increased risk was found in the

Table 5: Predictors of abnormal BMD results in cirrhotic patients

Variable	BMD at lumber spine		BMD at femoral neck	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender	4.80 (1.47-15.73)	0.01*	0.67 (0.26-1.70)	NS
Age	1.00 (0.78-1.27)	NS	1.14 (0.90-1.45)	NS
BMI	0.57 (0.31-1.02)	0.06	0.88 (0.51-1.52)	NS
Calcium	0.02 (<0.001-1.08)	0.05	0.15 (0.01-3.83)	NS
Phosphorus	2.58 (0.32-21.14)	NS	4.33 (0.52-36.27)	NS
Vitamin D	0.96 (0.94-0.99)	0.01*	0.98 (0.96-1.01)	NS
PTH	0.99 (0.97-1.02)	NS	1.00 (0.98-1.02)	NS
MELD	0.95 (0.49-1.84)	NS	0.81 (0.42-1.55)	NS

BMD: Bone mineral densitometry; NS: Not significant; BMI: Body mass index; PTH: Parathyroid hormone; MELD: Model for end stage liver disease. *Multivariate analysis was also significant for both gender (P=0.0495) and vitamin D (P=0.02). No other variable was significant with multivariate analysis

analysis of specific etiologies of liver disease. This can be due to the low sample size under each etiology. For instance, our study showed that patients with viral hepatitis are not at an increased risk of having an abnormal BMD reading including both osteopenia and osteoporosis at both LS and FN. The role of viral hepatitis has been investigated in different studies. A recent meta-analysis for three case-controlled and one cohort study showed an increased risk of osteoporosis in hepatitis C patients.[18] In our study, no significant difference was noticed in the ratio of osteopenia or osteoporosis between controls and hepatitis C patients, which supports the findings of two of the case control studies reported in the meta-analysis.[19,20] Furthermore, patients with hepatitis B were found to have an increased risk of BMD loss by many studies.[21,22] Although our study showed a higher ratio of abnormal BMD finding in cirrhotic patients, although this difference was not statistically significant.

Few studies have evaluated the risk of osteoporosis in patients with cryptogenic cirrhosis and NAFLD. This study has shown no increased risk of having osteopenia or osteoporosis in both groups of patients. A meta-analysis that included more than 1,000 patients and controls did not show any significant BMD decrease in patients with NAFLD when compared to controls, while other observational studies have shown the effect of NAFLD in only certain groups.[23,24] Our study supports this finding; however, this conclusion is limited by the small sample size of this study.

The level of 25-hydroxy vitamin D was found to be significantly lower in patients with CLD and cirrhosis, especially in hepatitis B and cryptogenic liver disease patients. This finding is supported by different observational studies and by the physiological role of liver to hydroxylate vitamin D3 to 25-hydroxy vitamin D.[14,17] Paradoxically and despite the vitamin D decrease, parathyroid hormone levels were significantly lower in patients when compared to the control group. This decrease was significant in cirrhotic patients secondary to hepatitis C and cryptogenic liver disease. This paradoxical relationship has been noted by other studies of CLD and cirrhosis. The cause of this relationship is unknown, however it is possibly due to polymorphisms in vitamin D receptor gene leading to the suppression of the parathyroid hormone.[14,25-27] Despite the significant decrease in 25-hydroxy vitamin D, patients showed similar levels of corrected calcium and phosphate when compared to controls.

Analysis of predictors of decreased BMD in liver disease patients found that lower vitamin D level and female gender are predictors of increased risk of abnormal BMD at the LS. However, lower levels of 25-hydroxy vitamin D had a significant but small effect, in view of the small OR of 0.96. The effect of vitamin D on osteoporosis has been previously studied, however the evidence is contradictory. A recent study from Saudi Arabia showed no effect of 25-hydroxy vitamin D on BMD at both LS and FN.[28] All other factors including age, BMI, calcium, phosphate, and PTH did not affect the BMD level at the LS. Results also showed that none of the factors tested had a significant effect on the BMD level at the FN. Previous studies have reported different predictors of low BMD in CLD patients. For instance Ormarsdottir *et al.*[16] have reported that low BMI and age are the main determinants for loss of BMD in CLD patients, a finding that was not supported by more recent studies like Wariaghli *et al.*[29] A contributing factor to this might be the variability in the cohorts of different studies. Furthermore, the results showed that MELD score did not influence BMD at both LS and FN. Despite that the effect of severity of cirrhosis is frequently reported in review articles but the available literature lacks consensus and most studies have used Child–Pugh score. More studies are needed to evaluate the sensitivity of MELD score in assessing the risk of osteoporosis in cirrhotic patients.

This study is limited by its retrospective nature, as a temporal relationship between cirrhosis and BMD loss cannot be made. This design prevented us from using more patient-oriented models of evaluating patient's risk of having fractures such as FRAX[30], which calculates the 10-year risk of developing fractures. Furthermore, a larger sample size might be needed to investigate this risk for the specific etiologies of liver diseases.

CONCLUSION

This study showed that cirrhotic patients are at increased risk of BMD loss at the LS when compared to the general

population. Out of the possible predictors tested (gender, age, BMI, phosphorus, calcium, PTH, vitamin D, and MELD score), female gender was the main predictor of loss of BMD at LS. Our results support undertaking prophylactic measures for patients with cirrhosis, especially for females. Larger prospective studies are needed to investigate the correlation between cirrhosis and metabolic bone disease.

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Conflicts of interest

There are no conflicts of interest.

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