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The Relationship Between Chronic Liver Disease and Osteoporosis: A Retrospective Single-Center Experience

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Abstract

***Background*:** Present evidence discussed in literature reviews shows that chronic liver disease (CLD) leads to an increased risk of osteoporosis. Our study aimed to investigate the association between CLD and bone mineral density (BMD), a key indicator of osteoporosis.

Methods and Results: This retrospective study included 53 patients (mean age of 63.7± 9.3 years) with CLD who underwent a DEXA scan at the lumbar spine and femoral neck. A majority (83.0%) of the patients were females. Overall, 22.6% of the patients were suffering from liver cirrhosis, 17.0% from hepatitis, and 60.4% had NAFLD. The mean T-scores for the femoral neck and lumbar spine were 1.67±1.07 and -2.43±1.11, respectively. Based on the T-scores, 47.2% of the patients had osteoporosis, and 41.5% had osteopenia. No statistically significant relationship was observed between BMD and liver disease (P=0.388).

Conclusion: Despite the high prevalence of osteoporosis (47.2%) and osteopenia (41.5%), no statistically significant changes in BMD were found among the study population with CLD. Adjustments for age, sex, and BMI did not help to identify a confirmed association between the diagnosis of CLD and osteoporosis in the study population. Further investigation is warranted to explore the potential association between specific CLD subtypes and osteoporosis risk.**(International Journal of Biomedicine. 2024;14(4):659-663.)**

Keywords: bone mineral density • chronic liver disease • cirrhosis • nonalcoholic fatty liver disease • osteoporosis

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Abbreviations

ALT, alanine transaminase; **AST**, aspartate transaminase; **BMD**, bone mineral density; **BMI**, body mass index; **BTM**, bone turnover marker; **CLD**, chronic liver disease; **DEXA**, dual-energy x-ray absorptiometry; **DM**, diabetes mellitus; **IGF-1**, insulin growth factor-1; **LC,** liver cirrhosis; **NAFLD**, nonalcoholic fatty liver disease; **NASH**, nonalcoholic steatohepatitis; **T2DM**, type 2 diabetes mellitus.

Introduction

Chronic liver disease (CLD) is characterized by a progressive deterioration of liver function. It is a continual process of inflammation, destruction, and regeneration of the liver parenchyma that causes fibrosis and cirrhosis.[1] The prevalence of CLD in Saudi Arabia is unknown.[2] However, liver-related morbidity and death rates have grown globally over time, making CLD more common in all countries.[3] One of the main causes of CLD is nonalcoholic fatty liver disease (NAFLD), which currently affects one in four individuals worldwide. CLD can cause a variety of severe complications, including metabolic bone diseases (e.g., osteoporosis, osteopenia, and bone fractures), which frequently go unnoticed until the advanced stages.[4]

Patients with CLD show a higher prevalence of osteoporosis (10–40%) than is found in the general population without liver disease.[5,6] The group of changes in bone mineral metabolism recognized in patients with CLD is referred to as hepatic osteodystrophy,[7] and its most prevalent form is osteoporosis, which is linked to an increased risk of fragility fractures.[8] The pathogenesis of this type of hepatic osteodystrophy is poorly understood; however, several proteins and cytokines, such as IGF-1, fibronectin, and sex hormones, have been linked to changes in liver parenchyma function.[2] The severity of CLD, older age, and duration of cholestasis are the primary risk factors for hepatic osteodystrophy. Alterations in hormonal homeostasis, such as vitamin D deficiency, are also risk factors.[9] Type 2 diabetes mellitus (T2DM) has a strong relation to the development of NAFLD. It is widely acknowledged as an independent predictor of moderate-to-severe liver fibrosis, as well as overall and liver-related mortality.[10] A high-quality study has also shown that DM can lead to more complications and mortality in CLD patients, suggesting an association between DM and osteoporosis through this relationship with CLD.[11]

Osteoporosis is a systemic bone disease characterized by decreased bone mineral density (BMD) and an increased risk of fragility fractures.[12] It occurs when formation and resorption processes are interrupted, and several assays are available for measuring bone turnover markers.[13] The bone turnover markers can be used to quantify the amount of collagen breakdown products and other compounds generated by osteoclasts and osteoblasts during the resorption and formation of bone.[13] The risk of osteoporosis is enhanced in different hereditary and acquired diseases, as well as in systemic diseases such as central obesity, T2DM, and metabolic syndrome.[14] However, osteoporosis is also a common complication seen in patients with CLD, especially in patients with cirrhosis and cholestatic liver disease. Most studies have observed a profound impairment of bone formation, suggesting osteoporosis in patients with cirrhosis is a multifactorial disease in which different mechanisms work together to reduce bone mass until the skeleton becomes fragile.[12] A patient with cirrhosis is recommended to have the BMD evaluated annually.[8]

The gold standard test for assessing BMD, which ultimately predicts fracture risk and monitors changes in bone density over time, is a DEXA scan of the spine, hip, or forearms. Tests other than the DEXA scan are not as sensitive or generate insufficient data for a valid assessment.[15] The World Health Organization (WHO0 criteria define osteoporosis, osteopenia, and normal BMD as having T-scores of ≤ -2.5, -2.5 to -1, and > -1, respectively. DEXA scans are typically used to quantify BMD at the femoral neck and lumbar spine.[16] Present evidence discussed in literature reviews shows that CLD leads to an increased risk of osteoporosis. Our study aimed to investigate the association between CLD and BMD, a key indicator of osteoporosis.

Materials and Methods

This retrospective study included 53 patients (mean age of 63.7± 9.3 years) with CLD who underwent a DEXA scan (HOLOGIC; Discovery 14768) at Alhada Armed Forces Hospital from January 2022 to February 2023. CLD was confirmed by an ultrasound procedure performed as recommended by the manufacturer (SIEMENS 43500) using a 3.5MHz transducer. The DEXA scan was conducted with the patient in a supine position. Measurements were taken at the lumbar spine and femoral neck, and the patient was diagnosed according to WHO criteria. Figure 1 shows the report of the DEXA scan for a patient with osteoporosis. The study included patients aged 18 years and older.

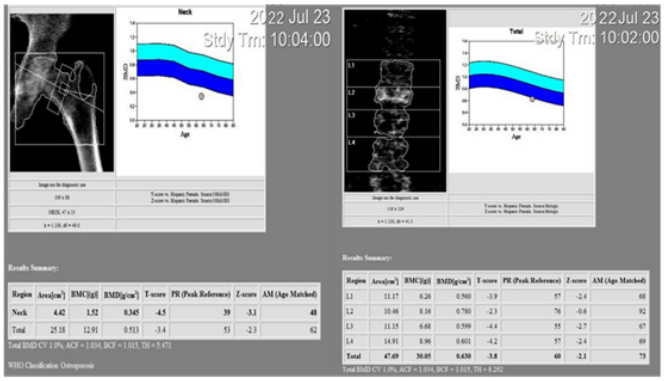

Fig. 1. *BMD measurements at the lumbar spine and femoral neck of a patient with osteoporosis.*

The main criterion for diagnosing normal body weight or obesity was BMI (kg/m^2). According to WHO recommendations, a BMI of 18.5-24.99 kg/m^2 corresponds to normal body weight, ≥30 kg/m^2 corresponds to obesity.

Patients who were undergoing any BMD-related medical treatment or who had diseases affecting bone metabolism (for instance, thyroid disorders) were excluded.

Statistical analysis was performed using statistical software package SPSS version 28.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean ± standard deviation (SD) for continuous variables. Group comparisons concerning categorical variables were performed using the chi-square test. Multiple comparisons were performed with one-way ANOVA test. A univariate analysis was performed with the diagnosed CLD as an independent variable. The dependent variables were age, gender, body

mass index (BMI), vitamin D, and BMD measurements. A variable was analyzed using logistic regression if its univariate *P*-value was 0.20, and a backward stepwise likelihood ratio regression was selected for adjustment. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. *P*-value ≤ 0.05 was considered statistically significant.

Results

A majority (83.0%) of the patients were females (Figure 2). Of the 53 patients, 22(41.5%) were obese and 34(64.2%) had T2DM. Overall, 22.6% of the patients were suffering from liver cirrhosis, 17.0% from hepatitis, and 60.4% had NAFLD (Figure 3). The mean ages at which osteopenia and osteoporosis were diagnosed were 62.8±9.2 and 65.3±9.5 years, respectively. The mean T-scores for the femoral neck and lumbar spine were 1.67±1.07 and -2.43±1.11, respectively. Based on the T-scores, 47.2% of the patients had osteoporosis, and 41.5% had osteopenia. The mean vitamin D level was 47.86±22.40 ng/mL. The liver function tests showed a mean AST level of 27.98±26.10 U/L and an ALT level of 23.22±17.25 U/L (Table 1).

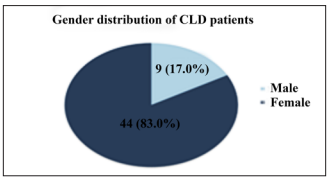

Fig. 2. *Gender distribution of CLD patients.*

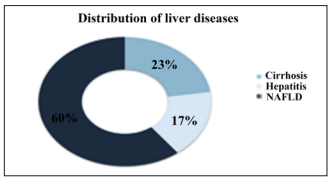

Fig. 3. *Distribution of CLD among study patients.*

Table 1.

Baseline characteristics of patients with CLD.

Gender	Male	9 (17.0%)
	Female	44 (83.0%)
Age, years	Mean age: 63.7 ± 9.3	
	40–55	10 (18.9%)
	56–70	32 (60.4%)
	≥71	11 (20.8%)
BMI	Normal	10 (18.9%)
	Overweight	21 (39.6%)
	Obese	22 (41.5%)
T2DM	No	19 (35.8%)
	Yes	34 (64.2%)
Liver disease	Cirrhosis	12 (22.6%)
	Hepatitis	9 (17.0%)
	NAFLD	32 (60.4%)
Femoral neck T-score	-1.67 ± 1.07	
Lumbar spine T-score	-2.43 ± 1.11	
BMD	Normal	6 (11.3%)
	Osteopenia	22 (41.5%)
	Osteoporosis	25 (47.2%)
Vitamin D, ng/mL	47.86 ± 22.40	
AST, U/L	27.98 ± 26.10	
ALT, U/L	23.22 ± 17.25	

No statistically significant differences were observed between the two genders in the distribution of liver diseases (*P*=0.339) (Table 2). No statistically significant relationship was observed between BMD and liver disease (*P*=0.388). In addition, the mean femoral neck T-score and lumbar spine T-score did not differ significantly between different liver diseases (*P*>0.05). Similarly, no statistically significant relationship was observed when the BMI of the patients was compared with different types of CLD (*P*=0.397). However, the occurrence of T2DM was significantly higher among patients with NAFLD than with other liver diseases (*P*<0.001). The vitamin D levels were significantly higher in NAFLD patients (55.6±19.7 ng/mL) than in LC patients (35.1±22.0 ng/mL) (*P*=0.014). The AST level was exceptionally high in LC patients (53.7±45.6 U/L) compared to hepatitis (19.8±8.2 U/L) and NAFLD cases (21.2±10.7 U/L) (*P*<0.001). Similar findings were noted for the ALT level, as LC patients showed significantly higher values (35.7±28.90 U/L) than patients with hepatitis (20.0 ± 10.9 U/L) or NAFLD (19.6 ± 10.3 U/L) (*P*<0.02).

Table 2.

Relationship between CLD and other clinical characteristics.

		CLD			*P*-value
		Cirrhosis (n=12)	Hepatitis (n=9)	NAFLD (n=32)	
Gender	Male	2 (22.2%)	3 (33.3%)	4 (44.4%)	0.339
	Female	10 (22.7%)	6 (13.6%)	28 (63.6%)	
Age, years		66.3 ± 10.1	58.4 ± 9.1	64.3 ± 8.8	0.140
BMI	Normal	2 (20.0%)	3 (30.0%)	5 (50.0%)	0.397
	Overweight	7 (33.3%)	3 (14.3%)	11 (52.4%)	
	Obese	3 (13.6%)	3 (13.6%)	16 (72.7%)	
BMD	Normal	2 (33.3%)	1 (16.7%)	3 (50.0%)	0.388
	Osteopenia	3 (13.6%)	6 (27.3%)	13 (59.1%)	
	Osteoporosis	7 (28.0%)	2 (8.0%)	16 (64.0%)	
DM	None	6 (31.6%)	8 (42.1%)	5 (26.3%)	<0.001
	Type 2 DM	6 (17.6%)	1 (2.9%)	27 (79.4%)	
Femoral neck T-score		-1.7 ±1.3	-1.4 ± 0.6	-1.7 ± 1.1	0.769
Lumbar spine T-score		-2.4 ± 0.9	-2.1 ± 0.9	-2.5 ± 1.2	0.579
Vitamin D, ng/mL		35.1 ± 22.0	37.5 ± 22.6	55.6 ±19.7	0.014
AST, U/L		53.7 ± 45.6	19.8 ± 8.2	21.2 ± 10.7	<0.001
ALT, U/L		35.7 ± 28.9	20.0 ± 10.9	19.6 ± 10.3	<0.020

Multivariate logistic regression analysis to predict the risk factors of low bone mineral density showed that none of the independent variables were associated with low bone mineral density(Table 3).

Table 3.

Multivariate logistic regression

Dependent variable = Low BMD		B	Std. Error	Wald	Odds ratio (95% CI)	*P*-value
Independent variables	Gender	-19.321	10907.727	0.000	0.69 (0.23–0.92)	0.432
	Age	0.787	1.170	0.452	2.19 (0.22–21.76)	0.501
	BMI	-3.025	1.665	3.303	1.04 (0.96–1.13)	0.069
	DM	0.855	1.479	0.334	0.049 (0.01–0.53)	0.563
	Vit D	0.041	0.042	0.970	1.04 (0.96–1.13)	0.325

Discussion

Our initial assumption was that a relationship existed between CLD and low BMD, as we found that the prevalence of osteoporosis and osteopenia in our patients with CLD was 47.2% and 41.5%, respectively. Several studies that have explored the pathophysiological connections between CLD and osteoporosis have suggested a likely connection to an imbalance in remodeling involving increased bone resorption and decreased bone production. In the literature, patients with CLD and LC were reported to have osteoporosis prevalences of 72.1% and 20.3%, respectively. However, our statistical analysis did not show any significant relationship between CLD and osteoporosis, as the T-scores at the lumbar spine and the femoral neck were not significantly different.

Most of our data (60.4%) came from patients with NAFLD, which is the most common hepatic disease worldwide. The association between NAFLD and BMD in adults remains unclear in clinical studies. In addition, the literature contains conflicting evidence on the possible relationship between the severity of liver disease and a decrease in bone density. However, low BMD appears more closely linked to progressing NAFLD than early NAFLD. According to a study in South Korea, NAFLD may be an additional risk factor for decreasing BMD in postmenopausal women.

Although our data analysis did not show significant and consistent differences in BMD at various skeletal sites, osteoporosis is a well-known condition commonly seen in cirrhotic patients. In our study, patients with cirrhosis represented 23% of the total; therefore, this was a small sample to use to clarify the relationship with low BMD. However, we cannot exclude the possibility that patients with more severe hepatic disorders, such as cirrhosis, could have a lower BMD and a higher risk of fracture. Other studies have found a relationship between BMD and advanced cirrhosis.

CLD is frequently seen with other metabolic syndromes characterized by changes in vitamin D, T2DM, ALT, and AST levels. These four factors were the only ones statistically associated with CLD in our study. Consistently, in our study, lower vitamin D was demonstrated to be a risk factor for osteoporosis in patients with CLD. This finding is supported by Muhsen et al. and Alessandro Ma et al. In general, the previously published findings support the notion that patients are more likely to develop T2DM if they have NAFLD than if they have other CLDs. Patients with NAFLD usually have T2DM, which increases the risk of disease progression to steatohepatitis, NASH, advanced cirrhosis, and even hepatocellular carcinoma. Significantly higher ALT and AST levels have been reported in LC patients than in patients with other liver diseases.

Some potential limitations of our study are that the sample size was relatively small and the data in this study were obtained from one center. Thus, a multicenter study in Saudi Arabia with a larger sample size is required.

In conclusion, despite the high prevalence of osteoporosis (47.2%) and osteopenia (41.5%), no statistically significant changes in BMD were found among the study population with CLD. Adjustments for age, sex, and BMI did not help to identify a confirmed association between the diagnosis of CLD and osteoporosis in the study population. Further investigation is warranted to explore the potential association between specific CLD subtypes and osteoporosis risk. This research could inform the development of targeted screening and management strategies for osteoporosis in patients with CLD. Conducting comprehensive screening of patients in the Kingdom of Saudi Arabia would facilitate early detection of liver diseases, thereby reducing complications and treatment costs. To optimize future expanded studies, a database of patients with liver diseases in Saudi Arabia must be created and continuously updated as needed.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Ethics Committee at the Alhada Armed Forces Hospital (H-02-T-078) (Taif, Saudi Arabia). Due to the retrospective nature of the study, no written informed consent was required from the participants.

Competing Interests

The authors declare that they have no competing interests.

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