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Evaluation of Bone Mineral Density Among Patients with Chronic Liver Disease and Associated Risk Factors

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ABSTRACT

Osteoporosis (OP) is a common complication of liver cirrhosis. It can cause morbidity and mortality due to high fracture risk and impaired quality of life. is to assess the frequency of OP among patients with liver cirrhosis and to find risk factors associated with it. Between January 2020 and February 2021, patients who had liver cirrhosis or newly diagnosed with cirrhosis were arranged to do bone mineral density (BMD), BMD was measured by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral neck. Osteopenia and osteoporosis were defined according to WHO criteria, after taking informed oral consent followed by full history, examination and demographic data. A total of 150 patients (males 108(72%) and females 42(28%)) with a mean age of 50.85+_12.9 years were enrolled in this study. Prevalence of OP was found to be 46.6% (70/150). On multivariate analysis, child-Pugh classification, menopausal state and body mass index(BMI) were significantly associated with OP, while age, gender and etiology of cirrhosis were non significantly found to be associated with OP. Low BMD is highly prevalent in patients with chronic liver disease(CLD) of variable etiologies and commonly overlooked. We advocate more randomized and prospective studies to be conducted on homogeneous groups with CLD in its various stages. In view of numerous therapeutic options available both for liver disease and bone disease, it is prudent to characterize this condition in order to give these patients a better chance of survival with good quality of life.

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1. Introduction

Chronic Liver Disease (CLD) is a major cause of morbidity and mortality worldwide. It involves haemodynamic and metabolic complications. Osteoporosis(OP) is a metabolic bone disease that may occur in individuals with chronic liver disease. It can significantly affect morbidity and quality of life of these patients. Fractures are also associated with an excess mortality.

In recent decades, The frequency of osteoporosis among patients with all causes of chronic liver disease ranges from 12% to 55% [1].

Improvements in liver transplantation and the treatment of complications from cirrhosis have raised survival rates and enhanced the lives of cirrhotic patients. But because these patients have lived longer, there is a greater chance that they will get extrahepatic symptoms like osteoporosis, but regardless of the liver disease etiology, the presence of cirrhosis implies a risk of fractures two-fold higher than in noncirrhotic people [1].

The most common bone disorder among liver insufficiency patients is osteoporosis, a progressive, systemic illness that reduces bone mass and strength, raising the risk of fractures and lowering quality of life because of discomfort and abnormalities [2]. Moreover, this is the only side effect of cirrhosis that lasts for years following liver transplantation [3- 6].

Despite that, OP is often overlooked and few cirrhosis patients are submitted to exams to diagnose it. Even those who were diagnosed are sometimes precluded from starting a treatment due to the few options that can be offered. As a result, osteoporosis affects many individuals with liver cirrhosis, which might have a significant effect on them. Patients undergoing liver transplantation or using glucocorticoids in particular have an extra loss of bone mass as a result of immunosuppressive medication use. As a result, several writers have argued that the assessment conducted prior to orthotopic liver transplantation (OLT) needs to include bone densitometry [2], [7]. Furthermore, recent data have suggested that bone status must be assessed in all cirrhotic patients [8], [9]. The first studies of osteoporosis in liver diseases evaluated patients with alcoholic cirrhosis or chronic cholestatic diseases, such as primary biliary cholangitis (PBC) [10- 15]. Then, other studies assessed patients before and after OLT [16], [17]. Regardless of the cause of the liver cirrhosis or the extent of liver impairment, the majority of them have demonstrated that osteoporosis is frequent in all cirrhotic patients [7], [9], [18], [19]. In order to present the most recent research and create some comparisons between cirrhotic individuals under various circumstances, the review's objective was to assess the physiopathology, effect, diagnosis, and management of osteoporosis in patients with liver cirrhosis.

While the exact causes of cirrhosis-related osteoporosis remain unknown, it is widely recognized that an imbalance in bone turnover, which is dependent on osteoblastic and osteoclastic activity, is the cause of the link between liver and bone illnesses [20]. The majority of research indicates a more substantial reduction in bone production, indicating that osteoporosis in individuals with cirrhosis is a complex illness where various mechanisms work in concert to lower bone mass until skeletal fragility is reached [2]. Histological specimens from bones of cirrhotic patients with bone loss are similar to those obtained from elderly or postmenopausal women [21].

Screening for osteoporosis is an important part of cirrhosis management, but it is not always performed [22]. Moreover, densitometry indications have been applied just for patients considered for OLT and for those with cholestatic diseases or those under glucocorticoid therapy.

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It is well acknowledged that the most accurate way to assess skeletal strength is measuring the bone mass [23]. Therefore, the guidelines stated that all patients with cirrhosis should undergo an initial dual-energy X-ray absorptiometry (DEXA) exam for screening of OP. They emphasized that a normal result should never be used as a reason to rule out the possibility of osteoporosis and that any additional risk factor should raise awareness to a higher level [23]. In order to detect severe bone loss, the test should be repeated after two to three years and allows for the determination of BMD, especially in the presence of the previously indicated risk factors [24]. DXA should be performed again in a year for cholestatic patients with multiple risk factors and those who have just begun glucocorticoid medication [48]. Furthermore, BMD should be assessed once more before to OLT [25].

Regarding DXA accuracy, some limitations must be taken into account. The presence of ascites causes underestimation of the real BMD value. This problem is even worse in the lumbar spine and in patients with a large volume of ascites, leading to vertebral BMD values of 4.2 to 7% higher after paracentesis and changing the diagnosis of 12% of patients [91], [92]. Therefore, it is recommended to measure BMD just after paracentesis to not overestimate bone alterations [25], [26].

Child-Turcotte-Pugh (CTP) classification of the severity of cirrhosis

	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant-induced)	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

CTP score is obtained by adding the score for each parameter
CTP class: A = 5-6 points
B = 7-9 points
C = 10-15 points

study design

This was an observational, prospective, cross-sectional hospital-based study which had been carried out in Gastroenterology and Hepatology Teaching Hospital at Medical City Complex, Baghdad, Iraq, over a period of 12 months from January 2020 to February 2021.

study population

Patients from medical wards and outpatient department of Gastroenterology and Hepatology hospital, at Medical City Complex, Baghdad, Iraq, were included in the study. The informed oral consent was obtained from all study participants.

Sample size

It was a convenience sample limited by the duration of the study and the availability of cases.
150 patients who are fit for inclusion criteria were the targeted population of this study.

Ethical consideration

In accordance to Helsinki ethical principles, an ethical clearance was obtained from Gastroenterology and Hepatology Teaching Hospital and management directorate in addition to agreement of scientific committee of Arab Council of Medical Specialization of Iraq and Basrah college of medicine ethical committee. An informed verbal and written consent also were taken from all study participants.

The study tools

All patients diagnosed as chronic liver disease/cirrhosis based on clinical, biochemical and radiological features were enrolled, the clinical criteria included the presence of well-known stigmata of CLD/ cirrhosis, the biochemical tests included deranged synthetic function of liver like low albumin and prolonged prothrombin time, the ultra-sonographic findings suggestive of cirrhosis (the presence of nodular irregular surface, distorted vascular pattern, or ascites). Signs of portal hypertension (endoscopically proven esophageal varices or dilated portal venous system with ultrasonography.

All patients underwent a detailed clinical assessment included full relevant history and remarkable clinical examination regarding aetiology, severity and complications of CLD and relevant laboratory investigations. The investigations included a complete blood profile, renal function tests and liver function tests (LFTs) including prothrombin time (international normalized ratio(INR)) and albumin level to assess Child-Pugh (figure 1) score of severity. Etiological work-up for liver cirrhosis included HBsAg, anti-hepatitis C virus (HCV) antibody, antinuclear antibodies (ANA), anti-smooth muscle antibodies(ASMA), anti-liver-kidney-microsomal (LKM) antibodies, serum ceruloplasmin, and iron studies.

Ultrasound and Upper gastrointestinal (GI) endoscopy were performed in all patients and triphasic computed tomography (CT) of the abdomen was conducted when there was suspicion of HCC. FibroScan and liver biopsy were performed once indicated.

Special form of questionnaire was conducted to gather data and it was revised and reviewed by supervisor for validity and enrichment of information taken.

The questionnaire form consisted of following sections

(1): Include question about the identity information (name, age. gender, address, weight, height and body mass index)

(2): Include questions about past medical and surgical history, drug, social, habits history and menopausal status.

(3): Clinical presentation, etiology of chronic liver disease

(4): Investigation: include all investigations mentioned in base line work up.

Diagnostic procedures

The patients sent either to Radiology Institute or to Rheumatology consultation department at medical city complex to do DEXA scan.

Exclusion criteria: we applied strict exclusion criteria to avoid any cofounding factors, so:

1-Patients with chronic kidney disease CKD or on regular haemodialysis HD,

2- A known history of bone disorder or fragility fracture,

3- Using glucocorticoid more than 10 mg for 3 months or longer,

4- Those who currently smokes or quit less than 6 months and

5-Those who use drugs which are well known to affect BMD especially proton pump inhibitors PPI and loop diuretics e.g. furosemide for more than 6 months, were considered ineligible for this study.

6. patients with severe ascites and those with hepatic encephalopathy

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Statistical analysis

Statistical Package for Social Sciences (SPSS) version 24 had been used for data analysis, descriptive statistics expressed in form of, frequencies, percentages, while inferential statistics for testing of associations by test of significance(chi-square test, analysis of variance test ANOVA),means and standard deviations were used to present data of continuous variables. A p-value < 0.05 was considered statistically significant.

3. Results

A total of 150 patients with chronic liver disease were involved in this study, 108 males (72%) and 42 females (28%), with mean age of 50.85 ± 12.79 years (16-99), the mean BMI was 26.14 ± 4.89 (Kg/M2) (15-40). According to the child-Pugh (C.P.) score 54 patients(36%), 77 patients (51.3%) and 19 patients (12.7%) were classified as stage A,B and C cirrhosis respectively. Table 1. This study showed that 34 patients (22.7%) had normal bone mineral density(BMD), 46 patients (30.7%) had osteopenia, while 70 cirrhotic patients (46.6%) had osteoporosis. Figure 1 of the studied female patients 25 (40.5%) of them were menopausal.

Also, this study revealed that the most common etiologies of chronic liver disease were cryptogenic (41 patients) (27.1%) followed by chronic viral hepatitis B (24 patients) (16%), chronic viral hepatitis C (21 patients) (14%). Figure 2

Table 1. Frequency distribution of the variables within the sample (n 150)

Variable		Frequency	%
Gender	*Male*	108	72
	Female	42	28
Age (years)	Mean 50.85 ± 12.79	(Minimum 16 – Maximum 99)	
BMI (Kg/M^2)	Mean 26.14 ± 4.89	(Minimum 15 – Maximum 40)	
C.P.	*A*	54	36
	B	77	51.3
	C	19	12.7
B.M.D.	*Normal*	34	22.7
	Osteopenia	46	30.7
	Osteoporosis	70	46.6
Menopause (n 42)	*Yes*	25	40.5
	No	17	59.5
Etiology	*AIH*	9	6
	Alcoholic	26	17.3
	Cryptogenic	41	27.3
	HBV	24	16
	HCV	21	14
	Metabolic	7	4.7
	NASH	7	4.7

	Overlap syndrome	6	4
	Wilson	9	6

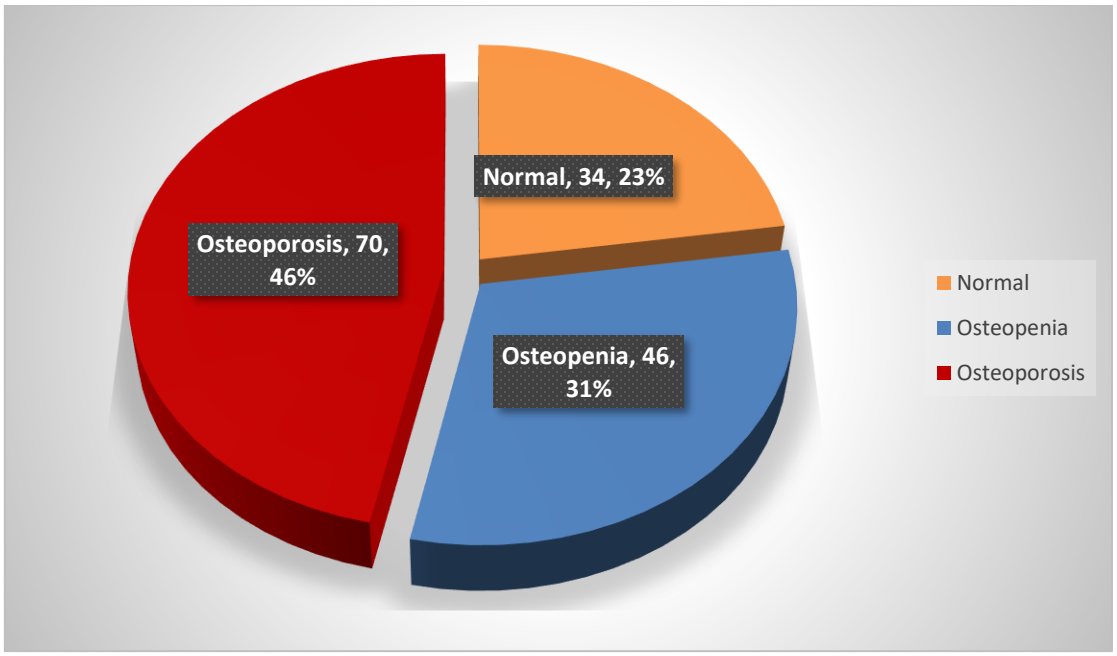

Figure 1. Frequency distribution of the sample according to the bone mineral density (n 150).

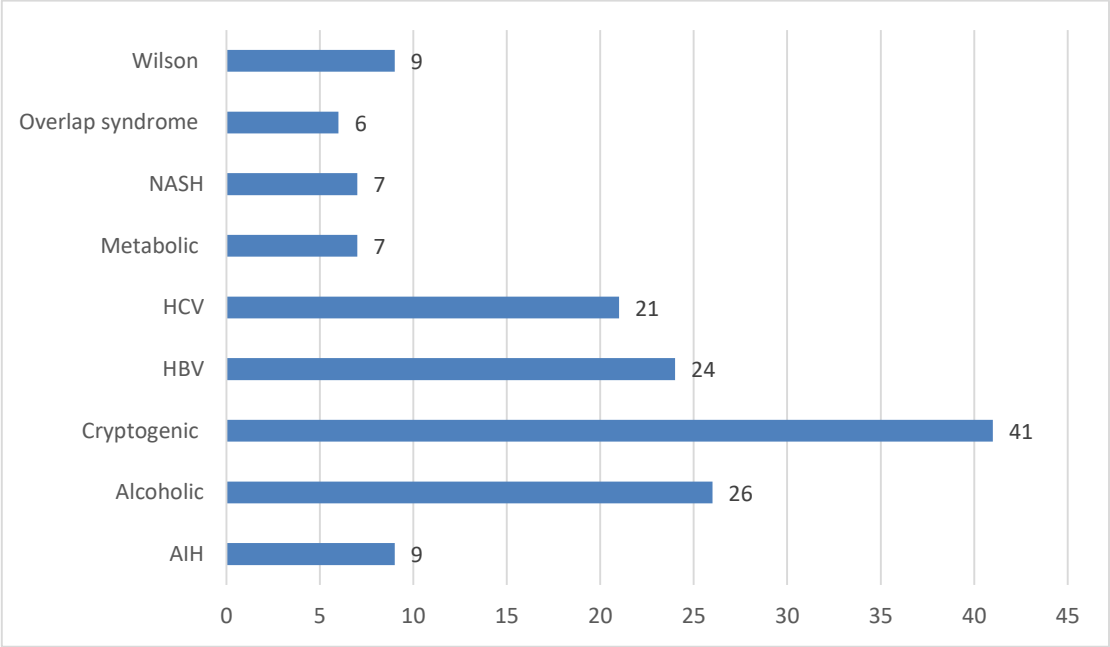

Figure 2. Frequency distribution of the sample according to the etiology (n 150).

This study showed that Child -Pugh class of the studied population and the menopausal state of the studied cirrhotic female patients were significantly associated with bone mineral density (BMD) state with p-values(0.002, 0.022) respectively , while the sex, etiology of CLD were not significantly associated with the BMD of the patients with p-values(0.905,0.586) respectively. Table 2

AMJ
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Table 2. BMD distribution within the categorical variables (n 150)

Variable		**Normal (n 34)**		**Osteopenia (n 46)**		**Osteoporosis (n 70)**		***P*** value
		Freq.	**%**	**Freq.**	**%**	**Freq.**	**%**	
Gender	*Male*	25	23.1	32	29.6	51	47.2	0.905 (NS)
	Female	9	21.4	14	33.3	19	45.2	
C.P.	*A*	15	27.8	23	42.6	16	29.6	0.002 (*)
	B	19	24.7	19	24.7	39	50.6	
	C	0	0	4	21.1	15	78.9	
Menopause (n 42)	*No*	5	29.4	7	41.2	5	29.4	0.022 (*)
	Yes	4	16	7	28	14	56	
Etiology	*AIH*	1	11.1	2	22.2	6	66.7	0.586 (NS)
	Alcoholic	4	15.4	8	30.8	14	53.8	
	Cryptogenic	11	26.8	13	31.7	17	41.5	
	HBV	8	33.3	9	37.5	7	29.2	
	HCV	3	14.3	8	38.1	10	47.6	
	Metabolic	2	28.6	2	28.6	3	42.9	
	NASH	1	14.3	2	28.6	4	57.1	
	Overlap sy.	0	0	1	16.7	5	83.3	
	Wilson	4	44.4	1	11.2	4	44.4	

Chi square *test used to measure the association.*
(NS) *Not Significant.*
(*) *Statistically significant at alpha level of less than 0.05.*

It also had been founded that the BMI was significantly associated with the BMD state with p-value(0.045), while the patients' age was not significantly associated with the BMD state of the studied patients , p-value=0.634 .Table 3

Table 3. BMD distribution within the continuous variables (n 150)

Variables	**Normal (n 34)**	**Osteopenia (n 46)**	**Osteoporosis (n 70)**	***P*** value
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age (years)	51.32 ± 18.78	49.35 ± 10.26	51.60 ± 13.46	$0.634^{(NS)}$
BMI (Kg/M^2)	26 ± 4.49	27.5 ± 4.92	25.3 ± 4.93	0.045

ANOVA *test (analysis of variance) used to measure the mean difference.*

(NS) *Not Significant.*

4. Discussion

In this study, we evaluated the prevalence of osteopenia, osteoporosis and risk factors for osteoporosis stratified according to the Child-Pugh classification in 150 cirrhotic patients due to hepatitis B, C, AIH, Wilson, alcoholic or cryptogenic liver diseases. The majority of the cohort was in Child-Pugh B stage and the low number of patients in a state of child - Pugh class C (19 out of 150).

In this study, regarding the etiology of CLD, chronic viral hepatitis (B&C) was the commonest cause 30% followed by cryptogenic 27.3% then alcoholic by 17.3%, while [19], founded that alcohol as the most common cause 24.8% followed by NASH 13% and then cryptogenic causes 9.8% and this could be explained by increasing alcoholic habit in western countries and the wide use of diagnostic procedure like liver biopsy.

This study showed that the prevalence of osteoporosis and osteopenia were present in 46.6% and 30.7% respectively and the prevalence of abnormal BMD was 77.3% which is comparable to the results of [19], who founded 66% the prevalence of BMD, while [27], founded 70% the prevalence of low BMD.

The prevalence of osteopenia and osteoporosis across studies ranges from 11.5% to 48.1% and 1.9% to 36.6%, respectively. Demographic characteristics, nutritional factors and underlying diseases may account for the different results. The prevalence of abnormal BMD results in our study were consistent with a previous large (489 patients with cirrhosis) cross sectional study conducted by [7], reported that 72% of their cohort had low BMD, the high rate seen in our study could be explained by the nutritional factors that may be different in our country.

[28], reported osteoporosis in 37% of their 55 cirrhotic patients in Turky. While [29], carried a cross-sectional study, investigating 104 cirrhotic patients on the waiting list for liver transplantation (51.9% male, median age: 54.4 years) reporting osteopenia in 34.6% and osteoporosis in 11.5%, all patients in this study group were being treated with multivitamin supplements containing vitamin D. This may explain the lower rates of osteoporosis in this study compared to ours.

In our study the underlying cause of cirrhosis was not associated with osteoporosis; however, the severity of liver disease was associated with osteoporosis and this was similar to what was founded in [30], and this can be explained by the fact that advanced stages of cirrhosis reflect longer disease duration and consequently more nutritional depletion, frequent and sometimes prolong hospitalization and more impairment in hepatocellular functions, which have been linked with bone disorders, also multiple factors have been implicated in osteoporosis. The prevalence of hypogonadism is higher in chronic liver disease then in the general population, which is an established risk factor for osteoporosis. Reduced estrogen in women and testosterone in men have been shown to be associated with lower bone mass in cirrhotic patients as well.

This study also shown that the child-Pugh classification of the cirrhotic patients is associated with the development of OP, similar finding also had been seen in study done by [30].

Menopausal women were considered risk for development of OP in this study, a finding also had been reached by [31] and this can be explained by the reduced liver of estrogen in the menopausal women.

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In this study, the patients age and sex were not significantly associated with risk of OP development, while the low BMI significantly associated with increased risk of OP, these finding were consistent with [27], but differed from that seen by [32] which found that increasing age and female gender and low BMI were risk factors for development of OP in patients with liver cirrhosis.

5. Conclusions

Low BMD is highly prevalent in patients with chronic liver disease of variable etiologies and commonly overlooked. We advocate more randomized and prospective studies to be conducted on homogeneous groups with chronic liver disease in its various stages. In view of numerous therapeutic options available both for liver disease and bone disease, it is prudent to characterize this condition in order to give these patients a better chance of survival with good quality of life

Declarations:

Ethics approval and consent to participate statement : In accordance to Helsinki ethical principles, This study was approved by the Ethics Committee of the Arab scientific council of Gastroenterology & Hepatology for researches and committee guidelines, Baghdad, Iraq and Basrah college of medicine ethical committee, verbal and written informed consent had been taken from the patients enrolled in the study and in order to support privacy and confidentiality, I concealed the unique identifying information of people in the data gathering.

Consent to publication : Written informed consent had been taken from participants

Availability of data and material: the datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS: Authors have declared that no competing interests exist.

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Authors' contributions: the three authors contributed to the design and implementation of the research, to the analysis of the results and the writing of the manuscript.

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