(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 3, Page No: 230-238
May-June 2022

IJMSCR

A Study Of Bone Mineral Density Assessment In Chronic Liver Disease Patients In A Rural Tertiary Care Hospital In North India

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Background: Metabolic bone disease is a common complication of long-standing liver disease. Also known as hepatic osteodystrophy, its prevalence in cirrhotic patients varies from 12 to 70% regardless of the liver disease etiology with a fracture rate of 3%-44%. It can result in spontaneous low-trauma fractures that significantly impact on the morbidity, quality of life, and even survival, through pain, deformity and immobility. We carried out this research to better characterize the disease entity in our rural Indian population.

Method: This was a cross sectional study consisting of 100 patients diagnosed as chronic liver disease and 100 controls at Department of General Medicine at BPS GMC, Sonepat from March 2021 to November 2021. Child Turcotte Pugh (CTP) score was calculated for patients with cirrhosis and patients were classified into the following groups: Class A, B and C. Bone mineral densitometry (BMD) was then collected for thoracic and lumbar spine (LS, L1–L4), skull, pelvis, bilateral arms, legs and ribs by using dual energy x-ray absorptiometry (DEXA) scan.

Result: Of the 100 patients, 28 belonged to Class A, 34 were in Class B and remaining 28 in Class C. The mean bone mineral density observed in patients was 0.962(0.194) gm/cm^2. 30 patients had osteoporosis with T score less than -2.5 while 24 patients had osteopenia with T score between -1 and -2.5. The average T score observed in patients was -1.047(2.081). Bone mineral density decreased progressively from 1.078(0.187) gm/cm^2 in Class A to 0.787 (0.136) gm/cm^2 in Class C and was significantly lower than their control group (p =0.01 in Class B and C). T score also decreased as liver disease progressed with T score 0.885 (1.690) in Class A, -1.438 (0.905) in Class B and -3.193 (0.864) in Class C. Overall prevalence of hepatic osteodystrophy was 54% with 7.1% risk of osteoporotic fragility fractures.

Keywords: alcoholic, bone mineral density, cirrhosis, DEXA, liver disease, lumbar spine osteodystrophy, T score

Introduction

Metabolic bone disease is a common complication of long-standing liver disease, ranging from cholestatic disorders to alcoholic, autoimmune and post-viral cirrhosis[1]. Also known as hepatic osteodystrophy (HO), it is well-recognized among patients of chronic liver disease (CLD). Prevalence in cirrhotic patients varies from 12 to 70% and osteoporosis is common among all cirrhotic patients regardless of the liver disease etiology[2]. Its etiology is poorly understood and varies according to the type, severity and progression of the liver disease, along with a

multitude of other contributing factors including the ethnicity of the population studied. Hepatic osteodystrophy can manifest in the form of osteopenia, decreased bone mineral density and increased risk of osteoporotic fractures[3]. Possible mechanisms contributing to this are decreased synthesis of vitamin D by dysfunctional liver cells, corticosteroid treatment induced osteoporosis, decreased bone turnover and increased bone resorption. Many studies have shown low serum levels of 25-hydroxyvitamin D in patients with chronic liver disease[4,5] and levels fall with disease progression in cirrhosis[6]. Severe deficiency is more common in those stricken by cirrhosis and/or cholestatic diseases, because jaundice can make them more prone to malnutrition, malabsorption, and suppressed skin synthesis[7]. Other factors implicated in development of osteoporosis are alcohol abuse, smoking, immobility, hypogonadism, poor nutritional status, reduced muscle mass, premature menopause, and preexisting osteopenia [8,9]. It can result in spontaneous low-trauma fractures that significantly impact on the morbidity, quality of life, and even survival, through pain, deformity and immobility. In various international studies, the overall incidence has varied from 11% to 48%, with a fracture rate of 3%-44%[10]. However this has not been extensively studied in the rural Indian population[11].

Review of literature:

Many studies have been carried out in different parts of the world on hepatic osteodystrophy and establishing its correlation with different etiologies. Germán López-Larramona et al[12] conducted a similar study in 2011 and concluded that the origin of HO is multifactorial and its etiology and severity varies parallel to underlying liver disease. They found mean prevalence of osteoporosis is significant in viral cirrhosis (55%) as compared to chronic cholestasis (13%-60%). Unlike our study results however they established that alcoholic liver disease is not always related to osteopenia.

Another study conducted by N. S. Choudhary, et al[13] in 2011 again on 115 patients had concluded that hepatic osteodystrophy was more significant in alcoholic liver disease patients, where low BMD was present in 97% of patients with alcoholic cirrhosis and 93.7% with viral cirrhosis ($p > 0.05$). They found that both alcoholic and viral groups had similar baseline characteristics except albumin levels. They similarly categorised patients in Child's class A, B, C categories. Among 115 patients the score was B in 72 patients and C in 43.

Fatima Aparecida Ferreira Figueiredo et al[14] conducted a cross sectional study at Rio de Janeiro in 1998 on 92 patients to determine the prevalence of metabolic bone disease in non cholestatic liver disease specifically. They found that prevalence of osteopenia in non cholestatic liver disease patients was quite high as 78% at lumbar spine and 71% at femoral neck.

Also Chun-Chia Chen et al[15] conducted a study in 1996 consisting of 74 cirrhotic men and 16 healthy controls where they found again the bone mineral density was significantly less in post necrotic cirrhosis patients as compared to controls. The spinal osteoporosis more than 2 SD below the mean value was found 20% in cirrhotic patients as compared to 10% in controls. However they didn't correlate it with severity of liver cirrhosis. We went a step ahead to establish this correlation.

A similar study was conducted in in India in Uttar Pradesh by Yogesh et al[16] in January 2014 -2015 where they used similar methods to assess bone mineral density in 72 CLD patients and found 70.8% i.e. 51 patients having low BMI.

Another previously conducted study in India in 2012-2013 by Rinkesh et al[17], New Delhi on 215 patients established that severity of liver disease doesn't correlate with hepatic osteodystrophy. However it was significantly affecting patients of liver cirrhosis as 2/3rd of the patients were found having low bone mineral density.

Objectives:

Metabolic bone disease is a well-recognized disease entity in chronic liver disease patients. However, data in literature for Indian population is lacking. Therefore, the overall aim of this study was:

1. To determine correlation between severity of metabolic bone disease with progression of chronic liver disease in rural Indian population

2. To assess severity of hepatic osteodystrophy according to etiology of chronic liver disease- in both alcoholic and non-alcoholic CLD.

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3. To compare our results with studies done elsewhere.

Methodology:

Study Population

This was a case control study of 200 subjects which was carried out from March 2021 to November 2021 in patients diagnosed as chronic liver disease at Department of General Medicine in BPS GMC Khanpur Kalan, Sonepat. Hundred of the 200 study participants were cases/patients whereas other hundred were healthy subjects acting as age-gender matched control group. The diagnosis in each case was confirmed by examination of the appropriate biochemical, serologic and imaging data. Patient was a diagnosed case of chronic liver disease at least 6 months before enrollment into the study.

Inclusion Criteria

The inclusion criteria includes

1. All chronic liver disease patients with Child A, Child B, Child C
2. Age group - Male -21yrs – 70 years and Female -21yrs – till menopause.

Exclusion Criteria

Baseline exclusion criteria includes

1. Patient having a history of an ileal resection
2. Renal failure, abnormal thyroid function, diabetes, significant cardiopulmonary disease
3. Postmenopausal status
4. Any other known bone disorder other than osteoporosis or osteopenia
5. Solid or hematological malignancies
6. Use of corticosteroids for more than 3 months.

Materials And Methods:

Demographic and disease information including age, gender, diagnosis and duration of disease and any history of pathologic fracture was documented using a baseline questionnaire.

Biochemical investigations which were performed to establish CLD are total, direct and indirect bilirubin levels, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase levels and serum electrolytes. Complete hemogram and prothrombin time of study participants was done. Serologic data included testing for HBsAg and IgG titers to HBV and HCV. All the patients underwent ultrasonography of abdomen to confirm the findings suggestive of chronic liver disease which included altered/coarsened echotexture, hypoechoic regenerative nodules in liver parenchyma and increased diameter of portal vein and reversal of flow and dilatation of intrahepatic of biliary radicles, if present. Physical manifestations of hepatic decompensation such as history of hematemesis due to bleeding esophageal varices, ascites, splenomegaly, caput medusae and hepatic encephalopathy were assessed by clinical examination. At the time of BMD evaluation, none of the patients were on their calcium supplementation, vitamin D or other treatments that could have affected bone mass such as calcitonin, estrogens, sodium fluoride, bisphosphonates or corticosteroids.

Ethical Approval

Written informed consent was taken from each study participant after the study gained approval from Institute's Ethics Committee.

Procedure

To decrease confounding variables, age, and gender were used to match the study sample. Age matching was done using preset 10 years age groups (i.e., [20-29], [30-39], etc.). Based on age and gender, each patient was randomly assigned a control in a ratio of 1:1. Child Turcotte Pugh (CTP) score was calculated for patients with cirrhosis and patients were classified into the following groups: Class A: 5-6, Class B 7-9 and Class C 10-15. Bone mineral densitometry (BMD) was then collected for thoracic and lumbar spine (LS, L1–L4), skull, pelvis, bilateral arms, legs and ribs. Dual energy x-ray absorptiometry (DEXA) scan was used in measuring bone mineral density. The results were classified according to T-score into: normal: <–1 SD, osteopenia: between –1 and <–2.5 SD, and osteoporosis: >–2.5 SD at both lumbar spine and pelvis.

Statistical Analysis

Statistical analysis was performed by using the software package SPSS version -262. Descriptive statistics for the continuous variables was reported as mean and categorical variables summarized as frequencies and percentages. Continuous variables were compared by Student's t-test, whereas

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categorical variables were compared by Chi-square test. The p value < 0.05 was considered as statistically significant and p value <0.01 was considered as statistically highly significant.

Result And Observation:

The study was conducted on 200 subjects consisting of 100 cases and 100 controls. Of the 100 cases, 56 patients had alcoholic liver disease while 44 patients had liver disease attributable to non alcoholic causes. A comparison of different laboratory parameters was made between cases and controls as shown in Table 1. The mean bone mineral density observed in patients was 0.962(0.194) gm/cm^2 which was lower than the age matched control group - 1.135(0.177) gm/cm^2 (p = 0.01). 30 patients had osteoporosis with T score less than -2.5 while 24 patients had osteopenia with T score between -1 and -2.5. The average T score observed in patients was -1.047(2.081) which is significantly lower than control group -0.102(1.719) with a p value of 0.02.

Table 1: Table showing mean and standard deviation of various lab parameters in both cases and controls.

Parameters	Cases- N1 Controls- N2	N	Mean	Standard Deviation	p-value
Duration of ALD (years)	N1	N	7.25	3.158	
Duration alcohol intake(yrs)	N1	46	11.36	4.236	
Amount of Alcohol (g/day)	N1	46	247.50	80.674	
BMD(gm/cm^2)	N1	100	0.962	0.194	0.01
	N2	100	1.135	0.177	0.01
Pelvis(gm/cm^2)	N1	100	1.013	0.276	0.03
	N2	100	1.115	0.176	0.03
Thoracic Spine(gm/cm^2)	N1	100	0.941	0.202	0.01
	N2	100	1.119	0.170	0.01
Lumbar Spine(gm/cm^2)	N1	100	0.935	0.227	0.17
	N2	100	0.991	0.105	0.12
T-score	N1	100	-1.047	2.081	0.02
	N2	100	-0.102	1.719	0.02
Total Bilirubin (mg/dl)	N1	100	2.468	1.455	0.01
	N2	100	1.516	0.594	0.01
Prothrombin Time(sec)	N1	100	21.94	8.26	0.01
	N2	100	14.62	3.23	0.01
S. Albumin(g/dl)	N1	100	2.934	0.946	0.28
	N2	100	3.134	0.876	0.28

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The severity of hepatic osteodystrophy with progression of liver disease was also assessed by classifying patients into Child Pugh Class A, B and C. Of the 100 patients, 28 belonged to Class A, 34 were in Class B and remaining 28 in Class C. Table 2 shows mean and standard deviations along with p values of various lab parameters in subjects and their respective controls. Bone mineral density decreased progressively from 1.078(0.187) gm/cm^2 in Class A to 0.787 (0.136) gm/cm^2 in Class C and was significantly lower than their control group (p =0.01 in Class B and C). T score also decreased as liver disease progressed with T score 0.885 (1.690) in Class A, -1.438 (0.905) in Class B and -3.193 (0.864) in Class C. It was also lower than their control group (p=0.02 in Class B and p=0.01 in class C).

Table 2: Table showing mean (standard deviation) along with p values of various lab parameters in subjects and their respective controls

Parameters	Subjects	Child A (n=19)	Child B (n=17)	Child C (n=14)
BMD (gm/cm^2)	Patient	1.078 (0.187)	0.975 (0.134)	0.787 (0.136)
	Control	1.167 (0.157)	1.140 (0.207)	1.084 (0.165)
	P value	0.12	0.01	0.01
Pelvis (gm/cm^2)	Patient	1.106 (0.314)	1.055 (0.259)	0.837 (0.143)
	Control	1.140 (0.151)	1.150 (0.203)	1.039 (0.160)
	P value	0.67	0.25	0.01
Thoracic Spine (gm/cm^2)	Patient	0.927 (0.248)	1.040 (0.137)	0.840 (0.148)
	Control	1.135 (0.156)	1.155 (0.207)	1.055 (0.130)
	P value	0.01	0.05	0.01
Lumbar Spine (gm/cm^2)	Patient	0.945 (0.310)	1.002 (0.129)	0.839 (0.158)
	Control	1.025 (0.095)	0.974 (0.112)	0.966 (0.104)
	P value	0.29	0.50	0.02
T-score	Patient	0.885 (1.690)	-1.438 (0.905)	-3.193 (0.864)
	Control	0.531 (1.475)	-0.088 (2.008)	-0.979 (1.326)
	P value	0.49	0.02	0.01
Total Bilirubin (mg/dl)	Patient	1.206 (0.483)	2.429 (0.487)	4.229 (1.304)
	Control	1.537 (0.633)	1.423 (0.517)	1.600 (0.656)
	P value	0.07	0.01	0.01
Prothrombin Time (sec)	Patient	14.79 (2.97)	22.18 (2.50)	31.36 (8.17)
	Control	14.63 (3.37)	14.35 (2.85)	14.93 (3.65)
	P value	0.88	0.01	0.01
Serum Albumin (g/dl)	Patient	3.67 (0.72)	2.97 (0.45)	1.89 (0.65)
	Control	3.41 (0.98)	3.09 (0.71)	2.81 (0.85)

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	P value	0.36	0.57	0.01

Discussion:

The aim of our study was to determine prevalence of hepatic osteodystrophy in chronic liver disease patients and to associate its severity with progression of liver disease. We saw a decreased bone mineral density and T-score (statistically significant in Class B and C) in patients of chronic liver disease as compared to their respective controls. The mean bone mineral density observed in patients was 0.962(0.194) gm/cm^2 which was lower than the age matched control group and 54% patients had a subnormal T score. Low BMD in liver disease patients was also found in similar studies carried out by Yogesh Karoli et al in 2016 [16] in which 99% patients had a subnormal T score and Arka De et al[18] in which prevalence of hepatic osteodystrophy was 83%. Flávio Pereira et al[19] also conducted a study in 2018 where the prevalence of bone disease of hepatic origin was found to be 79.8% and that of osteoporosis specifically (T score <-2.5) was 21.3%. This is incongruent to our results which showed prevalence of 54% and with osteoporosis in 30% of study subjects. The reason for this discrepancy could be due to the fact that they enrolled CTP- Class B and C patients only whereas we enrolled patients from Class A as well. Our CTP A patients mostly stood out of the criteria for osteodystrophy. However p values were significant in both the studies for CTP Class B and C ($p<0.05$). M A Chinnaratha et al[20] also in 2012 showed similar prevalence of 56% which is comparable to ours (54%).

The lowest BMD of 0.935(0.227) in our study was found at lumbar spine which is consistent with a similar study carried out by George J et al[11] in 2009 and Aparecida et al[14] in Brazil. However the former found no relation between severity of hepatic dysfunction (Child Class) and incidence of low BMD. A study carried out by Chun-Chia-Chen et al in Taiwan[15] also showed that the BMD of lumbar spine didn't went parallel to severity of cirrhosis by Pugh's classification This is in contrast to our study which showed statistically significant fall in BMD with progression of liver disease from Class A to C (p value = 0.01) as summarized in **Figure 1.** Similar finding was also reported by Aparecida et al in from their study. The vitiated liver cells produce cytokines which impair the activation of osteoblasts thus leading to decreased bone formation.

Figure 1: Figure showing Mean BMD and T Score of patients according to Child Pugh Classification.

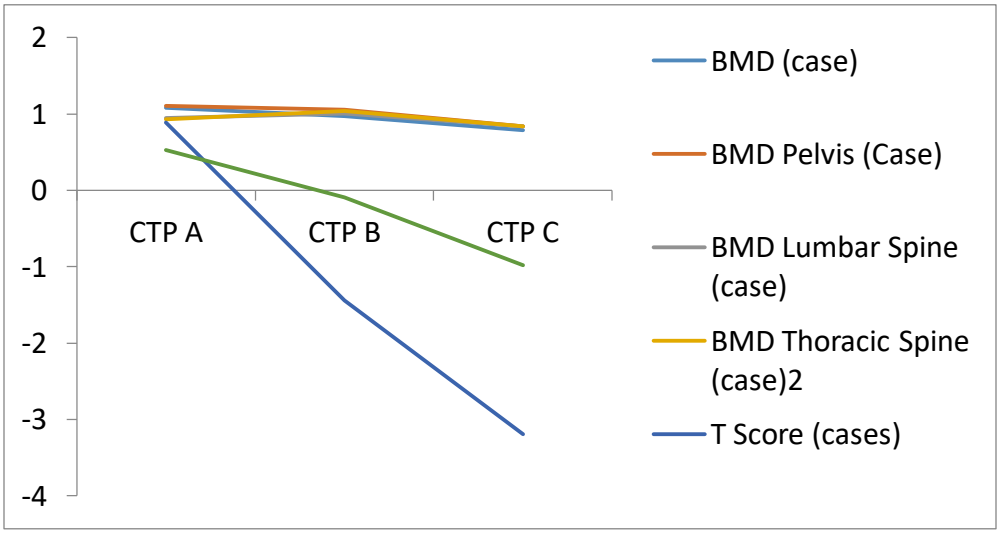

Table 3: Table showing comparison of various demographic and laboratory parameters between our study with previous international reports

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Parameters	Our Study (Haryana)	Aparecida et al [14] (Sau Paulo,Brazil)	Savic Z et al [2] (Serbia)	Chen et al [15] (Taiwan, China)	Choudhary et al [13] (Chandigarh India)	Bansal et al [17] (Delhi India)	Yogesh et al[16] (UP, India)	Arka De et al [18] (North India)
Median Age (yrs)	51.1(11)	52(11) years	59.1(5.19)	64.1(9.9)	49(5.5)	50.9(11)	50.04(11.24)	49(40-65)
Alcoholic Etiology	71.10%	52%	80%	-	93.70%	45.60%	31.37%	80%
Other Etiologies (%)	HBV(27.2%) HCV (31.8%)	Viral hepatitis, Autoimmune NASH, Cirrhosis	-	HBV HCV ALD Cirrhosis	Low levels of Vitamin D, Abnormal PTH levels.	NASH (24.2%), HBV(9.8%), HCV(6.5%)	HBV(29.4%), HCV (39.2%)	HBV(8.3%), HCV(5%), NASH (6.7%)
Prevalence of HOD	54%	77.5%	20%		38.20%		70.80%	83.30%
Osteoporosis (%)	30%	29.75%	20%	20%	39.25%	21.80%	29.40%	36.7%
Osteopenia (%)	24%	44.35%	-	-	57.05%	44.20%	71.00%	46.70%
Average T-Score	-1.047(2.081)	-1.0(0.3)	-	-	<-2.5 in 34.72%	-	-2.59 (1.31)	-2.2(0.85)
Mean BMD	0.962(0.194)	0.98(0.13)	0.898(0.112)	-	-	-	-	-
S. Albumin	2.934(.946)	3.43(.5)	3.212	3.13	2.63	2.5	3.03(.25)	2.9(2.6-3.4)
T. Bilirubin	2.468(1.455)	2.46(1.76)	3.984	3.17	3.74	2.9	-	2.8(2-12.6)

The study showed alcoholic etiology in 71.1% patients (20 out of 28 patients employed), being the leading cause of osteoarthropathy in liver disease. Another study conducted in North India by Arka De et al[18] showed similar results where they found alcoholic etiology in 80% of the patients employed (96 out of 120 patients), thus establishing evidence in favour of such pathophysiology. These findings are consistent with a study carried out by Savic Z et al[2] in alcoholic liver disease patients where they found correlation between decreasing levels of Vitamin D contributing to osteoporosis as the liver disease progressed. The progressive fall in BMD from Child Pugh A to Child Pugh C was probably because of decreased levels of vitamin D in affected patients due to decreased absorption and hepatic synthesis. Vitamin K deficiency also contributes to osteopenia in patients with alcoholic liver disease as it is an essential cofactor for osteoblasts to produce osteocalcin - bone matrix protein[19]. Alcohol also leads to increase in levels of TNF-α which increases bone resorption by RANKL-OPG -RANK system. **Table 3** summarizes our result and compares the findings of our study with previous international reports.

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It is important to recognize bone disease in chronic liver disease patients as it can result in spontaneous low-trauma fractures that significantly impact the morbidity, quality of life, and even survival, through pain, deformity and immobility. The study showed 7.1% risk of osteoporotic fragility fractures (calculated according to the FRAX score) which is comparable to the results from Arka D et al[18] where 10 year risk of osteoporotic fractures was 5.7% and hip fracture was 2.5% and M A Chinnaratha et al[20] where fragility fracture risk was 3%. The results compel us for regular screening of severe liver disease patients in order to improve morbidity and quality of life in them. DEXA can be considered as it is simple and non invasive.

In our study, among the predictive factors for hepatic osteodystrophy- prothrombin time, albumin and total serum bilirubin were found to be significantly different in patients with HOD in comparison to the controls. Total serum bilirubin which is a part of the LFT did not show any major difference among patients and controls with CTP score A (p value=0.07), but showed statistically significant difference in Class B and Class C ($p< 0.01$). Prothrombin time was significantly elevated in Class C ($p< 0.01$).

Limitations of this study could be lack of data on physical activity or BMI and sunlight exposure in patients (vitamin D status of patients and controls), lack of information on nutrition intake among patients and controls. This neglectance could have altered the results sparsely as compared to other studies.

Conclusion:

Although metabolic bone disease has emerged as one of the major determinants of survival and quality of life in CLD patients[21], yet it is a lesser known condition among treating physicians. This study is an effort to better characterize it in our population and hence sensitize the physicians to identify and manage it in early course of the disease. Significantly low bone mineral density can be seen in patients with chronic liver disease (CTP -C), and the progression of hepatic osteodystrophy correlates with the disease severity categorized according to the Child-Pugh classification. In 100 patients who participated in study, osteoporosis was diagnosed in 30%, osteopenia in 24% with increasing correlation with disease severity.

The findings of this study buttress the need for prescribing calcium and vitamin D in patients of chronic liver disease and generation of additional information on hepatic osteodystrophy. With liver transplantation steadily taking the center stage in treatment of end-stage cirrhosis, osteoporosis is the only complication that persists for years even after this novel intervention[22]. Hence it should be managed as an independent disease entity.

References:

1. Hay JE. Osteoporosis in liver diseases and after liver transplantation. *Journal of Hepatology*. 2003;38:856–865.
2. Savic Z, Damjanov D, Curic N, et al. Vitamin D status, bone metabolism and bone mass in patients with alcoholic liver cirrhosis. *Bratislava Medical Journal*. 2014; 115: 573-578.
3. J D Collier, M Ninkovic, J E Compston. Guidelines on the management of osteoporosis associated with chronic liver disease. *Gut.* 2002;50(Suppl I):i1–i9
4. Diamond T, Stiel D, Mason R, et al. Serum vitamin D metabolites are not responsible for low turnover osteoporosis in chronic liver disease. *The Journal of Clinical Endocrinology and Metabloism*.1989;69:1234–9.
5. Mobarhan SA, Russell RM, Recker RR, et al. Metabolic bone disease in alcoholic cirrhosis: a comparison of the effect of vitamin D2,-hydroxyvitamin D of supportive treatment. *Hepatology* 1984;4:266–73.
6. Masuda S, Okano T, Osawa K, et al. Concentrations of vitamin D-binding protein and vitamin D metabolites in plasma of patients with liver cirrhosis. *Journal of Nutritional Science and Vitaminology*. 1989;35:225–34.
7. Cholongitas E, Theocharidou E, Goulis J, et al. Review article: the extra-skeletal effects of vitamin D in chronic hepatitis C infection. *Alimentary Pharmacology and Therapeutics*. 2012; 35: 634–646.
8. Ng TM, Bajjoka IE. Treatment options for osteoporosis in chronic liver disease patients requiring liver transplantation. *Annals Pharmacotheapy*. 1999;33:233–5.

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1. 9. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *British Journal of Surgery*. 1973;60:646–9.
9. Hay JE, Guichelaar MM. Evaluation and management of osteoporosis in liver disease. *Clinical Liver Disease*.2005;9:747–766
10. George J, Ganesh HK, Acharya S, et al. Bone mineral density and disorders of mineral metabolism in chronic liver disease. *World Journal of Gastroenterology*. 2009;15(28):3516–3522. doi:10.3748/wjg.15.3516
11. López-Larramona G. Hepatic osteodystrophy: An important matter for consideration in chronic liver disease. *World Journal of Hepatology*. 2011;3(12):300.
12. Choudhary N, Tomar M, Chawla Y, Bhadada S, Khandelwal N, Dhiman R et al. Hepatic Osteodystrophy Is Common in Patients with Noncholestatic Liver Disease. *Digestive Diseases and Sciences*. 2011;56(11):3323-3327.
13. Figueiredo F, Brandão C, Perez R, Barbosa W, Kondo M. Low bone mineral density in noncholestatic liver cirrhosis: prevalence, severity and prediction. *Archives of Gastroenterology*. 2003;40(3):152-158.
14. Chen C, Wang S, Jeng F, Lee S. Metabolic bone disease of liver cirrhosis: Is it parallel to the clinical severity of cirrhosis? *Journal of Gastroenterology and Hepatology*. 1996;11(5):417-421.
15. Karoli Y. Study of Hepatic Osteodystrophy in Patients with Chronic Liver Disease. *Journal of Clinical and Diagnostic Research*. 2016;10(8):31-4. doi: 10.7860/JCDR/2016/21539.8367.
16. Bansal R, Kumar M, Sachdeva P, Kumar A. Prospective study of profile of hepatic osteodystrophy in patients with non-choleastatic liver cirrhosis and impact of bisphosphonate supplementation. *United European Gastroenterology Journal*. 2016;4(1):77-83.
17. De A, Ray D, Lamoria S, Sharma V et al. Hepatic osteodystrophy and fracture risk prediction using FRAX tool in Indian patients with cirrhosis. *JGH Open*. 2020 Jun 12;4(5):945-949. doi: 10.1002/jgh3.12369. PMID: 33102768; PMCID: PMC7578334
18. Pereira F, Azevedo R, Linhares M et al. Hepatic osteodystrophy in cirrhosis due to alcohol-related liver disease. *Rev Esp Enferm Dig*. 2020 Dec 3. doi: 10.17235/reed.2020.7301/2020.
19. Chinnaratha MA, Chaudhary S, Doogue M, McCormick RJ, Woodman RJ, Wigg AJ. Prevalence of hepatic osteodystrophy and vitamin D deficiency in cirrhosis. *Journal of Internal Medicine*. 2015 Dec;45(12):1230-5. doi: 10.1111/imj.12866. PMID: 26247615.
20. Akbari S, Rasouli-Ghahroudi A. Vitamin K and Bone Metabolism: A Review of the Latest Evidence in Preclinical Studies. *BioMed Research International*. 2018;2018:1-8.
21. Kaemmerer D, Schmidt B, Lehmann G, et al. Treatment of bone loss in patients with chronic liver disease awaiting liver transplantation. *Transplantation Research*. 2012 Jun 1;1(1):7. doi: 10.1186/2047-1440-1-7

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