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Original Research Article

A cross-sectional study of chronic liver disease patients complicating to hepatic osteodystrophy

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ABSTRACT

Background: Hepatic osteodystrophy encompasses the spectrum of metabolic bone diseases in chronic liver disease (CLD) patients. CLD causing changes in BMD is well known. Although BMD evaluation in CLD cirrhosis are recommended by societies of British and American gastroenterology ,very less number of literature exist from India and none from the North-eastern region of India. Aim of the study to determine the association and severity of bone mineral density changes in patients with CLD and to correlate it with different aetiologies and severity of CLD.
Methods: This cross-sectional study which included 79 patients with CLD was conducted in RIMS, Manipur from September 2017 to August 2019. All CLD patients of age 18-60 years were included. DEXA scan and other related blood investigations were performed.
Results: Chronic alcohol intake (56.9%), viral infection (20.3%) and mixed (17.7%) were the main aetiology of CLD in our study. Seventy three (92.4%) of the total 79 patients had low BMD (Osteopenia in 29 (36.7%) and osteoporosis in 44 (55.7%) patients). Osteoporosis was detected in 53.4% of alcohol related Cirrhosis, 25%of viral liver disease. Majority of the severe CLD patients (Child class C) had osteoporosis (70.6%) as compared to less severe groups (23.5% and 36.4% in class B and A respectively).
Conclusions: CLD patients have high prevalence of osteoporosis. Severity of liver disease, alcoholic liver disease, serum calcium and vitamin D deficiency predisposes to osteoporosis in these patients. Hence early screening of BMD is necessary in CLD patients.

Keywords: Bone mineral density, Chronic liver disease, Hepatic osteodystrophy, Osteoporosis

INTRODUCTION

Liver disease is one of the major diseases affecting the Indian population. The mortality death rate in India population is 22 per 1 lakh according to WHO data.[1] Amongst the liver disease, Chronic liver diseases (CLD) shares the main burden of the disease. Chronic liver disease is characterised by ongoing inflammation in the liver for at least 6 months from any cause which may progress to cirrhosis and end-stage liver disease. Chronicity of liver disease is determined either by duration of liver disease for more than 6 months or by evidence of either severe liver disease or physical stigmata of Chronic liver disease.[2,3] The etiologies of CLD are alcoholism, chronic viral hepatitis (hepatitis B and hepatitis C), autoimmune hepatitis, non-alcoholic steatohepatitis, biliary cirrhosis (primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune cholangiopathy and cardiac cirrhosis), inherited metabolic liver disease (hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency and cystic fibrosis) and cryptogenic cirrhosis.[4]

Chronic liver disease may result in complications including portal hypertension, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-pulmonary syndrome and hepato-renal syndrome. Alteration in bone metabolism is a less recognized chronic complication of liver disease which is defined under the generic term hepatic osteodystrophy.[5] Hepatic osteodystrophy (HO) manifest as osteopenia, osteoporosis and osteomalacia.[6] In west, prevalence rate of HO ranges from 13-70% and in India 68 and 95%.[7-10] Stronger association between cirrhosis and osteoporosis than between cirrhosis and osteomalacia is found. Decreased Bone mineral density (BMD) in form of osteopenia and osteoporosis is significantly associated with CLD in many of the western literature. Moreover, subsequent fracture rate of 3% to 44% is also reported.[11] Early screening of osteoporosis in patients with CLD is essential as advanced hepatic osteodystrophy adversely affect both the quality of life and long-term prognosis of CLD patients. As HO remains under diagnosed and undertreated complication, establishing this intricate relationship will help to improve outcome with timely intervention for HO. This association has not been studied extensively in the Indian population.[10] Therefore, this study was performed to see the correlation of hepatic osteodystrophy with the risk factors of CLD in this part of the country.

Aims and objectives of the study is to determine the association and severity of reduced BMD in patients with Chronic liver disease and to determine the correlation of hepatic osteodystrophy with different etiologies and severity of Chronic liver disease

METHODS

This cross sectional study was conducted over a period of 2 years from September 2017 to August 2019. Seventy nine patients diagnosed with Chronic Liver Disease with ages upto 60 years were included in the study. Cases included patients with chronic liver disease admitted to medicine ward and attended Medicine OPD, RIMS Imphal. Ultrasound whole abdomen to confirm the diagnosis was performed. DEXA scan of lumbar spine (L1-L4) and bilateral femur were taken using “Lunar Prodigy advance Direct-Digital Densitometry”. Patients with thyroid or parathyroid disorders, renal failure or malignancy were not included. Those who were on medications like corticosteroids; oestrogens, calcitonin, bisphosphonates, anticonvulsants, anticoagulants and sodium fluoride were also excluded. Ethical clearance for the study was taken from the Research Ethics Board, RIMS Imphal.

Bone mineral density was expressed in terms of T-score. The World Health Organization has defined reduced BMD in to two categories. Osteoporosis is characterised by BMD less than -2.5 standard deviations of the mean BMD of a sex matched, young healthy population, ie, a T score less than <-2.5. Osteopenia is defined as bone loss with a T score between -1 and -2.5.[12]

Serum vitamin D- ELISA reader (Multiskan) at wave length 450nm using ELISA Kit was used for vitamin D level estimation. For the purpose of analysis, 25 (OH) vitamin D concentrations were categorized based on K/DOQI. Vitamin D level above 30ng/ml was taken as optimal level. Levels between 20 and 30 ng/ml was considered as insufficient and a value less than 20ng/ml as vitamin D deficiency.[13]

Statistical analysis

Statistical analysis was done by IBM SPSS Statistics Data Editor 21.0. Descriptive statistics such as Mean±SD, frequency and percentages were used for analysis. Analysis of variance (ANOVA), student t test (two tailed, independent and Chi-square/ Fisher Exact test have been used to find the significance of study parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

The present cross-sectional study conducted in RIMS for 2 years duration consisted of 79 patients diagnosed to have Chronic Liver Disease with age 18 years - 60 years. The mean age of the participants was 45.77±7.77 years with majority of them over 41-50 years (40.5%). Majority of the subjects were males (87.3%) while the female constituted 12.7%. More than two-third of the patients were having significant alcohol intake (75.9%) followed by smokers (26.6%), Diabetes (13.9%) and Hypertension (15.2%). Pedal edema was the most common complaint (77.2%) followed by jaundice (64.6%), altered sleep pattern (57%) and malena (50.6%) (Table 1). Majority had Ascitis (in 75.9% patients) followed by Acute hepatitis (in 70.9%), Hepatic encephalopathy (in 62%) and Upper gastrointestinal bleed (in 50.6%), shown in Figure 1.

All the CLD patients were anemic (mean haemoglobin 8.78(g/dl) with low serum albumin level (2.57±0.58) and higher Mean serum bilirubin level (was 5.63 mg/dl with standard deviation 5.89), (Table 2). Serum alkaline phosphatase was more in osteoporosis group (309.84±141.29) as compared to non-osteoporosis group (239.94±115.71). Serum albumin level was positively and Serum alkaline phosphatase level was negatively associated with BMD values with significant p-values. Most of them had low serum vitamin D level (19.82±7.47). Serum calcium level was low in Osteoporosis group (8.08±0.43) as compared to Non osteoporosis group (8.69±0.57). There was no statistically significant association between serum bilirubin level, liver enzyme levels and prothrombin time with Osteoporosis.

Seventy three (92.4%) of the total 79 patients were having low BMD with osteopenia (36.7%) and osteoporosis (55.7%),out of which 4 (5.1%) of them had skeletal fractures and were regrouped into severe osteoporosis (shown in Figure 2). Osteoporosis frequency was more in those patients in whom aetiology of Liver disease was alcohol intake and this association was statistically

significant (p-value <0.001). All the 3 patients with non-alcoholic steatohepatitis (NASH) had osteoporosis and there was only one autoimmune hepatitis patient in the study group who was non-osteoporotic (Table 3). Majority of the patients (64.6%) were brought to hospital with Child Pugh class C, rest others are class B (21.5%) and class A (13.9%).More than two-third from severe liver disease patients were having osteoporosis (70.6%) compared to less than half in less severe groups and is statistically significant (p-value = 0.001), (Table 4). Vitamin D deficiency was present in 95.5% of the patients with osteoporosis and its association is statistically significant (Table 5).

Table 1: Distribution of Clinical symptoms of patients studied (N=79).

Presenting complaints	Frequency*	Percentage
Pedal edema	61	77.2
Jaundice	51	64.6
Altered sleep pattern	45	57.0
Malena	40	50.6
Constipation	34	43.0
Hematemesis	29	36.7
Altered behavior	22	27.8
Abdominal discomfort	18	22.8
Breathlessness	12	15.2
Decreased urine output	11	13.9
Fever	10	12.7

*Multiple answers were allowed

Pedal edema was the most common complaint (77.2%) in this study population followed by jaundice (64.6%), altered sleep pattern (57%) and malena (50.6%).

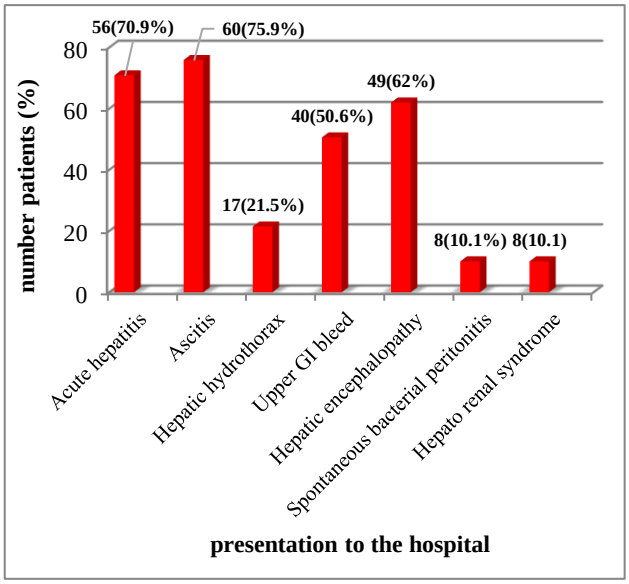

Figure 1: Presenting symptoms of CLD Subjects.

Majority had ascitis (in 75.9% patients) followed by acute hepatitis (in 70.9%), Hepatic encephalopathy (in 62%) and Upper gastrointestinal bleed (in 50.6%).

Table 2: Comparison of hematological parameters in relation to Osteoporosis (N=79).

Hematological parameters (unit)	Bone mineral density, mean±sd			p value
	Mean ±sd	No osteoporosis group	Osteoporosis group	
Hemoglobin (g/dl)	8.78±1.96	8.90±1.89	8.69±2.03	0.644
Leucocyte count (per mm^3)	8504.81±4272.53	7885.43±4016.38	8997.50±4449.40	0.253
Platelet count (lakhs/ mm^3)	1.58±0.76	1.67±0.67	1.51±0.82	0.364
Random blood sugar (mg/dl)	128.28±40.07	124.66±33.66	131.16±44.69	0.477
Serum albumin (mg/dl)	2.57±0.58	2.77±0.60	2.41±0.52	0.005*
Total bilirubin (mg/dl)	5.63±5.89	5.22±5.58	5.96±6.17	0.584
Aspartate aminotransferase (IU/l)	127.04±105.30	105.60±58.58	144.09±129.34	0.107
Alanine aminotransferase (IU/l)	94.46±78.68	95.49±93.04	93.64±66.21	0.918
Alkaline phosphatase (IU/l)	278.87±134.4	239.94±115.71	309.84±141.29	0.021*
Γ glutamyl transpeptidase (IU/l)	194.05±243.7	188.69±271.62	198.32±222.14	0.863
Urea (mg/dl)	32.39±21.13	28.66±15.80	35.36±24.34	0.163
Creatinine (mg/dl)	1.23±0.62	1.16±0.43	1.29±0.74	0.373
Sodium (meq/l)	133.70±4.15	134±3.71	133.45±4.5	0.565
Potassium (meq/l)	4.14±0.60	4.23±0.51	4.06±0.66	0.222
Calcium (mg/dl)	8.35±0.58	8.69±0.57	8.08±0.43	<0.001*
Prothrombin time (sec)	18.88±3.90	19.34±4.17	18.51±3.67	0.352
International normalized ratio	1.59±0.31	1.55±0.26	1.62±0.34	0.304
Vitamin d level (ng/ml)	19.82±7.47	26.26±6.13	14.69±3.28	<0.001*

Asterix* indicates Statistically significant

All the CLD patients were anemic (mean hemoglobin 8.78(g/dl) with low serum albumin level (2.57±0.58) and higher Mean serum bilirubin level (was 5.63mg/dl with standard deviation 5.89).

Most of them had low serum vitamin D level (19.82±7.47).

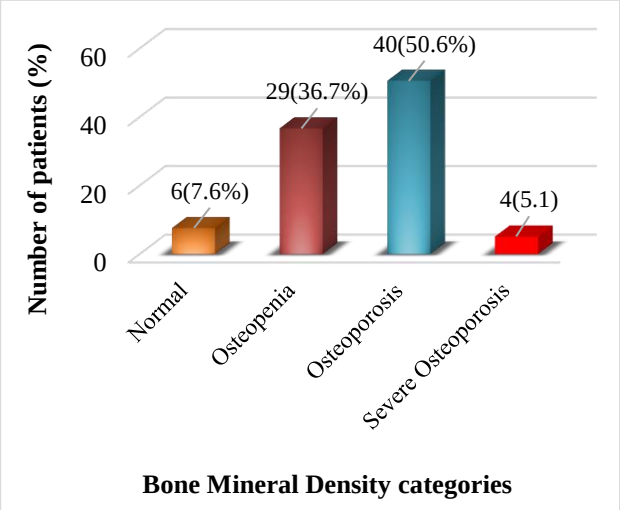

Figure 2: Distribution of patients by categories of Bone Mineral Density (N=79).

73 (92.4%) of the total 79 patients were having low Bone Mineral Density (osteopenia (36.7%) and osteoporosis (55.7%)).

Table 3: Distribution of causes of Liver disease with Osteoporosis (N=79).

Cause of Liver Disease(n)	BMD categories, n (%)		p value
	No osteoporosis	Osteopor-osis	
Alcohol related (45)	21 (46.6)	24 (53.4)	<0.001
Viral hepatitis (16)	12 (75)	4 (25)	
Alcohol and Viral(14)	1 (7.1)	13 (92.8)	
NASH (3)	0 (0)	3 (100)	
Autoimmune (1)	1 (100)	0 (0)	

Osteoporosis frequency was more in alcohol related CLD. (statistically significant, p-value <0.001).

Table 4: Distribution of osteoporosis with severity of Liver disease (N=79).

Severity by Child Pugh Score (n)	BMD categories, n (%)		p value
	No osteoporosis	Osteoporosis	
Class A (11)	7 (63.6)	4 (36.4)	0.001
Class B(17)	13 (76.5)	4 (23.5)	
Class C(51)	15 (29.4)	36 (70.6)	

More than two-third of severe (child class C) liver disease patients had osteoporosis (70.6%) (Statistically significant, p-value = 0.001).

In table 5 distribution of Vitamin D categories in relation to Osteoporosis (N=79): 95.5% of the patients with osteoporosis had deficient Vitamin D.

Table 5: Distribution of vitamin D categories in relation to Osteoporosis (N=79).

Vitamin D levels	Bone Mineral Density, n (%)		p-value
	No osteoporosis n=35	Osteoporosis n=44	
Deficiency	2 (5.7)	42 (95.5)	<0.001
Insufficient	25 (71.4)	2 (4.5)	
Sufficient	8 (22.9)	0 (0)	

DISCUSSION

Hepatic Osteodystrophy (HO) is the generic term representing alterations in bone mineral metabolism in chronic liver disease patients. Multiple pathophysiological basis are being suggested. Chronic inflammation and decompensated liver or cirrhosis in CLD induced by different etiological agents may be the potential mechanism.[14] Firstly, OPG/RANKL ratio is high in CLD patients leading to enhanced osteoclastic activity and bone mineral lost.[15-17] Secondly, Increased tumour necrosis factor -alpha (TNF-α) and Interlukin (IL-6)levels and decreased Insulin-like growing factor -1 (IGF-1) level in patients with cirrhosis may contribute to the development of hepatic osteodystrophy.[14] Chronic liver disease leads to hyperbilirubinemia, hypogonadism, deficient 25 hydroxy -vitD3, and deficient Vit K.[18] In advanced liver disease, 25-hydroxylation in the liver tissue is impaired leading to Vitamin D deficiency .This deficiency causes secondary hyperparathyroidism which in turn increases bone turnover and bone mineral lost. Vitamin k helps in formation of osteocalcin which is the main bone matrix protein. Its deficiency leads to osteopenia.[18] Most common type of CLD in Northeastern India is Alcoholic liver disease.[19] Alcohol inhibit changes in carboxy-terminal propeptide of type I procollagen,a protein representing synthesis of type-1 collagen which is required in bone metabolism. Osteocalcin formation is also decreased by alcohol.[20]

In this study, chronic alcohol intake was the main cause of liver disease (56.9%) followed by viral infection (20.3%), and mixed etiology -Alcoholic and viral (17.7 %) Similar findings were reported from various other study parts of India also. Sharma et al, reported 62.9% as alcohol related from 178 CLD patients from North India.[21] Seventy percentage were alcohol related in entire liver diseases in a study conducted by Perme et al, in North-East India which was followed by viral etiology in 29%.[22] Similar alcohol predominance is reported by Ray in Eastern India.[23]

Seventy three (92.4%) of the total 79 patients were having low bone mineral density in which 36.7% were having osteopenia and remaining 55.7% were having osteoporosis. Similar findings of increased frequency of osteoporosis were found in case control study by Arora et al, with 42% had osteoporosis as compared to 20% in control.[24] Four patients (5.1%) from osteoporotic group had skeletal fractures and were regrouped into severe osteoporosis. Even though frequency of osteoporosis was more in the age group of 51-60 years this observation was not statistically significant. There was no statistically significant gender association with frequency of osteoporosis.

Osteoporosis occurrence was more in alcohol related cirrhosis as compared with viral liver disease with p-value <0.001. Number of patient detected to have osteoporosis were 24 of alcoholic etiology and 13 from combined alcoholism with viral hepatitis etiology.

But further association with etiology of liver disease could not be studied as patients with NASH and autoimmune hepatitis were less in number.

Nearly two third of patients (64.6%) were in severe group as per Child Pugh score. Only 13.9% were from Child class A. More than two-third from severe liver disease (Child Pugh score C) patients were having osteoporosis (70.6%) compared to less than half in less severe groups and is statistically significant (p-value=0.001). These findings were correlating with the study of Monegal et al, where they established association of low BMD with severity and etiology of the CLD.[25] Further they reported that alcoholic and Child Pugh score C patients were having lowest BMD values. Nicoll et al, reported only 19% with osteoporosis in 252 cirrhotic patients.[26] This may be because majority of patients were in good prognostic group (87.4% in Child Pugh class A) and alcohol related cirrhosis was only 33.3% in that study. Patil et al, and Diamond et al, reported association between osteoporosis and severity of Liver disease in their studies.[27,28] Both of these studies failed to find out the association with etiology of liver disease. Arora et al, also reported this association with severity of Liver diseases.[28] On the irony, Loria et al, reported that there is no association between osteoporosis and severity of liver disease.[29] This may be because of the smaller sample size (35) of the study.

Vitamin D deficiency also was common and was there in 95.5% of the patients with osteoporosis and had statistically significant association with BMD. Only 22.9% of the entire sample population had sufficient serum vitamin D level. Karoli et al, also had reported the significant association between osteoporosis and vitamin D level.[30] Low levels of vitamin D in cirrhotic patients as compared to control group were reported by Monegal et al, also in his study.[25] Serum calcium level was generally low (8.35±0.58) in the study population. Statistically significant association was there between calcium level and osteoporosis.

Limitation of the study is first, small sample size of the study may not show exact scenario of the community. Second, cross sectional design of the study limited extension of interpretation to the causality of associations. Third, all the patient included were from same centre and hence selection bias could not be excluded. Despite these limitations, this study had the advantage of being the first study evaluating bone health in cirrhotic patients in North East India where there is high prevalence of liver cirrhosis.

CONCLUSION

Chronic liver disease is associated with decreased BMD, more so with alcohol eitology. Severity of liver disease was statistically associated with BMD reduction. Other contributing factors include smoking, hypertension, hypoalbuminemia, vitamin D and calcium deficiencies. Hepatic Osteodystrophy is one of the important complications of CLD, hence screening for BMD is highly recommended in all cirrhotic patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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