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Original Article

Internal Medicine Section

Study of Hepatic Osteodystrophy in Patients with Chronic Liver Disease

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ABSTRACT

Introduction: Chronic Liver Disease (CLD) is a major cause of morbidity and mortality worldwide. It involves haemodynamic and metabolic complications. Hepatic Osteodystrophy 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. It has been an under recognized and inadequately studied complication among Indian population. An early diagnosis is essential to correct reversible risk factors which predispose to bone mass loss.

Aim: To assess the prevalence of metabolic bone disease and identify the risk factors associated with hepatic osteodystrophy in patients with cirrhosis.

Materials and Methods: This was an observational, cross-sectional, hospital based study conducted at a medical college hospital. All patients more than 20-year-old, diagnosed with chronic liver disease/Cirrhosis were enrolled. They were subjected to haematological, biochemical investigations, evaluation of Vitamin D and other hormonal parameters. Bone Mineral Density (BMD) was estimated by Dual Energy X-ray Absorptiometry (DEXA).

Results: A total of 72 patients with mean age 50.04±11.24 years were included in the study. Amongst causes of chronic liver disease were alcoholic liver disease 22 (30.6%), CLD due to hepatitis B 24 (33.3%) and chronic hepatitis C 26 (36.1%). Twenty one (29.2%) patients had normal BMD while 51 (70.8%) had a low BMD. Out of these 51 patients, 36 (70.6%) were diagnosed of osteopenia and 15 (29.4%) others were found to have osteoporosis. Vitamin D levels and severity of liver disease had correlation with low BMD.

Conclusion: Low BMD is highly prevalent in patients with chronic liver disease of variable aetiologies. We advocate more randomised 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.

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

INTRODUCTION

Hepatic osteodystrophy generally refers to presence of bone disease in patients who have CLD. The umbrella of hepatic osteodystrophy comprises of osteopenia, osteo-porosis and osteomalacia [1]. It is enlisted in the causes of osteoporosis but less recognized as a complication of chronic liver disease in this group of patients [2,3]. It may lead to fractures and immobilization that adversely affects both the quality of life and the long-term prognosis of patients with CLD [4].

CLD is a major cause of morbidity and mortality worldwide. It involves haemodynamic and metabolic complications, such as liver failure, portal hypertension, encephalopathy, ascites, hepatorenal syndrome and gastrointestinal bleeding from oesophageal varices [5]. In addition to this, CLD also affects skeletal health and acts as an important risk factor for the development of osteoporosis and bone fractures.

Two distinct bone metabolic processes, Osteoporosis and Osteomalacia are combined together in various proportions in CLD. Osteopenia and osteoporosis are common and characterized by loss of BMD and a disorganization of bone microarchitecture, which leads to fragile bones. Osteomalacia, which occurs due to Vitamin D deficiency, is relatively infrequent in CLD [6]. The association of chronic cholestatic diseases with poor bone health as a result of decreased BMD and increase in fragility fracture risk has been known since long time [7] but increased prevalence of osteopenia and osteoporosis has been demonstrated in patients with chronic liver disease of different aetiologies in the recent times [8-12].

Hepatic osteodystrophy has been an under recognized and less extensively studied complication in Indian population. Prevalence of hepatic osteodystrophy varies from 13% to 70% in Western countries while it has been reported higher 68% and 95% from India [3,4,13,14]. An early diagnosis is essential to correct reversible risk factors which predispose to bone mass loss. Therefore, we planned a study with an aim to estimate the prevalence of metabolic bone disease and identify risk factors of hepatic osteodystrophy in patients with cirrhosis.

MATERIALS AND METHODS

This was an observational, cross-sectional hospital based study which was conducted from January 2014 to June 2015. Patients from medical wards and outpatient departments of Department of Medicine, Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India, were included in the study. The study was approved by Institutional Ethics Committee and written informed consent was obtained from all study participants.

All patients aged more than 20 years, diagnosed as chronic liver disease/cirrhosis were enrolled on the basis of ultrasonographic findings suggestive of cirrhosis (the presence of at least two of the findings of nodular irregular surface, distorted vascular pattern, or ascites). Signs of portal hypertension (endoscopically proven esophageal varices or dilated portal venous system with ultrasonography, ascitic fluid with high Serum Ascites Albumin Gradient (SAAG ratio) was taken as additional corroborative evidence. The aetiology of post-viral cirrhosis was proven if any of the serological markers were positive {hepatitis B surface

antigen by ELISA, anti-Hepatitis C Virus antibodies (HCV) by third generation ELISA, or HCV RNA}. Diagnosis of alcoholic cirrhosis was made with a positive answer to more than one question in the CAGE questionnaire and a history of significant alcohol consumption of >30g/day in men and >20g/day in women [15]. Markers of inherited metabolic diseases (serum ceruloplasmin, ferritin alpha 1antitrypsin, transferrin saturation and autoimmune hepatitis were assessed. Coagulation profile including prothrombin Time (PT) was measured in seconds. The reference range was 10 to 13 seconds. Renal function tests, serum protein, albumin calcium and phosphorus were also assessed. Serum testosterone, estradiol, Follicle stimulating hormone and leutinizing hormone were also estimated.

The patients who had previous history of chronic disorders associated with changes in mineral metabolism (thyroid disorders, parathyroid disorders, Cushing's syndrome, diabetes, prolonged immobilization in the past, early surgical menopause, premature ovarian/testicular failure, or renal failure) were excluded.

We also excluded those with intake of calcium, Vitamin D in last <1 year or any medication which might have influenced bone metabolism (corticosteroids, hormone replacement therapy, calcitonin, bisphosphonates, cytotoxics, antimetabolites, anticoagulants, anticonvulsants, thyroxine, interferon or lamivudine).

Detailed general and systemic examination was done.

Anthropometric assessment was done as mentioned below:

Waist Circumference: Measurement at the approximate midpoint between the lower margin of last palpable rib and the top of the iliac crest was made in centimeters.

Hip Circumference: Measurement at the level of greatest protrusion of the gluteal (buttock) muscles.

Waist-Hip Ratio: Measured waist circumference was divided by the measured hip circumference.

Body Mass Index: Body mass index was calculated by dividing weight in kg by square of height in meters.

Vitamin D status of the study participants was defined as per the Endocrine Society Clinical Practice Guidelines by Holick et al., on evaluation, treatment and prevention of Vitamin D deficiency [16]. Vitamin D deficiency, severe Vitamin D deficiency, very severe Vitamin D deficiency, Vitamin D insufficiency and normal Vitamin D levels were defined as serum 25(OH) D concentrations ≤ 20ng/ml, < 10ng/ml, <5ng/ml, 21–29ng\ml and ≥ 30ng/ml respectively.

The serum 25 (OH) D concentrations were determined by an immunoassay technique using the Elecsys Vitamin D3 assay. It was an electrochemilumniscence immunoassay supplied by Roche diagnostics. It measured the serum 25 (OH) D concentrations in the range of 4–100 ng/ml.

Bone Mineral Density (BMD) was measured in g/cm^2 in all patients at the lumbar spine and total hip by dual energy X-ray absorptiometry (DEXA) scan using Lunar Prodigy, version 12.20 General Electric Healthcare system, USA. Results were expressed in T-score {difference in Standard Deviation (SD) between the patient's measured BMD value and the maximum mean BMD of young adult of same gender} and Z-score (difference in SD between the patient's measured BMD and individuals of his age from that population).

BMD value and the normal reference for age and gender). According to the World Health Organization (WHO) criteria [17] Normal BMD is represented by a T score of more than -1. Osteopenia (low bone mass) is represented by a T score between-1and -2.5. Osteoporosis is presented by a T score less than -2.5. Established osteoporosis is represented by a T score of less than -2.5 and a previous history of a fragility fracture.

STATISTICAL ANALYSIS

The SPSS 13.0 (SPSS Inc., Chicago, Ill) statistical software package was used for statistical analyses. All continuous data were expressed as means±SD and categorical data in percentage and numbers. The statistical significance between means was calculated by Student's t-test, analysis of variance (ANOVA), or Mann-Whitney U-test when appropriate. Differences between proportions were assessed by the χ^2 test. A $p < 0.05$ considered significant. Pearsons correlation coefficient was calculated to assess correlations between low BMD and other variables.

RESULTS

Our study enrolled a total of 126 patients. Out of them, in 72 patients, bone mineral density, Vitamin D and other hormonal parameters could be measured so analysis included 72 patients. [Table/Fig-1] Shows the demographic profile of study patients. [Table/Fig-2] Shows the biochemical parameters of the study participants. [Table/Fig-3] Shows the prevalence of hepatic osteodystrophy in patients with chronic liver disease. [Table/Fig-4] shows distribution of causes of liver diseases between normal BMD and low BMD patients. In low BMD group, 16(31.37%) were alcoholic liver disease patients, 15(29.41%) chronic hepatitis B patients, and 20(39.21%) had hepatitis C. The Child-Pugh score was used to assess the prognosis of chronic liver disease. In our study 17(23.61%) patients were placed under Class A, 29(40.27%) diagnosed for Class B and remaining 26(36.11%) were considered for Class C. It had correlation with low BMD (r=0.32,p=0.01).

Hormonal parameters were studied in normal BMD and low BMD patients [Table/Fig-5]. The variation in the hormone levels between normal and low BMD patients were not statistically significant.

Vitamin D deficiency was significantly greater in patients with low BMD than normal BMD. It was present in 25/51 patients of chronic liver disease who had low BMD as compared to 4/21 in normal BMD which was significantly different, (p=0.001) [Table/Fig-6].

Demographic profile	Mean±Std. Deviation
Age (Year)	50.04±11.24
BMI (kg/m^2)	21.15±1.72
Gender (Male:Female)	40:32
Alcoholic liver disease	22(30.6%)
Chronic hepatitis B	24(33.3%)
Chronic hepatitisC	26(36.1%)

[Table/Fig-1]: Demographic profile of study patients.
Data is expressed in mean±SD ornumber (%)

Parameters	Mean±Std. Deviation
Alkaline phosphatase (U/l)	119.82±43.9
Serum calcium (mg/dl)	8.578±0.47
Serum phosphorus(mg/dl)	4.089±0.37
SGOT(U/l)	68.43±30.4
SGPT (U/l)	65.88±31.7
Serum albumin(mg/dl)	3.03±0.25
Serum Creatinine(mg/dl)	1.19±0.32
25 (OH) D (ng/dl)	18.51±5.52
Prothrombin time (sec)	14.08±1.72
Tscore(gm/cm^2)	-2.59±1.31

[Table/Fig-2]: Biochemical data of the study participants.
Data is expressed in mean±SD

Status	Number(%)=72
Normal	21(29.2%)
Low BMD	51(70.8%)
Osteopenia	36 (71%)(36/51)
Osteoporosis	15 (29%)(15/51)

[Table/Fig-3]: Prevalence of hepatic osteodystrophy in patients with chronic liver disease.

DISCUSSION

The aim of our study was to estimate the prevalence of low bone mineral density and Vitamin D deficiency and to identify the factors associated with bone disease in a cohort of CLD of mixed aetiology.

Metabolic disturbances of bone are frequent in patients with CLD. BMD loss and the consequent increase in fracture risk initially had been described mainly in chronic cholestatic diseases and in advanced stages of liver cirrhosis. Recent literature has shown BMD alterations in patient with liver diseases of other aetiologies as well [18]. The aetiology of bone disease is poorly understood and is thought to vary 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.

Causes	Normal BMD N=21	Low BMD N=51
Alcoholic liver	6(28.57%)	16(31.37%)
Chronic hepatitis B	9(42.85%)	15(29.41%)
Chronic hepatitis C	6(28.57%)	20(39.21%)

[Table/Fig-4]: Shows causes of liver disease among Normal and Low BMD.
Data is expressed in number (%)

Clinical and Biochemical Parameters	Normal BMD N=21	Low BMD N=51	p-value
Age (years)	47.02±10.5	54.5±12.6	0.019
BMI (kg/m^2)	18.2±1.6	19.7±1.7	0.009
ALP (U/l)	102.57±35.43	126.92±45.39	0.31
Serum calcium (mg/dl)	8.9±0 .55	8.0±0.44	<0.001
Serum phosphorus (mg/dl)	4.2±0.44	4.1±0.33	0.124
SGOT (U/l)	61.14±21.8	71.43±33.08	0.194
SGPT (U/l)	57.3±18.1	69.39±35.4	0.144
Serum albumin (mg/dl)	3.05±0.22	2.6±0.26	0.704
Serum Creatinine (mg/dl)	1.16±0.23	1.20±0.34	0.632

[Table/Fig-5]: Clinical and biochemical characteristics of patients with normal BMD and those with low BMD.
Data is expressed in mean±SD

Hormonal Parameters	Normal BMD N=21	Low BMD N=51	p-value
25 (OH) D (ng/dl)	24.14±5.46	12.0±7.25	0.001
LH(IU/L)	12.64±8.21	,11.60±8.19	0.6264
FSH(mIU/ml)	33.42±24.43	30.96±24.32	0.6980
Estradiol(pg/ml)	78.8±41.78	71.26±41.62	0.4875
Testosterone(ng/dl)	568.50±96.52	537.4±94.94	0.2160

[Table/Fig-6]: Hormonal parameters of patients with normal BMD and low BMD.
Data is expressed in mean±SD

The available Indian data is scarce on this subject. The largest prospective study from India on the prevalence of hepatic osteodystrophy in patients with non-cholestatic liver cirrhosis was done by Bansal et al., who studied 215 patients and reported a prevalence of 66% [19]. Bansal et al., also observed in their study that higher liver stiffness as determined by transient elastography was significantly associated with hepatic osteodystrophy, though severity scores of liver disease and aetiology of liver cirrhosis did not affect hepatic osteodystrophy. They also studied the effect of Ibandronic acid that showed significant improvement in BMD in patients with liver disease along with osteoporosis.

Another study by Choudhary et al., on prevalence of hepatic osteodystrophy in patients with noncholestatic liver disease reported that low BMD was present in 97% of patients with alcoholic cirrhosis and 93.7% with viral cirrhosis [20].

Chronic liver disease leading to secondary osteoporosis predisposes to occurrence of bone fractures and increased mortality. It has multiple reasons that accelerate loss of BMD such as lack of physical exercise, reduced lean body mass and hypoVitaminosis D. hypogonadism, hypercortisolism and dysregulation of the hypothalamic-pituitary-gonadal axis associated with CLD also contribute to osteodystrophy [21].

Disturbance in endocrine calcium-PTH-Vitamin D axis seems to play a role in pathogenesis of osteometabolic disturbance. The liver is an important organ in hydroxylation of Vitamin D into its active metabolites. Vitamin D and PTH regulate bone mineral serum levels and bone remodeling. Consequently, chronic liver disease interferes with Vitamin D activation and bone metabolism. Its prevalence varies considerably and ranges from 20% to 50%. Malnutrition is highly prevalent in patients with CLD and this leads to increased morbidity and mortality rates.

Role of IGF-1deficiency in CLD has been implicated causing negative impact on bone mineralization [22].

Ethanol has a direct dose-dependent toxic effect on osteoblasts, which inhibits bone formation and turnover. Alcoholism can cause alterations in nutritional status and Vitamin D deficiency which may contribute to bone disease [23].

In present study, prevalence of Hepatic Osteodystrophy (HO) in patients with CLD was studied. Out of 72 patients, 29.2% had normal BMD while low BMD was found in 70.8% of patients. Among these patients 50% were classified as Osteopenia and Osteoporosis was observed to be 20.83%. Diamond et al., found in their two separate studies that the prevalence of osteoporosis was 30%-48% in patients with chronic liver disease of different aetiologies [24,25].

The severity of cirrhosis assessed by the Child-Pugh score emerged in the majority of series as being a factor which is strongly associated with a bone mass deficit especially osteoporosis which was similar to our study [26,27].

In this present study, the serum calcium, and 25(OH) Vitamin D level showed significant difference between normal BMD and low BMD and seems to be the important contributory factor. Vitamin D deficiency is pandemic, yet it is the most under-diagnosed and under-treated nutritional deficiency in the world. Several studies from different parts of our country have pointed towards widespread Vitamin D deficiency in Indians of all age groups residing in rural or urban areas [28,29]. As the prevalence of Vitamin D deficiency in Indian population is quite high so it was difficult for us to differentiate whether Vitamin D deficiency was due to CLD or it was pre-existing.

BMD loss is a common complication of CLD as a whole, The aetiopathogenesis of osteoporosis in CLD is multifactorial, and impaired bone formation appears to be the main mechanism involved in the onset of osteopenia as a result of direct alcohol toxicity on bone, associated macro- and micronutrient disturbances, endocrine-metabolic disorders secondary to alcoholism and CLD, and the release of various cytokines with harmful effects on bone mass. Bone densitometry is critical for the diagnosis of osteoporosis, and analytical studies are also recommended to rule out concomitant disturbances in gonadal function and Vitamin D levels in all patients with Alcoholic Liver Disease (ALD). It would be beneficial to have access to randomised, prospective, multicentre studies conducted on homogeneous groups with chronic liver disease in its various stages. The performance of studies on treatment with bisphosphonates and new anti-osteoporotic agents in patients would be useful to improve the clinical management of osteoporosis in this population.

LIMITATION

Our study had many limitations, most importantly small sample size. No healthy patients were enrolled. Being a cross sectional study causal relationship could not be proved.

CONCLUSION

Low BMD is highly prevalent in patients with CLD of variable aetiologies. Causes may be multifactorial. Early screening of osteoporosis in patients with liver cirrhosis will reduce the risk of morbidity and mortality. Attention needs to be drawn towards documentation and management of this metabolic disorder.

Note: CAGE Questionnaire: (It is standard and recommended clinical approach to diagnose alcohol dependence and abuse).

C-Have you ever felt you ought to **cut** down on your drinking?

A-Have people **annoyed** you by criticizing your drinking?

G-Have you ever felt **guilty** or bad about your drinking?

E-Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover **(eye -opener)**.

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