ORIGINAL ARTICLE

Assessment of Bone Mineral Density and Vitamin D3 in Patients with Chronic Liver Disease

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ABSTRACT

Introduction: Hepatic osteodystrophy is rather a common yet underdiagnosed entity. It leads to significant morbidity. Exact prevalence of hepatic osteodystrophy is not known but varies depending on etiology of chronic liver disease.

Aims: To measure bone mineral density by Dual Energy X-ray Absorptiometry (DEXA) scan, to measure level of serum 25(OH) vitamin D3 in patients with chronic liver disease and also to measure frequency of osteodystrophy in chronic liver disease.

Methodology: A cross sectional study on total fifty diagnosed patients with chronic liver disease (34 males within age 39.8±10.3 and 16 females within age 33.5±5.3) was done to determine frequency of hepatic osteodystrophy. Patients had undergone clinical and laboratory investigation for diagnosis of chronic liver disease and to exclude other comorbid conditions that may cause osteodystrophy. Severity of chronic liver disease was measured in terms of Child-Turcotte-Pugh (CTP) scoring. Each patient had undergone DEXA scanning to determine bone mineral density and also serum levels of 25(OH) vitamin D3 ,calcium and phosphate were measured. Patients with DEXA scan T score lower than -1 were diagnosed to have osteodystrophy.

Results: Out of 50 patients, 22 patients (44%) had alcoholic liver disease, 6 patients (12%) had chronic hepatitis B, 2 patients (4%) had autoimmune hepatitis and 20 patients (40%) had cryptogenic chronic liver disease. In our study 18 patients had osteopenia and 15 patients had osteoporosis. So out of 50 patients 33 patients had osteodystrophy and frequency of osteodystrophy in our study was 66%. Importantly severity of osteodystrophy had positive correlation with severity of chronic liver disease.

Conclusions: Hepatic osteodystrophy is a common complication of chronic liver disease and mostly asymptomatic. Severity of osteodystrophy increases with severity of chronic liver disease.

Keywords: Hepatic Osteodystrophy, Chronic Liver Disease, DEXA scan, Bone Mineral Density

INTRODUCTION

Hepatic osteodystrophy is an important and common complication of chronic liver disease. Yet it is an underdiagnosed and rather a neglected condition. It is mostly an asymptomatic condition or presents with vague complaints of body ache, low back pain. It increases risk of fractures and thus may cause significant morbidity. Exact prevalence of hepatic osteodystrophy is unknown and varies depending on studies and etiologies of chronic liver disease. It ranges from 20% in chronic viral hepatitis to as high as 60% in chronic cholestasis.[1] Mechanisms of osteodystrophy in chronic liver disease are many. Proposed mechanisms are altered vitamin D absorption and metabolism,[2,3,4] low serum levels of insulin like growth factor 1(IGF1) in patients of chronic liver disease,[6,7] hypogonadism associated with chronic liver disease,[8] altered vitamin K level,[5] direct inhibitory influences of raised billirubin on osteoblasts,[14,15] medications e.g. glucocorticoid and other immunosuppressive agents (used in autoimmune hepatitis),[9,10] malnutrition and sedentary lifestyle associated with chronic liver disease[11].

Different studies also consider that osteodystrophy increases with severity of chronic liver disease measured by Child-Turcotte-Pugh scoring.[12,13]

Objective of our study was to measure frequency of osteodystrophy among patients of chronic liver disease. We measured bone mineral density by DEXA scanning and also measured serum levels of 25(OH) vitamin D, calcium and phosphate in patients of chronic liver disease.

METHODOLOGY

Total 50 patients of established chronic liver disease, either admitted indoor or followed up at outpatient department of General Medicine, Medical College & Hospital, Kolkata were included in our study. Diagnosis of chronic liver disease was based on history, clinical examination, biochemical investigations, radiological investigation (Ultrasonography abdomen, fibroscan), upper GI endoscopy and liver biopsy (occasionally). Diagnosis of alcoholic liver disease was based on history (more than one positive response to the questions of CAGE questionnaire and history of significant alcohol intake). Diagnosis of post-viral cirrhosis was based on positive serological markers (Hepatitis B surface antigen by ELISA, anti-Hepatitis C Virus antibody by third generation ELISA). Markers of autoimmune hepatitis were also assessed for diagnosing autoimmune hepatitis. Markers of inherited metabolic liver diseases (serum ceruloplasmin, serum ferritin and serum transferrin saturation) were also assessed. Diagnosis of non-alcoholic fatty liver disease was based on ultrasonographic demonstration of hepatic steatosis without history of significant alcohol intake. Patients with cirrhosis without any demonstrable cause were labeled to have cryptogenic cirrhosis. Severity of chronic liver disease was determined by Child-Turcotte-Pugh scoring. Relevant investigations were also done to exclude other comorbid illness that may cause osteodystrophy notably chronic kidney disease, hyperparathyroidism, hyperthyroidism, Cushing syndrome, infection with human immunodeficiency virus (HIV). Postmenopausal women, women with surgical menopause and pregnant women were also excluded from our study. Each patient then undergone DEXA scanning to measure bone mineral density and serum levels of 25(OH) vitamin D_3 , calcium and phosphate were measured. DEXA was done by DEXA machine model- DPL LUNAR version 9.30.044 and vitamin D was measured by ELISA method using Euroimmun kits. Informed consent was taken from all the patients and study protocol was approved by ethical committee for human research, Medical College and Hospital, Kolkata.

Analysis: Categorical variables are expressed as Number of patients and percentage of patients. Continuous variables are expressed as Mean ± Standard Deviation and compared across the 3 groups using Kruskal Wallis Test. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant. Normal values of our study parameters: DEXA scan-normal bone mineral density is defined as T score between +1 to -1. Osteopenia is defined as T score between -1 to -2.5. Osteoporosis is defined as T score below -2.5. [21]

Normal values of serum 25(OH) vitamin D_3: 30-100 ng/ml [20]
Normal value of serum calcium: 8.7-10.2 mg/dl [20]
Normal value of serum phosphate: 2.5-4.3 mg/dl [20]

RESULTS

Out of 50 patients in our study 34 (68%) were males and 16 (32%) were females. Most of them were in 21-40 years age group (18% in 21-30 and 52% in 31-40 years age group, mean age 38.2±9.9). 44% cases had alcoholic liver disease, 40% had cryptogenic chronic liver disease, 12% had chronic hepatitis B and rest of the patients had autoimmune hepatitis (TABLE-1). Out of total study population, 38% belonged to Child class A, 32% belonged to Child class B and 30% were in Child class C. Bone mineral density was found to be low in patients of chronic liver disease (DEXA scan T score -1.81±1.17). Also serum levels of 25(OH) vitamin D_3 and calcium were low among most of the patients (22.75±9.59 ng/ml and 7.66±0.44 mg/dl respectively).

18 out of 50 patients (36%) had osteopenia and 15 cases (30%) were found to have osteoporosis. So in our study 33 out of 50 patients had osteodystrophy. So frequency of osteodystrophy in our study was 66%. Importantly only 18% patients had symptoms of bone pain and none had history of fracture, underscoring the importance of the fact that hepatic osteodystrophy is mostly an asymptomatic condition (Table-2). More importantly we found significant negative correlation between DEXA scan T score and Child-Turcotte-Pugh score proving the fact that severity of osteodystrophy increases with severity of chronic liver disease (Table-3 and 4, Figure-1). It was also found that there is significant negative correlation between serum levels of 25(OH) vitamin D_3 ,calcium, phosphate and CTP scoring proving that deficiency of these three parameters increases with severity of chronic liver disease (Table-3,4, Figure-1).

Table 1: Aetiology of CLD in our study population

Diagnosis	Frequency (%)
Alcoholic liver disease	22 (44)
Autoimmune hepatitis	2 (4)
Ch. Hep B CLD	6 (12)
Cryptogenic CLD	20 (40)
Total	50 (100)

Table 2: Symptoms of hepatic osteodystrophy (history of bone pain and fracture) in study population

History	Yes (%)	No (%)
Bone Pain (n=50)	9 (18)	41 (82)
Fracture(n=50)	0 (0)	50 (100)

Table 3: Relationship of DEXA scan 'T' score, serum 25(OH) vitamin D_3 level, serum calcium level and serum phosphate level with CTP class:

Child-Turcotte-Pugh Class		Dexa Scan T Score	Serum 25(Oh) -Vit D Level (Ng/Ml)	Serum Phosphate Level (Mg/Dl)	Serum Calcium Level (Corrected) (Mg/Dl)
A (n=19)		-1.34 ± 0.98	27.7 ± 10.55	3.7 ± 0.45	7.95 ± 0.34
B (n=16)		-1.79 ± 0.92	19.61 ± 7.35	3.53 ± 0.33	7.56 ± 0.33
C (n=15)		-2.45 ± 1.39	19.83 ± 8.19	3.42 ± 0.41	7.39 ± 0.44
p Value	A Vs B	0.149	0.014	0.158	0.001
	A Vs C	0.024(significant)	0.036	0.044	<0.001
	B vs C	0.105	0.906	0.706	0.377
	Overall	0.040(significant)	0.026	0.118	<0.001

Table 4: Correlation coefficient of DEXA scan T score, serum 25(OH) vitamin D_3 level, serum calcium level and serum phosphate level with CTP scores

Correlations (CTP SCORE)		Correlation Coefficient	P Value
Spearman's rho	Dexa Scan T Score	-0.653	<0.001
	Serum 25(Oh)-Vit D Level	-0.402	0.004
	Serum Calcium (Corrected)	-0.573	<0.001
	Serum Phosphate Level	-0.344	0.014

DISCUSSION

Metabolic bone disease is a significant problem in primary cholestatic conditions e.g. primary billiary cirrhosis and primary s clerosing cholangitis. But other aetiologies of CLD also have this problem probably because of hepatocellular dysfunction. Osteodystrophy may present as osteopenia or osteoporosis, osteomalacia being uncommon. Patients are commonly asymptomatic or complain of body ache, low back pain. Fracture of vertebrae or femoral neck can be a devastating complication if the condition remains untreated. Factors leading to osteodystrophy are multiple and incompletely understood. Altered vitamin D metabolism, reduced serum level of IGF-1, hypogonadism associated with chronic liver disease, direct inhibitory influence of ethanol and hyperbilirubinaemia on osteoblasts, malnutrition and lack of physical activities are some of the proposed mechanisms of hepatic osteodystrophy.

Liver is an important organ for hydroxylation and conversion of vitamin D into its active metabolite. So in chronic liver disease there is reduced synthesis of active metabolite of vitamin D resulting in diminished intestinal absorption of calcium and phosphate which contributes to osteodystrophy.

Ethanol has direct toxic effect on osteoblasts and so does indirect hyperbillirubinaemia. Reduced serum level of IGF-1 has also been proposed to interfere with bone metabolism. Malnutrition is particularly associated with alcoholic liver disease.

Preventive measures should be taken early in the course of chronic liver disease to reduce the morbidities associated with osteodystrophy. Bone mineral density should be measured in patients with chronic liver disease. Calcium and vitamin D supplementation along with bisphosphonate therapy should be started in patients diagnosed with hepatic osteodystrophy.

In our study frequency of osteodystrophy was found to be 66%, with 36% patients having osteopenia and 30% having osteoporosis. This finding is consistent with previous studies which have shown prevalence of hepatic osteodystrophy ranging from 13%-70%[1] depending on studies and etiology of chronic liver disease.

A study by Yogesh Karoli et al. showed that out of 72 patients of chronic liver disease 29.2% had normal bone mineral density while low bone mineral density was found in 70.8% of patients.[17] Among these patients 50% were classified as osteopenia and 20.83% patients were found to have osteoporosis. 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.[18,19] Another study by Bansal et al. who studied total 215 patients of non cholestatic liver disease found 66% prevalence of osteodystrophy.[16] Another study by Lopez Larramona G et al. says prevalence of osteodystrophy in chronic liver disease is uncertain. Different studies vary in ranges depending on etilogies. Prevalence varies from 13-60% in chronic cholestasis to 20% in chronic viral hepatitis and 55% in viral cirrhosis.[1]

Hepatic osteodystrophy is mostly an asymptomatic condition or presents with non specific complaints of bone pain, low back pain. In our study only 18% patients had symptoms of bone pain and none had history of fracture. So it is important to screen patients of chronic liver disease for presence of osteodystrophy and start treatment to prevent its complications e.g. fractures.

Serum levels of 25(OH) vitamin D_3 (22.75±9.59 ng/ml) and calcium (corrected for albumin) level (7.66±0.44 mg/dl) were lower among study population compared to reference normal levels. Importantly our study shows that severity of osteodystrophy has significant correlation with severity of chronic liver disease measured by Child-Turcotte-

Pugh score. With increasing Child-Turcotte-Pugh scores there is decreasing trend of DEXA scan T score (correlation coefficient -0.653). Similarly with increasing Child scores there is decreasing trend of serum levels of 25(OH) vitamin D_3, calcium and phosphate (correlation coefficient -0.402, -0.573, -0.344 respectively). These findings are explainable because with progression of cirrhosis there is progressive impairment in vitamin D metabolism (both intestinal absorption and 25 hydroxylation get impaired), progressive reduction in IGF-1 synthesis and aggravation of hypogonadism. Nutrition gets further compromised with progression of cirrhosis. Patients become more bed bound and physical activity diminishes due to comorbidities associated with progression of cirrhosis. All these factors get summed up and lead to progressive osteodystrophy.

LIMITATIONS

Our study has many limitation, small sample size and lack of healthy control population being the most important. Ours was a cross sectional study and we could not assess long term complications of hepatic osteodystrophy.

CONCLUSIONS

Hepatic osteodystrophy is a very common complication of chronic liver disease. Severity of osteodystrophy increases with progression of cirrhosis. Vitamin D, calcium and phosphate levels are also low in patients with cirrhosis and their deficiency increases with progression of cirrhosis. So it is important to be aware of this complication for early diagnosis and prevention to prevent morbidities like fracture.

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