Bone mineral density and disorders of mineral metabolism in chronic liver disease

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AIM: To estimate the prevalence and identify the risk factors for metabolic bone disease in patients with cirrhosis.

METHODS: The study was performed on 72 Indian patients with cirrhosis (63 male, 9 female; aged < 50 years). Etiology of cirrhosis was alcoholism (n = 37), hepatitis B (n = 25) and hepatitis C (n = 10). Twenty-three patients belonged to Child class A, while 39 were in class B and 10 in class C. Secondary causes for metabolic bone disease and osteoporosis were ruled out. Sunlight exposure, physical activity and dietary constituents were calculated. Complete metabolic profiles were derived, and bone mineral density (BMD) was measured using dual energy X ray absorptiometry. Low BMD was defined as a Z score below -2.

RESULTS: Low BMD was found in 68% of patients. Lumbar spine was the most frequently and severely affected site. Risk factors for low BMD included low physical activity, decreased sunlight exposure, and low lean body mass. Calcium intake was adequate, with unfavorable calcium: protein ratio and calcium: phosphorus ratio. Vitamin D deficiency was highly prevalent (92%). There was a high incidence of hypogonadism (41%). Serum estradiol level was elevated significantly in patients with normal BMD. Insulin-like growth factor (IGF) 1 and IGF binding protein 3 levels were below the age-related normal range in both groups. IGF-1 was significantly lower in patients with low BMD. Serum osteocalcin level was low (68%) and urinary deoxypyridinoline to creatinine ratio was high (79%), which demonstrated low bone formation with high resorption.

CONCLUSION: Patients with cirrhosis have low BMD. Contributory factors are reduced physical activity, low lean body mass, vitamin D deficiency and hypogonadism and low IGF-1 level.

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Key words: Bone mineral density; Liver disease; Chronic disease; Cirrhosis; Bone mineral metabolism; Hepatic osteodystrophy

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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]. Often known as hepatic osteodystrophy (HO),
it is well-recognized among individuals with chronic liver disease (CLD). Its etiology 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. 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. With liver transplantation steadily taking the center stage in treatment of end-stage cirrhosis of varying etiology and offering long-term survival, bone disease has snowballed into one of the major determinants of survival and quality of life in this cohort.

Keeping in view the numerous therapeutic options for bone disease already available and those under development, it is prudent to characterize this condition in order to give these patients a better chance of survival. The medical fraternity around the world has recognized this and has started characterizing the disorder. In various international studies, the overall incidence has varied from 11% to 48%, with a fracture rate of 3%-44% [1]. This has not been studied extensively in the Indian population.

MATERIALS AND METHODS

Patients

The study was performed on 72 Indian patients with cirrhosis. The group consisted of 63 men and nine women with a median age of 45 years (43.1 ± 7.4, range 22-50 years). Twenty-five patients had hepatitis B (22 men and 3 women), 10 had hepatitis C (5 men and 5 women), and 37 had alcoholic cirrhosis (36 men and 1 woman). A diagnosis of cirrhosis was confirmed histologically or clinically if biopsy was not available. A clinical diagnosis was established in patients who demonstrated a Child-Pugh index > 6 or ultrasound 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) were taken as additional corroborative evidence. The etiology of post-viral cirrhosis was proven if any of the serological markers were positive [hepatitis B surface antigen by ELISA, anti-hepatitis C virus (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 previous history of alcohol intake of > 80 g/d in men and > 40 g/d in women for > 10 years. An aspartate aminotransferase to alanine aminotransferase (AST/ALT) ratio of > 1.5 was taken as corroborative evidence. We selected only patients who had abstained from alcohol for > 3 mo prior to the study.

All patients with acute exacerbation or flair of disease (suggested by a bilirubin concentration > 5 mg/dL, AST > 2.5 times the upper limit of normal, leukocytosis > 10000/mm³, or diagnostic lesions of hepatitis on biopsy) and those with recent gastrointestinal bleeding were excluded. Patients with serum creatinine levels > 1.4 mg/dL were excluded, as were those with any form of acute illness. None of the patients had a previous history of chronic disorders associated with changes in mineral metabolism (thyroid disorders, parathyroid disorders, Cushing’s syndrome, diabetes, immobilization in the past, or renal failure). None had a family history of osteoporosis, nor did they receive calcium, vitamin D or any medication which may have influenced bone metabolism (corticosteroids, hormone replacement therapy, calcitonin, bisphosphonates, cytotoxics, antimetabolites, anticoagulants, anticonvulsants, thyroxine, interferon or lamivudine). Nineteen patients were receiving spironolactone and 14 were receiving spironolactone and furosemide. Patients with major sclerosis of the aorta, osteophytes, or sclerosis on X-ray, which precluded accurate measurements of lumbar bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA), and those who had the criteria for more than one etiology of chronic liver disease were also excluded. All patients signed informed consent and the protocol was approved by the institutional ethics committee.

Methods

Demographic and disease-related data including anthropometry at the time of enrollment were captured. Each subject was interviewed to characterize sunlight exposure, physical activity and dietary intake.

Sunlight exposure was calculated in terms of length of usual weekly outdoor activity, sunscreen use, and usual outdoor attire. The “rule of nine” was adapted to estimate the fraction of body surface area (BSA) exposed to sunlight by each subject’s usual outdoor attire [2]. With this, sun index was calculated as the product of hours of sun exposure per week and fraction of BSA exposed to sunlight. Mumbai is at latitude 18° 56’ North and all of the study population were from areas below 37° latitude. Only sunlight exposure between 8 am to 5 pm in summer and 9 am to 3 pm in winter was measured. All our patients belonged to the same ethnicity and were of skin type 5. Physical activity was assessed using the Global Physical Activity Questionnaire (GPAQ) developed by WHO [www.who.int/chp/steps]. Nutritional intake was calculated using a questionnaire with specific reference to calorie, protein, calcium (dairy and non-dairy), phosphorus and salt intake. These parameters were calculated in two different periods of life; prior to illness (5 years prior to patient perceived onset) and present state of illness.

Biochemical and hormonal determinations

Blood samples were drawn in the morning after an overnight fast. In addition to standard liver function tests, serum levels of calcium, phosphate, magnesium, alkaline phosphatase, and creatinine were measured on the same day with an auto analyzer (Biosystems S.A.,
Table 1  Demographic data of patients with normal and low BMD

| Parameter       | Low BMD            | Normal BMD          | P value |
|-----------------|--------------------|---------------------|---------|
| Age (yr)        | 44.4 ± 6.1 (47)    | 42 ± 8.7 (45.5)     | 0.220   |
| BMI (kg/m²)     | 21.1 ± 3.55 (20.3) | 23.16 ± 5.46 (22.4) | 0.275   |
| Child score     | 7.4 ± 1.8 (7)      | 7.85 ± 1.9 (8)      | 0.350   |
| Lean body mass (kg) | 43.3 ± 7.3 (43) | 46.7 ± 8.75 (44.7) | 0.290   |
| Fat mass (kg)   | 11.6 ± 6.5 (11.2)  | 14.4 ± 7.1 (12.43)  | 0.150   |

BMD: Bone mineral density. Parameters are expressed as mean ± SD. Median value is given in parentheses.

RESULTS

BMD

Among the 72 patients, 49 (68%) had low BMD. There were no significant differences in demography between the patients with normal and low BMD (Table 1). When patients were classified according to etiology of liver disease, the incidence was 56.7% alcoholic, 72% hepatitis B, and 100% hepatitis C. Incidence of low BMD was the same across all Child classes. Lumbar spine was the most frequently and severely affected site. It was involved in all patients with low BMD. Mean BMD at each site was: spine, -2.28 ± 1.1; hip, -1.27 ± 0.74; trochanter, -1.3 ± 0.8; and femoral neck, 0.75 ± 0.86. Bone mass loss in trabecular bone (lumbar spine) was more severe than that in cortical bone (femoral neck). The percentage of patients with low BMD of the hip was 14%, trochanter was 18%, and femoral neck was 7%.

Risk factors for low BMD

Patients were evaluated further for the possible predisposing factors for low BMD. The following data pertain to the 63 men in the study. As there were only nine women, they were analyzed separately. Patients were subdivided into low BMD (Z score ≤ -2, 43 patients) and normal BMD (Z score > -2, 20 patients) groups and further analyzed.

Relationship of BMD with physical activity, sunlight exposure and diet

Both groups showed considerable reduction in sunlight exposure and physical activity after the onset of illness (Table 2). Past and present sunlight exposure was lower in the group with low BMD, although it reached significance (P < 0.05) only with present exposure. Low physical activity (defined as < 600 MET·min/wk) was seen in 15 patients (23%) prior to disease onset but in 76% after developing chronic liver disease. It can be seen that the median activity level and sunlight exposure in the affected population was zero, compared to some amount of activity (120 MET·min/wk) and sunlight exposure (sun index of 0.15) in patients who were able to maintain their bone strength.

Dietary intake was comparable between the two groups. Calorie and protein intake were adequate. Calcium intake was also adequate according to the Indian Council of Medical Research guidelines (ICMR). The calcium:protein ratio (8.5-11.5) was much below the advocated range of 16-20. The calcium:phosphorus ratio (0.45) was also not in the recommended range of 1:1.
Relationship of BMD with biochemical parameters and markers of bone turnover

Biochemical parameters were comparable between both groups (Table 3). Serum calcium, magnesium, phosphorus and alkaline phosphatase levels were normal. Prevalence of vitamin D deficiency was high among patients with CLD. Among the 63 patients, vitamin D values were < 10 ng/mL in 38 patients (60%), 10-20 ng/mL in 20 patients (32%), and > 20 ng/mL in 5 patients (8%). Despite having a low vitamin D level in 92%, PTH was within the physiological range in 87% of patients.

Markers of bone turnover indicated high resorption with low formation. Serum osteocalcin was low in 43 patients (68%) and UDPD: creatinine ratio was high in 50 patients (79%). This suggests uncoupling of bone remodeling as the cause for low BMD in CLD. The levels of bone turnover markers were comparable between the two groups.

Relationship of BMD to hormone parameters

There was a high incidence of hypogonadism in patients with cirrhosis. Twenty-six patients (41%) had low calculated free testosterone. This was distributed equally between the low and normal BMD groups. Among the hypogonadal patients, 18 (69%) had central hypogonadism and eight (31%) had primary testicular failure. An FSH value of > 10 IU/L with normal free testosterone was seen in an additional nine (14%) patients. Serum estradiol level was significantly elevated \((P < 0.05)\) in patients with normal BMD as compared to those with low BMD (Table 4). Forty-six patients (73%) had a high estradiol level, which was distributed unequally within the groups, with 90% of patients with normal BMD and 65% in the group with low BMD having values above the physiological upper range of 50 pg/mL.

IGF-1 levels were below the age-related normal range in both groups, but significantly lower \((P < 0.05)\) in patients with low BMD (Table 4). Forty-one patients (95%) of patients in the low BMD group and 15 (75%) in the normal BMD group had IGF-1 level below normal, which accounted for 89% of patients with CLD.

### Table 2  Sunlight exposure, physical activity and dietary parameters in men with normal and low BMD

| Parameter                          | Low BMD | Normal BMD | \(P\) value |
|------------------------------------|---------|------------|-------------|
| Sun index                          | Past    | 2.49 ± 3.3 (1.3) | 3.54 ± 5.3(2.5) | 0.13 |
|                                    | Present | 0.21 ± 0.41 (0)  | 0.85 ± 1.4 (0.15) | 0.035 |
| Physical activity (MET.min/wk)     | Past    | 2188 ± 2340 (1920) | 2378 ± 1855(2450) | 0.7   |
|                                    | Present | 468 ± 1260 (0)   | 351 ± 659.7 (120) | 0.47  |
| Total Calorie (kcal/d)             | Past    | 2111 ± 768 (2078) | 1867 ± 524 (1878.0) | 0.18  |
|                                    | Present | 2020 ± 662 (2071) | 1997 ± 422 (2078) | 0.65  |
| Total Proteins (g/d)               | Past    | 59.9 ± 22.6 (59.7) | 54.9 ± 20 (56) | 0.3   |
|                                    | Present | 59.3 ± 20.7 (50.6) | 60.2 ± 18.6 (61.2) | 0.56  |
| Calcium (mg/d)                     | Past    | 550 ± 160 (426.5) | 582.6 ± 197 (557.8) | 0.45  |
|                                    | Present | 528 ± 180.7 (391.3) | 620.3 ± 259.7(399.8) | 0.3   |
| Phosphorus (mg/d)                  | Past    | 1456 ± 652 (1478) | 1214.8 ± 535.7(1202) | 0.1   |
|                                    | Present | 6.9 ± 2.9 (7) | 7.2 ± 2.8 (7.4) | 0.53  |

*Statistically significant, \(P < 0.05\).

### Table 3  Biochemical parameters and markers of bone turnover in men with normal and low BMD

| Parameter                          | Low BMD | Normal BMD | \(P\) value |
|------------------------------------|---------|------------|-------------|
| Serum calcium (mg/dL)              | 9.17 ± 0.52 (9.22) | 9.29 ± 0.47 (9.33) | 0.29 |
| Serum phosphorus (mg/dL)           | 3.63 ± .9 (3.59) | 3.74 ± 1 (3.8) | 0.69 |
| Serum alkaline phosphatase (IU/L)  | 138 ± 61 (132.7) | 140.2 ± 65.6(128.5) | 0.96 |
| Serum magnesium (mg/dL)            | 2.0 ± 1.9 (1.58) | 1.42 ± 0.3 (1.48) | 0.08 |
| Urine calcium/creatinine ratio     | 0.06 ± 0.1 (0.03) | 0.053 ± 0.053 (0.035) | 0.72 |
| 25 (OH) vit D (ng/mL)              | 11.2 ± 7.6 (9.4) | 10.5 ± 5.7 (8) | 0.90 |
| 1,25 (OH) 25vitD (pg/mL)           | 46.54 ± 26.4 (41) | 36.6 ± 21.6 (30) | 0.19 |
| Serum PTH (pg/mL)                  | 45.5 ± 28.1 (43.9) | 42.2 ± 18.9 (42.1) | 0.95 |
| Serum osteocalcin (ng/mL)          | 2.99 ± 2.5 (1.8) | 2.14 ± 1.8 (1.14) | 0.37 |
| UDPD/creatinine ratio              | 11.5 ± 4.5 (12.1) | 12.5 ± 6.2 (11.6) | 0.84 |

1Corrected calcium is used; 2Unit - nM DPD/mmol/L creatinine.

### Table 4  Hormone parameters in men with normal and low BMD

| Parameter                          | Low BMD | Normal BMD | \(P\) value |
|------------------------------------|---------|------------|-------------|
| FSH (IU/L)                         | 8.2 ± 9.4 (4.62) | 19.8 ± 40.2 (7.53) | 0.34 |
| LH (IU/L)                          | 6.8 ± 6.2 (4.78) | 11.1 ± 13.9 (6.47) | 0.31 |
| Estradiol (pg/mL)                  | 76.1 ± 61.5 (63.8) | 100.6 ± 61.8 (79.2) | 0.02 |
| SHBG (nmol/L)                      | 76.7 ± 51.1 (75.4) | 72.3 ± 25.4 (72.6) | 0.60 |
| Free testosterone (ng/dL)          | 7.6 ± 4.7 (7.27) | 7.2 ± 4.0 (7.06) | 0.85 |
| IGF-1 (pmol/L)                     | 44.8 ± 24.7 (35.2) | 73.7 ± 58.54 (38.4) | 0.03 |
| IGFBP3 (μg/mL)                     | 1.21 ± 0.6 (1.03) | 1.8 ± 1.2 (1.51) | 0.071 |

1Statistically significant, \(P < 0.05\); 2Calculated from total testosterone.
Low IGFBP3 was almost a universal finding in patients with CLD (61 of 63 patients; 97%), although it did not differ significantly between the groups ($P = 0.071$).

**DISCUSSION**

The purpose of the current study was to determine the prevalence of low BMD, to estimate the bone turnover and hormonal status, and to identify the factors associated with bone disease in patients with CLD. The only available Indian data on this subject are those of Sachdev et al.\cite{4} from 1976. The current study shows that patients with CLD have a high prevalence of decreased BMD, with the lumbar spine being the most frequently and intensely affected site. Furthermore, there was no relation between severity of hepatic dysfunction (Child class) and incidence of low BMD. These factors point to the need for early evaluation for HO in patients with CLD.

In the present cohort, low BMD was found in 68% of patients. This is comparable to the only available Indian data of Sachdev et al.\cite{4}, in which 64% of cirrhotic patients had low BMD. The method of evaluation and diagnosis differed greatly in that era. In the earlier study of 25 patients with cirrhosis (all aged < 40 years), diagnosis of cirrhosis was made from liver biopsy and osteoporosis from iliac crest biopsy. Scanning through western studies has indicated marked heterogeneity in BMD findings in CLD, ranging from no effect to a large BMD deficit. Leslie et al.\cite{10} have pooled the results from uncontrolled and controlled studies of bone mineral content in CLD. They have shown a $Z$ score less than -2 in 21% of patients. Studies on patients with end-stage liver disease of varying etiology confirm a high but variable incidence of osteoporosis (11%-48%) and osteopenia (18%-35%)\cite{9}. The incidence of 68% in the present study is much higher than that in any previous study. This may be because Indians have a lower BMD as compared to Caucasians\cite{8,9}. Thus, the use of $Z$ scores based on a Caucasian database might have resulted in overestimation of osteoporosis. However there are no published data for BMD in healthy Indian populations.

The major influences on bone metabolism are genetic, but also essential are mechanical stress (exercise and muscle activity), good nutrition, adequate calcium and vitamin D, and a normal hormonal environment. The patient with CLD could have any of these factors acting alone or in concert, which potentially predispose him/her to thin bones. Each of the above factors were assessed and compared between patients with low and normal BMD. It was found that patients with CLD had all the above and known risk factors: low sunlight exposure, reduced physical activity, low lean body mass, vitamin D deficiency and hypogonadism. The presence of risk factors in the low and normal BMD groups was probably the reason for the absence of a statistically significant difference in risk factors between the normal and low BMD groups. This indicates that all patients with cirrhosis, unless prevented, will develop the disease. In addition, although the calcium intake was adequate by ICMR guidelines, it was well below the internationally accepted daily allowance. This added to an unfavorable calcium:protein ratio of 8.5-11.5 mg/g, and calcium:phosphorus ratio of 0.45 may have resulted in inadequate recommended daily allowance of calcium in these patients.

Vertebrae consist of 50% trabecular bone, while other bones (hip, neck and trochanter) consist mainly of cortical bone. Sites with a high proportion of trabecular bone are affected earliest in diseases that produce increased bone turnover\cite{10}. In the present study, serum osteocalcin was low in 68% and UDPD: creatinine ratio was high in 79% of patients, which indicated a high resorptive state added to low formation. This suggests uncoupling of bone remodeling as the cause of low BMD in CLD. This can explain the predominant involvement of the spine in HO. This is also compatible with other similar studies\cite{11,12}.

In the present study, 41% of patients were hypogonadal, although this was not correlated with the severity of bone loss. Diamond et al.\cite{11} and Monegal et al.\cite{13} have shown that hypogonadism is common in men with cirrhosis but it is not correlated with osteoporosis. A particularly interesting finding in the present study was the significantly elevated estradiol level ($P < 0.05$) in patients with normal compared with low BMD. Estrogen is known to have a positive influence on the male skeleton\cite{14}. It is also known to be increased in men with cirrhosis. Probably the anabolic and antiresorptive qualities of estrogens in bone act as protective factors in preventing bone loss in these patients with cirrhosis.

More than 90% of circulating IGF-1 is synthesized in the liver. It is a proven early marker of hepatocellular functional capacity\cite{15,16}, and shows a marked decline in the early stages of cirrhosis (Child-Pugh class A). It starts decreasing before other liver-function parameters such as albumin, bilirubin and prothrombin become involved\cite{17}. GH levels are increased correspondingly, which creates a state of IGF resistance\cite{18}. IGF-1 is also a major determinant of BMD in healthy men\cite{19}. In the present study, IGF-1 levels were below the age-related normal range in both groups, and were significantly lower ($P < 0.05$) in patients with low BMD. IGF-1 values were low in 89% of patients with CLD. Previous studies have shown IGF-1 levels to correlate directly with BMD and inversely with disease severity\cite{12,19,20}. Studies have described a role for decreased serum IGF-1, even in idiopathic osteoporosis\cite{21}. IGF-1 expression is increased during early osteoblast recruitment, but declines as these cells undergo differentiation. It is known to stimulate osteoblast proliferation\cite{22} and play a key role in bone remodeling and maintenance of bone mass. Simonet et al.\cite{22} have shown that low levels of IGF-1 may lead to increased bone resorption. Thus, the link between cirrhosis and bone loss also involves low levels of IGF-1. A significant difference in IGF-1 level between normal and low BMD patients may be a pointer to why some patients deteriorate faster, despite sharing equally all the risk factors.
IGFBP3 play a very important role in bioavailability of circulating IGF-1. It forms a stable ternary complex with an acid-labile subunit and IGF-1, and binds > 95% of circulating IGF-1. In the present cohort, low IGFBP3 was seen in 97% of patients with CLD, although this did not differ significantly between the normal and low BMD groups \( (P = 0.071) \). This is plausible because hepatocytes are the major site of IGFBP3 synthesis. This may have further decreased the tissue bioavailability of IGF-1 \cite{11,25}.

In conclusion, the present study confirms the high incidence of low BMD in patients with CLD. Disease onset is early in the course of cirrhosis. Decreased bone formation with increased bone resorption imply that uncoupling of bone remodeling is the mechanism involved. Contributing factors are inadequate sunlight exposure, reduced physical activity, low lean body mass, vitamin D deficiency and hypogonadism. The presence of most risk factors in low and normal BMD groups indicates that all patients with cirrhosis are vulnerable, and unless prevented, will develop the disease. Our results provide evidence of the key roles played by IGF-1 and estrogen in this condition. Although risk factors are prevalent in all patients, the severity of bone loss may be accelerated in patients with low IGF-1 level.

The present study also suggests a possible protective role for the high estrogen level seen in cirrhosis.

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