ORIGINAL ARTICLE

Hepatic osteodystrophy and fracture risk prediction using FRAX tool in Indian patients with cirrhosis

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Abstract

Background and Aim: The main clinical relevance of hepatic osteodystrophy is the increased risk of fractures. Dual-energy X ray absorptiometry (DEXA)-based assessment of bone mineral density, the current gold standard for diagnosing osteoporosis, is not the sole determinant of fracture risk. Other clinical risk factors also play an important role. This study was carried out to assess the prevalence and risk factors of hepatic osteodystrophy and estimate the entailed fracture risk by using the FRAX tool in a cohort of Indian cirrhotics.

Methods: Consecutive patients with cirrhosis ($n = 120$) were recruited. Etiologic workup, liver function tests, serum calcium, phosphate, 25(OH)D, HbA1c, and DEXA scan were performed. Hepatic osteodystrophy was defined as a T score of < -1. FRAX scores were calculated using the Indian calculator.

Results: The study cohort was predominantly male (86.7%) with a median age of 49 (40–65) years. Alcohol was the most common etiology (80%). All patients had Child-Turcotte-Pugh class B (63.3%) or class B (36.7%) cirrhosis. Hepatic osteodystrophy was present in 83.3% patients. On multivariate analysis, smoking (odds ratio [OR]: 3.1 [1.76–4.7], $P < 0.001$) and serum 25(OH)D (OR: 0.23 [0.09–0.94]; $P = 0.03$) showed significant association with hepatic osteodystrophy. The 10-year probability of major osteoporotic fracture and hip fracture was 5.7% (2.1–28.9) and 2.5% (1.4–7.4), respectively. Using a FRAX probability cut-off of 20% for major osteoporotic fracture and 3% for hip fracture, 30% patients qualified for osteoporosis treatment.

Conclusion: Hepatic osteodystrophy is widely prevalent among Indian patients with cirrhosis and entails a high risk of fractures. Approximately one-third of patients with cirrhosis need treatment to reduce the risk of osteoporotic fractures.

Introduction

Osteoporosis is the most common metabolic disorder and is characterized by a decrease in bone mass and microarchitectural distortion of bone tissue, which increases the risk of fractures.[1] Hepatic osteodystrophy is a common complication of cirrhosis.[2] Although hepatic osteodystrophy includes both osteomalacia and osteoporosis, histomorphometric techniques confirm that osteoporosis is the predominant bone abnormality.[3] The pathogenesis of hepatic osteodystrophy is not well understood. Studies suggest that, while both are at play, osteoblast dysfunction is probably more important than excessive bone resorption.[2,3]

The main importance of hepatic osteodystrophy, and indeed osteoporosis in general, is the risk of fragility fractures, which

adversely impacts morbidity, quality of life, and possibly even survival.[4] Dual-energy X ray absorptiometry (DEXA) is the gold standard for diagnosing osteoporosis. While bone mineral density (BMD) is an important predictor of fracture risk, its predictive value is constrained by the lack of information on clinical risk factors for fractures. Hence, composite scores inculcating BMD and validated clinical criteria have been developed to better estimate the future risk of fractures. Among them, the best studied is the FRAX tool, which was developed by the World Health Organization (WHO).

There is little published literature from the Indian subcontinent on hepatic osteodystrophy, and its associated fracture risk is unknown.[5–8] This study was thus designed to assess the prevalence and risk factors of hepatic osteodystrophy and estimate the associated fracture risk as predicted by the FRAX tool.

Methods

A total of 120 consecutive patients with cirrhosis presenting to the Departments of Internal Medicine and Gastroenterology at a tertiary medical college of a city in North India were recruited for the study after providing informed consent. The diagnosis of cirrhosis was based on history, physical examination, biochemical tests, imaging, and endoscopy. The study protocol was approved by the Institutional Ethics Committee.

Only patients older than 40 years were recruited as the FRAX tool does not accept lower-age entries. Patients with chronic kidney disease, skeletal deformities, and known osteoporotics taking bisphosphonates, teriparatide, calcitonin, or other hormonal therapy were excluded. Detailed inclusion and exclusion criteria are provided in the Supplementary text.

A detailed history (focusing on clinical risk factors of osteoporosis) and physical examination were carried out in all patients. In patients with ascites, bodyweight was adjusted by 5–15% depending on the grade of ascites, with an additional reduction of 5% in the presence of bilateral pedal edema.[9] Investigations performed included Hepatitis B surface antigen (HB sAg), anti-Hepatitis C antibody (anti-HCV), anti-nuclear antibody (ANA), liver function tests including serum albumin and prothrombin time-international normalised ratio (PT-INR), serum calcium, phosphate, 25(OH)D, and glycosylated Hemoglobin (HbA1c). Vitamin D deficiency was diagnosed at a cut-off of <20 ng/mL, while insufficiency was diagnosed at Vitamin D levels of 20–30 ng/mL.[10] DEXA scan (Hologic Inc. USA) was performed at the level of the neck of the femur. T scores were classified as per WHO criteria.[11] Osteoporosis was defined by a T score ≤ −2.5 and osteopenia as a T score between −1 and −2.5, while a T score ≥ −1 was considered normal. Severe osteoporosis was defined by the history of fragility fractures in the presence of osteoporosis (T score ≤ −2.5). Hepatic osteodystrophy was defined by the presence of suboptimal T score of < −1.

The FRAX tool is an internet-based tool that incorporates clinical risk factors with BMD at the femoral neck to estimate the 10-year probability of a major osteoporotic fracture (spine, forearm, hip, or shoulder fracture) and hip fracture. The details of clinical risk factors included in the FRAX model is provided in the Supplementary protocol. Although BMD is not mandatory when using the FRAX tool, BMD data were used for calculating the FRAX scores in all our patients. Only BMD values at the neck of femur are considered for calculating fracture risk using the FRAX tool. The calculator meant for India was used for obtaining the FRAX-predicted fracture risks (www.sheffield.ac.uk/FRAX/tool.aspx?country=51).

Statistical analysis was conducted using Microsoft Excel (Office 365) with Solver add-in and Real Statistics Resource Pack. Data have been reported as mean ± SD or median with range. Quantitative data were analyzed using Student T test or Mann–Whitney U test for normally distributed and skewed data, respectively. Categorical data were compared using Chi square test or Fisher's exact test as applicable. Multivariate logistic regression was conducted to analyze factors associated with hepatic osteodystrophy. All statistical tests performed were two-sided, and a *P*-value <0.05 was considered significant.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Results

The majority of our patients were males (86.7%) with a median age of 49 (40–65) years and a mean body mass index of 22.48 ± 4.26 kg/m^2. The majority of our patients had cirrhosis secondary to alcohol consumption (80%), while the rest had chronic viral hepatitis and non-alcoholic steatohepatitis. All patients had advanced liver disease, with 76 patients (63.3%) having Child-Turcotte-Pugh (CTP) class B cirrhosis, while 44 (36.7%) belonged to CTP Class C. Alcohol consumption >3 units per day (80%) and current smoking (60%) were the most common risk factors for fracture risk identified in our study. Demographic and clinical risk factor data are shown in Table 1.

The median serum 25(OH)D was 18.6 ng/mL (7.6–46.9). Vitamin D insufficiency and deficiency was observed in 76 (63.3%) and 40 (33.4%) patients, respectively, and only 4 (3.3%) patients had optimal Vitamin D levels. The mean BMD was 0.615 ± 0.11 gm/cm^2 and was significantly higher in males (0.629 ± 0.10 gm/cm^2) compared to females (0.520 ± 0.064 gm/cm^2, $P = 0.03$). The mean T score was −2.2 ± 0.85 and was also higher in males (−2.08 ± 0.84 *vs* −2.93 ± 0.56, $P = 0.03$). BMD and T scores did not differ significantly between the different CTP classes ($P = 0.43$ and 0.67, respectively). Osteopenia was observed in 56 (46.7%) patients, while osteoporosis and severe osteoporosis were present in 39 (32.5%) and 5 (4.2%) patients, respectively. Hepatic osteodystrophy was present in 100 (83.3%) patients. On univariate analysis, smoking, serum

Table 1 Demography and clinical risk factors in study cohort

Characteristic	n=120
Age (years)	49 (40–65)
Gender (male:female)	104:16
BMI (kg/m^2)	22.48 ± 4.26
Child-Turcotte-Pugh class, *n* (%)	
A	0
B	76 (63.3)
C	44 (36.7)
Etiology, *n* (%)	
Alcohol	96 (80)
Chronic hepatitis B	10 (8.3)
Chronic hepatitis C	6 (5)
NASH	8 (6.7)
Clinical risk factors for fracture, *n* (%)	
Previous fragility fracture	5 (4.2)
Parent fractured hip†	1 (0.8)
Current smoking	72 (60)
Glucocorticoids‡	0
Rheumatoid arthritis	0
Alcohol (≥3 units/day)	96 (80)
No risk factors (except cirrhosis)	16 (13.3)

†Previous spontaneous fracture or fracture from trivial trauma unlikely to cause fracture in a healthy person.
‡Exposure for >3 months to a dose equivalence of prednisolone ≥5 mg.
BMI, body mass index; NASH, non-alcoholic steatohepatitis.

Table 2 Demographic, clinical, and biochemical parameters of patients with and without hepatic osteodystrophy

Characteristic	Hepatic osteodystrophy (n = 100)	Normal BMD (n = 20)	P value
Age	49 (42–65) years	50 (40–63) years	0.78
Gender: female	14 (14%)	2 (10%)	0.99
BMI	22.49 ± 4.12	22.41 ± 3.98	0.07
Child-Turcotte-Pugh class			
B	60 (60%)	16 (80%)	
C	40 (40%)	4 (20%)	0.13
Alcohol (≥3 units/day)	82 (82%)	14 (70%)	0.23
Current smoking	67 (67%)	5 (25%)	**<0.001**
Total bilirubin (mg/dL)	2.8 (2–12.6)	2.4 (1.9–9.7)	**0.04**
AST (U/L)	74 (39–198)	71 (44–178)	0.56
ALT (U/L)	65 (29–130)	64 (32–104)	0.62
Alkaline phosphatase (U/L)	147 (102–178)	144 (97–210)	0.77
Serum albumin (g/dL)	2.9 (2.6–3.4)	3 (2.7–3.7)	**0.04**
INR	1.54 (1.36–2.66)	1.58 (1.32–2.7)	0.56
Serum calcium (mg/dL)	8.1 ± 0.81	8.23 ± 0.9	0.18
Serum phosphate (mg/dL)	3.23 ± 1.1	3.37 ± 1.16	0.33
Serum 25(OH)D3 (ng/mL)	17.1 (7.6–31)	19.9 (8.7–46.9)	**0.03**
HbA1c	5.1 (3.9–7.1)	5.2 (4.3–7)	0.08

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; BMI, body mass index; INR, international normalised ratio. Significant p values are highlighted in bold.

bilirubin, albumin, and 25(OH)D were significantly associated with hepatic osteodystrophy (Table 2). On multivariate analysis, smoking (odds ratio (OR): 3.1 [1.76–4.7], $P < 0.001$) and serum 25(OH)D (OR: 0.23 [0.09–0.94]; $P = 0.03$) showed a significant association with hepatic osteodystrophy.

Using the Indian FRAX calculator, the 10-year probability of major osteoporotic fracture risk and hip fracture risk were 5.7% (2.1–28.9) and 2.5% (1.4–7.4), respectively. Using a FRAX score cut-off of 20% for major osteoporotic fractures and 3% for hip fracture (as recommended by National Osteoporosis Foundation (NOF), guidelines), 30% of the patients would require treatment for osteoporosis.[12]

Discussion

Hepatic osteodystrophy is a broad term for metabolic bone disease that occurs in patients with chronic liver disease. It is multifactorial in pathogenesis, with osteoporosis being the predominant component. Hepatic osteodystrophy has significant clinical relevance in this era of liver transplantation, not only because of the improvement in life expectancy but also because post-transplant corticosteroids and immobilization further accelerates bone loss. Studies across the world have reported a variable prevalence of osteoporosis (11–48%) and osteopenia (18–35%) in patients with cirrhosis.[13] There is a paucity of data on hepatic osteodystrophy in patients from the Indian subcontinent. An early study in 1976 reported low BMD in 64% of subjects. However, in that era, BMD was estimated by iliac crest biopsy and not by DEXA.[5] More recent Indian studies have documented hepatic osteodystrophy in 66–95% patients of cirrhosis.[6–8] A similarly high prevalence of hepatic osteodystrophy has been reported in a study from Bangladesh, where osteopenia and osteoporosis were observed in 50 and 10% patients, respectively.[14] The majority of the patients in our study

(83.4%) had subnormal T scores, confirming that hepatic osteodystrophy is widely prevalent.

Synthesis of Vitamin D is powered by sunlight. The Indian subcontinent is situated in the tropics and is blessed with sunshine throughout the year. Thus, conventional logic suggests that Indians would have normal Vitamin D levels. On the contrary, numerous studies on healthy individuals have shown that Vitamin D deficiency/insufficiency is practically universal among Indians.[10] In a cohort of Indian cirrhotics, Vitamin D deficiency and insufficiency were reported in 60 and 32% patients, respectively.[6] Similar findings were observed in our study, and only 3.34% patients had optimal Vitamin D levels. A significant independent association between serum 25(OH)D levels and hepatic osteodystrophy was noted in our study on multivariate analysis. The association between serum 25(OH)D levels and BMD is controversial, with studies reporting varying findings.[8,15–17] Caution must be exercised in interpreting the relationship between Vitamin D levels and BMD as other factors are also at play. Evidence suggests that an increase in serum parathormone (PTH) levels is the main determinant of bone health for any given value of 25(OH)D. Vitamin D-deficient patients in whom the PTH levels do not rise may be protected from the adverse impacts of Vitamin D insufficiency on BMD.[8,18] PTH levels were not measured in our study. Apart from serum 25(OH)D, smoking was also significantly associated with hepatic osteodystrophy on multivariate analysis in our study. The link between smoking and increased risk of osteoporosis is well established in medical literature.[19]

Interestingly, the severity of liver disease as assessed by CTP class was not associated with the increased risk of hepatic osteodystrophy in our study. The mean BMD and T score in CTP-B patients was not significantly different from that in CTP-C patients. Previously conducted studies have conflicting viewpoints on this issue. Sokhi *et al.*, in a study on cirrhotic patients awaiting liver transplantation, found that BMD values

differed significantly between Child Pugh B and C classes.[20] Similar results were also reported by Gallego-Rojo *et al.* in a study on 32 male patients of postviral cirrhosis.[21] However, other studies have not found any correlation between BMD and the clinical severity of cirrhosis.[22,23] Previous studies from the Indian subcontinent have also found no relation between low BMD and the severity of liver dysfunction as determined by the CTP score.[6,14,18]

The diagnosis of osteoporosis is based on the detection of abnormally low BMD. However, BMD is not the sole determinant of fracture risk. Many other clinical risk factors also affect the fracture risk, including age, past fragility fractures, history of hip fracture in parents, use of corticosteroids, excess alcohol consumption, smoking, and rheumatoid arthritis. The FRAX tool incorporates these clinical risk factors with or without BMD values to estimate the 10-year absolute risk of hip and major osteoporotic (hip, vertebral, humerus, and forearm) fractures.[24] It has been previously used in Western studies to estimate the fracture risk in patients with chronic liver disease.[25–29] However, there are no data about the use of FRAX tool in cirrhotics from the Indian subcontinent and the Asia-Pacific region. Ours is the first study to use the FRAX tool (Indian calculator) in a cohort of Indian patients with cirrhosis, and we estimated the 10-year probability of major osteoporotic fracture and hip fracture to be 5.7% (2.1–28.9) and 2.5% (1.4–7.4), respectively.

The FRAX tool has been incorporated into the therapeutic decision algorithms of various international osteoporosis societies, including National Osteoporosis Guideline Group and NOF.[4,12] The FRAX tool can be used without BMD values, and in the healthy adult population, it has been used to screen individuals who may benefit from DEXA scan.[4] Such a stratification approach is currently not recommended by the guidelines of various gastroenterology and hepatology societies who recommend DEXA scan for all cirrhotics.[9,30] There is also some evidence to suggest that pre-DEXA FRAX scores may underestimate the fracture risk, although this is controversial.[28,29] We calculated the FRAX score after incorporating the BMD values. Using the NOF-proposed post-DEXA FRAX cut-offs of 20% for major osteoporotic fractures and 3% for hip fracture, almost one-third of our patients would qualify for treatment of osteoporosis.

We acknowledge the limitations of our study. The majority of our patients were males and had advanced cirrhosis (CTP-B and -C). There were no patients with cholestatic or autoimmune liver disease. PTH and other markers of bone turn could not be investigated because of logistic and cost constraints.

In conclusion, hepatic osteodystrophy is widely prevalent among Indian patients with cirrhosis. The FRAX tool is a composite tool for estimating the fracture risk and stratifying the need for treatment in these patients. As many as one-third of patients with cirrhosis need treatment to reduce the risk of osteoporotic fractures. Further studies are needed to clarify the role of FRAX tool in making treatment decisions in this unique subgroup of osteoporosis secondary to liver disease. Future studies should also explore the role of pre-DEXA FRAX scores in stratifying the need for more expensive DEXA scans to fine-tune management decisions.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Data S1. Supplementary Information