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Proximal Hip Geometry, Trabecular Bone Score, Bone Mineral Density and Bone Mineral Parameters in Patients With Cryptogenic and Hepatitis B Related Cirrhosis- A Study From the Indian Subcontinent

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Abstract

The impact of cryptogenic cirrhosis on skeleton has not been studied in Indian context. So this study investigated bone health in male patients with early cryptogenic cirrhosis as defined by Child-Turcot-Pugh A (CTP-A) categorization and compared it with patients diagnosed to have hepatitis B related chronic liver disease (CLD) on treatment and age, sex-matched healthy controls. It was a cross-sectional study, in which thirty male subjects were recruited in each group. Bone mineral density (BMD), trabecular bone score (TBS), hip structural analysis (HSA) and bone mineral parameters were assessed. The mean ±SD age of the study subjects was 39.3 ± 9.2 years. The mean 25-hydroxy vitamin D was significantly lower in subjects with cryptogenic cirrhosis as compared to controls ($p = 0.001$). Subjects with cryptogenic cirrhosis had significantly lower (1.297 ± 0.099) TBS as compared to hepatitis-B related CLD (1.350 ± 0.094) control subjects (1.351 ± 0.088) ($p = 0.04$). BMD at the hip and lumbar spine was also significantly lower in subjects with cryptogenic cirrhosis as compared to hepatitis-B related CLD and healthy age matched controls ($p < 0.05$). Most components of HSA were significantly affected in subjects with cryptogenic cirrhosis as compared to control subjects ($p < 0.05$). Patients with cryptogenic cirrhosis had significantly low TBS and BMD lumbar spine and hip as well as poor proximal hip geometry which may be good predictor of future fragility fractures.

Key words: Bone microarchitecture; bone mineral density; cryptogenic cirrhosis; hip geometry; chronic liver disease.

Introduction

Cirrhosis of liver is a common public health problem leading to significant morbidity and mortality and has a reported prevalence of 4.5%–9% in the general population *(1)*. Alcohol, nonalcoholic fatty liver disease and viral hepatitis are the common causes of cirrhosis of liver worldwide with cryptogenic cirrhosis contributing to approximately five percent of the disease burden *(2)*.

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There is a difference in the prognosis and management of cryptogenic cirrhosis when compared to other etiologies of chronic liver disease (CLD) such as viral hepatitis. These patients particularly in those with early disease are reported to have slower progression when compared to viral hepatitis *(2)*. In addition, there is no definitive treatment option for cryptogenic cirrhosis when compared to viral hepatitis.

Patients with CLD are prone to many extrahepatic complications with hepatic osteodystrophy being one of them. Hepatic osteodystrophy refers to bone disease that is associated with chronic liver disease and includes osteoporosis and osteomalacia, the former being much more common. Osteoporotic fractures are associated with a significant morbidity, mortality, impaired quality of life *(3)* and impose a significant financial burden on the community *(4)*. Metabolic bone disease is common and is extensively studied in patients with cholestatic liver disease *(5,6)*. However, studies that explore the association between low bone mass and noncholestatic cirrhosis such as cryptogenic cirrhosis are scarce. The documented prevalence of osteoporosis in patients with advanced chronic liver disease ranges from 12% to 55% *(7)*.However, there was great heterogeneity in the study population and characteristics like age, sex, etiology, disease severity and the technique used for measurement of bone density has been widely variable in previous studies *(8)*. Moreover, there is limited literature available from the Indian subcontinent on bone health in patients with cryptogenic cirrhosis and Hepatitis B infection. Indians are known to have a lower peak bone mass, poor dietary calcium intake, higher prevalence of vitamin D deficiency, lower mean BMD and lower age of developing fragility fractures, thus making them more vulnerable after developing these hepatic disorders *(4)*. In addition, inherent limitations pertaining to measuring BMD alone, definitely warrants the evaluation of other parameters that reflect microarchitectural alterations and geometric changes of the bone, both of which contribute significantly to fracture risk but are not captured by routine assessment of BMD. Trabecular bone score (TBS) is a novel densitometric tool that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect measure of bone microarchitecture *(9)*. Hip structural analysis (HSA) is also performed by the DXA and evaluates different variables pertaining to proximal hip geometry *(10)*. There is limited literature on the utility of HSA and TBS in assessing skeletal integrity in subjects with cryptogenic cirrhosis.

Based on the research gaps mentioned above, it is likely that bone health is differentially affected by different liver disorders and the utility of additional tools assessing microarchitecture and hip geometry are yet to be explored this setting. In this study we tested this hypothesis and aimed to study bone health comprising BMD, TBS, HSA and bone mineral parameters in male patients with early cryptogenic cirrhosis as defined by Child-Turcot-Pugh A (CTP-A) categorization and compare it with patients diagnosed to have hepatitis B related cirrhosis on treatment and age, sex-matched healthy controls. Bone mineral parameters included serum calcium, phosphate, 25-hydroxy vitamin D, parathormone, bone turnover markers.

Hepatitis B subjects on treatment were chosen since they represent subjects having hepatic pathology and alterations on bone mineral profile secondary to the medications.

Materials and Methods

This was a cross-sectional study, done over a period of 23 months between July 2018 and May 2020 in a quaternary care teaching hospital located in southern India. Subjects in cryptogenic cirrhosis group (Group 1) and hepatitis B related CLD group (Group 2) were recruited from Gastroenterology and Hepatology OPD whereas age-matched healthy controls (Group 3) were recruited from the local community.

Consecutive male subjects attending the hepatology OPD between the age 18 to 50 years, who fulfilled the inclusion and exclusion criteria mentioned below were recruited for the study.

Inclusion Criteria

Cryptogenic cirrhosis (group-1): Men with cirrhosis in which other etiologies of cirrhosis like alcohol-related liver disease, chronic use of hepatotoxic drugs, hepatitis B surface antigen positivity (included in hepatitis B related CLD group), HCV antibody positivity, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis or genetic liver diseases such as hemochromatosis, alpha1-antitrypsin deficiency or Wilson's disease (based on clinical grounds, appropriate serum biomarkers or imaging findings) were ruled out were included in this group. Subjects with Child-Turcot-Pugh (CTP) A status were recruited.

Cirrhosis was diagnosed on the basis of compatible imaging/endoscopic (coarse-pattern, irregular liver surface, clear-cut evidence of portal hypertension such as splenomegaly and esophagogastric varices) and/or histopathological findings by an expert hepatologist at our institute.

Hepatitis B cirrhosis (group-2): Subjects who were hepatitis B surface antigen positive, on antiviral drugs for at least 6 months and CTP A status were recruited in this group.

Age and BMI matched healthy controls (group- 3): were recruited from the local community.

Exclusion Criteria

Female subjects, subjects having clinically detectable ascites, CTP-B or C status, diabetes mellitus, hepatocellular carcinoma, associated chronic diseases like hyperparathyroidism, hyperthyroidism, rheumatoid arthritis, inflammatory bowel disease, lupus erythematosus, ankylosing spondylitis, HIV, prolonged immobility, any carcinoma, and long term steroid, anticonvulsants or other bone active medications, current smoking and alcohol use (in the

previous one year) and subjects on medications that affect bone metabolism were excluded from the study.

The study was approved by the institutional ethics committee (IRB Min No: 10685 dated 01.06.2017) and written informed consent was obtained from each patient enrolled in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Assessment of Bone and Mineral Metabolism

Areal bone mineral density at hip and lumbar spine (LS 1 to 4) was measured using Hologic DXA Discovery A machine (Waltham, Massachusetts, USA). The precision error expressed as CV% was found to be less than 2 % for all DXA measurements. The scans for this study were done using the same DXA Machine by the same DXA technician, who has been formally trained to perform DXA as per the ISCD guidelines and has an experience of more than two decades. A Z-score $\leq$ -2.0 either at hip or lumbar spine was defined as low bone mass *(8)*. Trabecular bone score (TBS) was measured using iNsight Software version 3 (Med-Imaps, Bordeaux, France). TBS is a novel noninvasive method that evaluates pixel gray-level variations in the spine DXA image and helps in assessing the microarchitecture of the bone. A TBS value of more than or equal to 1.350 indicates normal microarchitecture, 1.200–1.350 indicates partially degraded microarchitecture and a TBS < 1.200 indicates degraded bone microarchitecture *(11)*. HSA is a simple tool to determine bone strength at the proximal femur by geometrical assessment. The HSA program performs its analysis at 3 femoral sites using averages from 5 parallel lines 1 pixel apart across the cross-section of three sites *(12,13)*.

(1) **Narrow neck (NN),** which is the narrowest point of the femoral neck
(2) **Inter-trochanteric region (IT),** along the bisector of the angle of the axes of the neck and femoral shaft
(3) **Femoral shaft (FS),** a site across the shaft at a distance of 1.5 cm minimum neck width distal to the intersection of the neck and shaft axes

The following four parameters of HSA were assessed in all the three sites:

a) **Cross-sectional area (CSA)** excluding soft spaces in the marrow and pores - an index of resistance to axial forces (cm^2)
b) **Cross-sectional moment of inertia (CSMI)-** estimate of resistance to bending forces in a cross-section (cm^4)
c) **Section modulus (Z)** - An index of strength calculated as the CSMI ÷ the distance from the bone edge to the centroid (assumed here to be half the subperiosteal width (cm^3).
d) **Buckling Ratio (BR)** - index of susceptibility to local cortical buckling under compressive loads.

Body weight was measured using an Atlas electronic scale (range = 400 g–200 kg) to the nearest 0.1 kg. Participants were asked to stand straight, relaxed and with minimum clothing. Height was measured to the nearest 0.1 cm by using the wall-mounted stadiometer. The height of the individuals was taken in the standing position, without footwear and keeping the head in the Frankfurt plane. BMI was subsequently calculated as weight in kilograms divided by the square of height in meters (kg/m^2).

An overnight fasting blood sample (of at least 8 hours) was obtained for estimation of serum samples of calcium (N: 8.6–10.2mg/dL), albumin (N:3.5–5.0 gm/dL), phosphate (N:2.5–4.5mg/dL), creatinine (N:0.6–1.2mg/dL), alkaline phosphatase (N:40–125 U/L), 25-hydroxy vitamin D (N:30–75 ng/mL) and parathyroid hormone (PTH) (N:8–50 pg/mL). Among the bone biochemical parameters, colorimetric methods were used for calcium, and phosphorus was estimated by the phosphomolybdate method. PTH was measured by chemiluminescent immunoassay (CLIA, Immulite Analyzer 2000). A 25 (OH) vitamin D (vitamin-D) level of < 20 ng/mL was considered as vitamin-D deficiency. Other biochemical parameters were measured in a fully automated and computerized microanalyzer (Hitachi Roche Modular P 800 model). 25 hydroxy vitamin D was analyzed using electro-chemiluminescent assay (ECLIA) and alkaline phosphatase was measured by the kinetic PNPP (paranitrophenyl phosphate) method. Bone turn over markers (BTMs) in the form of C-terminal telopeptide of type 1 collagen (CTx) and serum P1NP (N terminal propeptide of type 1 procollagen) were also measured on a fasting state using ECLIA.

All measurements including DXA Scan, bone mineral parameters and other blood biochemistry were done on the same day.

Statistical Methods

Statistical Package for Social Sciences (SPSS) 17 (Chicago, USA) program was used for statistical analysis. Descriptive statistics were reported using mean +/-SD for continuous variables that included Age (years), BMI (kg/m^2), Albumin corrected Calcium (mg/dL),

Albumin (g/dL), phosphorus (mg/dL), alkaline phosphatase (IU/L), creatinine (mg/dL), 25 (OH)Vitamin D (ng/mL), PTH (pg/mL), CTX (pg/mL), P1NP (ng/mL), mean BMD (g/cm2), TBS and parameters of hip geometry. Categorical variables including proportion of individuals with vitamin D deficiency and low bone mass were reported using frequency and percentage. Comparison between continuous variables that are mentioned above was done using independent students *t* test to compare between two groups and one-way ANOVA was used to compare the significance of difference in all the three

groups. Categorical variables were compared using chi-square/Fisher's exact test. A p value < 0.05 was considered statistically significant.

Results

A total number of 30 male subjects with cryptogenic cirrhosis, 30 with hepatitis B related cirrhosis and 30 age and BMI matched healthy controls were recruited for the study. All hepatitis B related CLD subjects were also on antiviral treatment either with tenofovir for at least 6 months (mean duration of treatment 48±16 months).

Baseline Characteristics and Biochemical Profile in Three Groups

The age and BMI were comparable in all three groups (Table 1). Serum albumin, serum creatinine and serum 25 (OH) vitamin D were significantly lower and serum ALP was significantly higher in the cryptogenic cirrhosis group

Table 1
Baseline Characteristics and Bone Mineral Profile in Cryptogenic Cirrhosis (Group 1), Hepatitis B Related CLD (Group 2) and Age and BMI Matched Controls (Group 3).

Variable	Group 1 Cryptogenic Cirrhosis (Mean±SD) N = 30	Group 2 Hepatitis B cirrhosis (Mean±SD) N = 30	Group 3 Healthy Controls (Mean±SD) N = 30	p Value (ANOVA)	p Value (t-test)
Age (years)	39.3±9.2	39.8± 8.3	39.3±3.5	0.9	group 1&3 – 1.0 group 2&3 – 0.8 group 1&2 – 0.8
BMI (kg/m^2)	23.1 ±3.8	24.8 ± 3.9	23.9±1.5	0.1	group 1&3 – 0.2 group 2&3 – 0.2 group 1&2 – 0.2
Albumin corrected Calcium (mg/dL)	8.7±0.4	8.9 ±0.3	8.8±0.4	0.2	group 1&3 – 0.2 group 2&3 – 0.8 group 1&2 – 0.08
Albumin (g/dL)	3.9±0.8	4.2±0.6	4.9 ±0.3	<0.001	group 1&3 - <.001 group 2&3 - <.001 group 1&2 – 0.1
Phosphorus (mg/dL)	3.3±0.5	3.4 ±0.5	3.5±0.5	0.2	group 1&3 – 0.1 group 2&3 – 0.2 group 1&2 – 0.7
ALP (IU/L)	102.3±35.8	97.9±26.1	82.4±18.2	0.01	group 1&3 – 0.009 group 2&3 – 0.01 group 1&2 – 0.6
Creatinine (mg/dL)	0.8 ±0.1	0.9 ±0.1	0.8±0.1	0.008	group 1&3 – 0.04 group 2&3 – 0.3 group 1&2 – 0.002
25 (OH)Vitamin D (ng/mL)	20.8±9.7	25.4±11.0	30.4±8.6	0.001	group 1&3 - <.001 group 2&3 – 0.06 group 1&2 – 0.09
PTH (pg/mL)	53.8 ±30.9	53.6±28.9	61.8±25.3	0.4	group 1&3 – 0.2 group 2&3 – 0.2 group 1&2 – 0.9
CTX (pg/mL)	554.1 ±233.3	586.0±305.1	507.2±179.5	0.4	group 1&3 – 0.4 group 2&3 – 0.2 group 1&2 – 0.6
P1NP (ng/mL)	82.7±51.9	84.1 ±61.5	62.2±33.8	0.2	group 1&3 – 0.07 group 2&3 – 0.09 group 1&2 – 0.9

Abbr: ALP, alkaline phosphatase; BMI -body mass index; CTX, C-terminal telopeptide of type 1 collagen and serum P1NP , N terminal pro-peptide of type 1 pro-collagen; PTH, parathormone

when compared to healthy controls ($p < 0.05$). Serum albumin was significantly lower and serum ALP was significantly higher in the hepatitis B related CLD group when compared to controls ($p < 0.05$). There was no difference in serum levels of PTH and CTX between the three groups. Sixteen (53%) subjects in the cryptogenic cirrhosis group, twelve (40%) subjects in the hepatitis B related CLD group and five (17%) of the healthy controls were found to have vitamin D deficiency (<20 ng/mL).

TBS and Bone Mineral Density

The trabecular bone score was also significantly lower in the cryptogenic cirrhosis group as compared to other two groups ($p = 0.04$). Bone mineral density was significantly lower ($p < 0.05$) in cryptogenic cirrhosis group at the lumbar spine (LS) and the total hip as compared to age matched healthy controls (Table 2**).** No significant difference was observed in bone mineral density in the hepatitis B related CLD group when compared to age matched healthy controls. Bone mineral density was significantly lower in the cryptogenic cirrhosis group when compared to the hepatitis B cirrhosis group at the total hip ($p = 0.04$) (Table 2**).**

Eleven (37%) subjects in cryptogenic cirrhosis group, two (7%) subjects in hepatitis B related CLD group and five (17%) subjects in healthy control group had low bone mass (Z-score ≤-2.0) at lumbar spine. Three (10%) subjects in cryptogenic cirrhosis, one (3%) subject each in hepatitis B related CLD and healthy controls groups had low bone mass (Z-score ≤-2.0) at hip.

Hip Structural Analysis

The hip structural analysis was done in all study subjects (Table 3) and comparison was made between the three study groups (Cryptogenic cirrhosis, Hepatitis B and control population). Hip geometry was significantly different for most parameters among the three groups (ANOVA $p < 0.01$ for all parameters except NN [CSMI]; FS [CSA] and FS [BR]). On individual group comparisons, it was found that individuals with cryptogenic cirrhosis had a significantly poor hip geometry in all parameters compared to healthy controls ($p < 0.001$, except for FS [BR]); whereas there were no significant differences among the different hip geometry parameters between patients with hepatitis B and controls.

Discussion

This is the first study from South India which looked at the bone health including trabecular bone and proximal hip geometry in male subjects with cryptogenic cirrhosis, hepatitis B related cirrhosis and their age and BMI matched healthy controls. Subjects with cryptogenic cirrhosis had a low TBS indicating deteriorated microarchitecture at spine and lower BMD at both spine and hip when compared to age and BMI matched controls. However there was no difference in BMD (both at LS and hip) between hepatitis B related cirrhosis and age and BMI matched controls. Most components of HSA were significantly affected in subjects with cryptogenic cirrhosis as compared to control subjects. The mean vitamin D level was also low in cryptogenic cirrhosis subjects.

There is minimal published literature on the impact of liver cirrhosis on bone microarchitecture. Moreover, bone microarchitecture in individuals with different etiologies of liver disease and its progression through different stages is not well established. In this study, we found that TBS was significantly more affected in individuals with cryptogenic cirrhosis rather than hepatitis B infected patients. A few previous histomorphometric studies found decreased trabecular bone thickness in patients with cirrhosis *(14,15)* . However, bone biopsy is an invasive procedure and carries risk of infection and trauma,

Table 2
Bone Mineral Density in Cryptogenic Cirrhosis (Group 1), Hepatitis B Cirrhosis (Group 2) and Age and BMI Matched Controls (Group 3).

Variable	Group 1 (Mean±SD) N = 30	Group 2 (Mean±SD) N = 30	Group 3 (Mean±SD) N = 30	*p* value ANOVA	*p* value (t-test)
Lumbar spine BMD (gm/cm^2)	0.875±0.144	0.941±0.135	0.976±0.147	0.02	group 1&3 – 0.009 group 2&3 – 0.3 group 1&2 – 0.07
Hip BMD (gm/cm^2)	0.877±0.104	0.930±0.105	0.966±0.123	0.09	group 1&3 – 0.004 group 2&3 – 0.2 group 1&2 – 0.04
Trabecular bone score (TBS)	1.297±0.099	1.350±0.094	1.351±0.088	0.045	group 1&3 – 0.035 group 2&3 – 0.4 group 1&2 – 0.03

Abbr: ANOVA, analysis of variance; BMD, bone mineral density; TBS, trabecular bone score.

Table 3
Comparison of HSA (Hip Structural Analysis) Parameters Between Cryptogenic Cirrhosis, Hepatitis B and Healthy Controls.

	Group 1 Cryptogenic cirrhosis N = 30		Group 2 Hepatitis B N = 30		Group 3 Controls N = 30		*p* ANOVA	1 vs 2	1 vs 3	2 vs 3
	Mean	SD	Mean	SD	Mean	SD				
NN (CSA)	2.92	0.43	3.09	0.48	3.27	0.48	0.015	0.142	0.004	0.155
NN (CSMI)	2.81	0.59	2.93	0.64	3.15	0.54	0.073	0.442	0.020	0.151
NN (Z)	1.50	0.26	1.64	0.27	1.70	0.25	0.011	0.440	0.003	0.362
NN (BR)	11.13	2.41	10.28	1.76	9.76	1.63	0.028	0.127	0.013	0.245
IT (CSA)	5.01	0.79	5.63	0.85	5.88	0.85	0.001	0.005	0.001	0.276
IT (CSMI)	14.74	3.54	17.30	4.25	18.45	3.32	0.001	0.015	0.001	0.254
IT (Z)	4.23	0.89	5.06	0.99	5.33	0.88	0.001	0.014	0.001	0.061
IT (BR)	8.93	1.51	7.98	1.11	7.79	1.27	0.004	0.034	0.003	0.318
FS (CSA)	4.31	0.65	4.68	0.67	4.75	0.62	**0.23**	0.036	0.010	0.691
FS (CSMI)	3.63	0.90	4.04	1.10	4.25	0.77	0.038	0.127	0.006	0.398
FS (Z)	2.28	0.39	2.53	0.47	2.65	0.38	0.004	0.035	0.001	0.289
FS (BR)	2.80	0.46	2.67	0.49	2.72	0.55	**0.574**	0.272	0.610	0.673

Abbr: ANOVA, analysis of variance; BR, buckling ratio; CSA, cross-sectional area; CSMI, cross-sectional moment of inertia; FS, femoral shaft; IT, inter-trochanteric region; NN, narrow neck; Z, Section modulus.

related to the procedure. Moreover, the information gathered from the bone biopsy at a particular site cannot be extrapolated to other skeletal sites. Trabecular bone score assessment is a novel noninvasive tool to evaluate bone microarchitecture. It is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA (Dual energy x-ray absorptiometry) image. In a study by Wakolbinger et al, it was found that both trabecular and cortical bone microarchitecture is deteriorated in patients with cirrhosis irrespective of the disease severity *(16)*.

In previous studies, the data are heterogeneous with regards to the prevalence of low bone mass in subjects with cirrhosis and it ranges between 16% and 68% in different studies *(8,17,18)*. This difference may be due to a heterogeneous study population with regards to etiology and severity of liver disease and variable definitions being used to define osteoporosis/osteopenia.

The striking finding which we observed was that there was no statistical difference in BMD between hepatitis B related cirrhosis and age and BMI matched controls which was in contrast to previous studies *(19,20)*. This may be attributed to the small sample size in this study, younger age, early cirrhosis (CTP A) and also that our subjects with hepatitis B were on antiviral treatment which could have led to improvement in their BMD, however this need to be proved in larger longitudinal studies. Although cryptogenic cirrhosis subjects were of CTP A status and a younger age, they were found to have more severe bone disease, probably because of lack of specific treatment for the same.

In previous studies, low IGF-1, hypogonadism, increased TNF-α and IL-6 are the other significant risk factors found to be associated with lower BMD in cirrhosis patients *(6,15,21)*. Bone turnover markers, PTH, albumin corrected calcium and phosphorus were comparable in the cirrhosis groups and the control group in our study. Most of the previous studies have reported similar findings *(5,8,15)*.

Hip structural analysis (HSA) has been utilized to calculate bone strength based on measurement of geometric characteristics in the proximal femur *(22)*. There is no information available about proximal hip geometry in subjects with cryptogenic cirrhosis. HSA has been shown to predict the occurrence of hip fractures *(23)*. The three regions assessed in present study were narrow neck (NN), intertrochanteric (IT) and femoral shaft (FS). The evaluation of four parameters included cross sectional area (CSA), cross sectional moment inertia (CSMI), section modulus (Z) and buckling ratio (BR). Low values of CSA, CSMI and Z and a high BR denote poor hip strength and a higher tendency to fracture. In the present study, HSA was significantly affected in subjects with cryptogenic cirrhosis as compared to control subjects probably indicating poor bone strength in them.

In a study of 33 patients with alcoholic liver cirrhosis by Culafic et al *(24)*, it was found that all components of HSA in the neck region were impaired. In subjects with

hepatitis B infection in the current study, these parameters were not deranged probably due to treatment with antiviral medication they received. Although, limited information is available in the literature in this cohort, it has been shown in a study by Byrne et al, untreated hepatitis-B subjects had an increased risk for hip fracture *(25)*.

Subjects with cirrhosis were found to have significantly lower levels of vitamin D and a high prevalence of vitamin D deficiency (40-53%), when compared to healthy controls (17%). A slightly higher prevalence of vitamin D deficiency in cirrhosis has been reported in previous studies *(19,26,27)*. A reduced 25-hydroxylation of vitamin D in liver, lesser exposure to sunlight, malabsorption, and impaired cutaneous synthesis of vitamin D in jaundiced patients are some of the factors which may lead to low vitamin D levels in patients with cirrhosis *(27,28)*. In the present study, all patients with cirrhosis were of CTP stage A (i.e. early disease), which means they may have less impairment of 25 hydroxylation of vitamin D, were more ambulatory and were having normal or only slightly elevated bilirubin levels. Similar to previous studies, these factors can explain the lower prevalence of vitamin D deficiency in present study *(19,29)*.

One of strengths of the present study is that this is the first study from south India, to analyse bone health including trabecular bone score and proximal hip geometry in subjects with cryptogenic cirrhosis. Also, the study population was homogenous in that only male subjects with CTP stage A were recruited and they were also compared with age and BMI matched healthy male subjects. The cross-sectional study design and lack of measurement of IGF-1, testosterone and cytokines which may be associated with low bone mass in cirrhosis, were the limitations of the study.

The findings of this study would help design future long-term studies on bone health and fragility fracture incidence in this cohort of subjects with hepatitis b and cryptogenic cirrhosis. It also emphasises the upcoming utility of HSA in clinical practice, especially in those subjects where BMD is normal. This study also forms a basis to study the impact of anti-osteoporotic treatment in individuals with hepatic osteodystrophy.

In conclusion, subjects with cryptogenic cirrhosis had a low TBS indicating deteriorated microarchitecture at spine and lower BMD at both spine and hip. Most components of HSA were significantly affected in subjects with cryptogenic cirrhosis as compared to subjects with hepatitis-B infection on treatment with antivirals and healthy controls. Vitamin D deficiency was seen in more than two-fifth of the subjects with cirrhosis as compared to one-fifth in healthy controls. This study lays the foundation for conducting future prospective studies to study the fracture risk and the role of anti-osteoporotic treatment in patients with hepatic osteodystrophy secondary to cryptogenic cirrhosis and hepatitis B infection.

Author's Contribution

PT, KEC and NK helped in the study planning, data collection and analysis, literature review, and writing the manuscript. UZ,AG, CEE helped in patient recruitment and data collection. PT,TVP, GR and NT helped in the study planning, literature review, data collection, and writing the manuscript. NK and TVP planned and supervised the study, evaluated patients included in the study, and did literature review and critical revision of the manuscript for important intellectual content. All the authors approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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