Indian J Med Res 158, September 2023, pp 284-291
DOI: 10.4103/ijmr.IJMR_1144_20

Quick Response Code:

Vitamin D status & bone health in patients with liver cirrhosis

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Received April 11, 2020

***Background & objectives*: Vitamin D plays an important role in bone metabolism, and liver is the intermediary site of vitamin D metabolism. The purpose of this study was to study the prevalence of vitamin D deficiency and bone health in patients with cirrhosis.**

***Methods*: Prospectively, serum 25-hydroxy vitamin D [25(OH)D] level were assessed in cirrhotics by chemiluminescence method. Endocrine Society Clinical practice guideline was used to define deficiency and insufficiency of vitamin D. Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry and the World Health Organization criteria was used to define osteoporosis and osteopenia. The lowest T score at the left hip neck or lumbar spine was taken as osteoporosis or osteopenia. The Child-Turcotte-Pugh score was used to assess the severity of cirrhosis.**

***Results*: Cirrhotics (n=350, male: 278, compensated: 210) were included. Mean serum 25(OH)D level was 8.75 ng/ml. The prevalence of vitamin D deficiency (VDD) and low-BMD (osteopenia and osteoporosis) was 89.4 and 86 per cent, respectively. VDD, insufficiency and osteoporosis was found in 86.7, 11.9 and 33.8 per cent, respectively, in patients with compensated cirrhosis; and 93.6, 3.6 and 40 per cent, respectively, in patients with decompensated cirrhosis. Body mass index of >25 kg/m^2 was protective for bone health.**

***Interpretation & conclusions*: VDD and low-BMD is prevalent in Indian patients with cirrhosis and should be looked for in patients with cirrhosis for its prevention.**

Key words Bone mineral density - cirrhosis - osteopenia - osteoporosis - vitamin D

The liver is an intermediary site in the metabolism of vitamin D, where 25-hydroxylation (25-OH) of vitamin D takes place. The liver also synthesizes albumin and vitamin D binding protein (DBP), which is the carrier of vitamin D in blood[1]. Vitamin D plays an important role in calcium and phosphorus homeostasis, and bone remodelling; and it also regulates cellular proliferation, differentiation, apoptosis, angiogenesis and immune function[2]. The vitamin D deficiency (VDD) produces various musculoskeletal symptoms, associated with osteomalacia, osteopenia and osteoporosis, and increased risk of falls and fracture in the general population[2]. The prevalence of VDD in India varies from 70 to 91 per cent in healthy adults

despite enough exposure to sunlight throughout the year[3,4].

Patients with cirrhosis are at increased risk for VDD and one of the contributing factors of metabolic bone disease (MBD)[1]. The prevalence of osteoporosis in patients with cirrhosis is estimated to be 12-47 per cent[5,6]. Only a few studies evaluated VDD among Indians with cirrhosis which reported the estimated prevalence between 35 to 92 per cent[7,8]. The prevalence of low bone mineral density (BMD) and osteoporosis in Indian patients with cirrhosis was reportedly 68 to 97 per cent[7] and 38.2 per cent[8], respectively, however both the studies had a low sample size[7]. VDD, low BMD along with the associated risk of fractures has been shown to be one of the contributors of increased morbidity and mortality, thus further decreasing the quality of life of cirrhotic patients[9].

So far there is limited literature available on VDD and bone health in cirrhosis from India. Hence, this study was undertaken to estimate the prevalence of VDD and bone health and the associated risk factors with low bone health in Indian patients with cirrhosis.

Material & Methods

This cross-sectional study was conducted at the department of Gastroenterology and Human Nutrition Unit, All India Institute of Medical Sciences, New Delhi, between August 2012 and July 2016. Individuals between 18-65 yr, presenting to the gastroenterology OPD and liver clinic with cirrhosis were enrolled in this study. Written informed consent was obtained from all the participants. The study was approved by the Institutional Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Exclusion criteria: Participants who were taking vitamin D or multivitamin supplementation four weeks at the time of enrolment, were excluded from the study. Furthermore, those with Cushing's syndrome, malignancy, severe cardiovascular, pulmonary and renal disease, pregnant or lactating women, with a history of immobilization or fracture in the past, known cases of osteopenia or osteoporosis, women with surgical menopause, and those receiving drugs which were likely to affect BMD were excluded.

Participant characteristics and demography: Demographics, aetiology of liver disease and nutritional assessment data were collected for each participant. For nutritional assessment, estimated dry weight (kg) was calculated using either the post paracentesis body weight or scale weight minus ascites weight based on severity (mild, 5%; moderate, 10% and severe, 15%). An additional five per cent was subtracted if bilateral pedal oedema was present. Body mass index (BMI) was calculated using estimated dry weight divided by height (kg/m^2)[10].

The aetiological work up of the cirrhosis included-hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-liver-kidney microsomal antibody (anti-LKM), serum ceruloplasmin and copper estimation, serum ferritin, lipid profile, transient elastography and whenever required liver biopsy were done. The diagnosis of cirrhosis was made based on the combination of clinical, endoscopic and radiological criteria. In some cases, for confirmation (such as autoimmune hepatitis, overlap syndrome and Wilson's disease), prognostication and also for diagnosis, particularly in cryptogenic cirrhosis liver biopsy was done. Alcohol was considered the cause of cirrhosis if the patients regularly consumed ≥80 g/day (for men) and ≥40 g/day (for women) of alcohol for ≥5 yr. The clinical staging of cirrhosis was assessed using Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD). The participants were categorized into two groups, *i.e*. compensated cirrhosis (CTP A) and decompensated cirrhosis (CTP B and CTP C).

Vitamin D estimation: Serum 25(OH)D levels were used to estimate VDD. At enrolment of the patients, 3 ml venous blood sample was collected from cubital fossa and centrifuged immediately, and sera were kept at −80°C for the estimation of vitamin D level. Serum vitamin D level was estimated using the chemiluminescence method (Liaison, DiaSorin USA). Serum 25(OH)D level <20 ng/ml was considered deficient, whereas serum level between 21 and 29 ng/ml and 30-100 ng/ml was considered insufficient (VDI) and sufficient, respectively[11].

Dual energy X-ray absorptiometry (DEXA) was used to assess bone health after paracentesis in patients with ascites. It was assessed at three sites, *i.e*. lumbar spine (L1-L4, total), left hip and left forearm. The same machine DEXA (QDR 4500 Acclaim series, Hologic Inc., Waltham, MA, USA) and the same software were used for the estimation and analysis of BMD in all the patients. Low BMD was defined as osteopenia or osteoporosis depending on the T score measurement

by the DEXA scan. The worst value at lumbar spine [total (L1- L4)] or left hip neck was taken to define osteopenia or osteoporosis. Normal T score was considered between +2.5 to −1, inclusive; osteopenia (−1 and −2.5); osteoporosis (<−2.5) and severe osteoporosis (<−2.5 and fragility fracture) according to World Health Organization (WHO) criteria[9].

The estimation of sample size for the prevalence of VDD was calcualted assuming a prevalence of VDD as 71 per cent where vitamin D levels are <20 ng/ml[11,12] the required sample size was 330 participants. For the prevalence of low BMD, assuming the prevalence of low BMD as 68 per cent[8], the required sample size was 350 participants. A five per cent margin of error and a 95 per cent level of confidence was considered while calculating the sample size. Hence, 350 participants were enrolled in the study for the prevalence of VDD and low BMD.

Statistical analysis: Data were analyzed using statistical software STATA version 14.0 (STATA Corp., TX, USA). The data were expressed as mean ± standard deviation or median (min-max). The normality of data was checked using summary measure information and drawing histograms for variables to be studied. The categorical data were expressed as percentages and Chi-square/Fisher's exact test was used to see the association between two groups. The variables following normal distribution was compared by using an independent t test. Mann-Whitney U test was used to compare the values of non-normal data. Relationship between vitamin D levels and BMD was assessed using Pearson's correlation. Univariate and multivariate logistic regression analysis was used to estimate odds and adjusted odds ratio, respectively. Those variables found significant in univariate analysis and having clinical importance (P<0.10) were included in multivariate analysis as well. P<0.05 was considered as significant. Stepwise multivariable logistic regression was used to find independently associated factors for low BMD.

Results

Of the 575 participants with cirrhosis screened for the study, 225 were excluded as per the exclusion criteria: <18 yr, >65 yr (n=14), those taking vitamin D or multivitamin supplementation ≤4 wk before enrolment (n=131), malignancy (n=9), severe cardiovascular disease (n=7), chronic kidney disease (n=12), pregnant or lactating women (n= 9), those with a history of immobilization in the past and known cases of osteopenia or osteoporosis (n=4), women with surgical menopause (n=5) and those receiving drugs (steroids, calcium supplements) which are likely to affect BMD (n=16), those who refused to participate (n=18).

A total of 350 participants (278 males and 72 females, mean age 43.7±11.8 yr) with liver cirrhosis were finally enrolled in this study. The aetiology of cirrhosis was viral (45.7%), cryptogenic (27.1%), alcohol (20.3%) and miscellaneous (7.1%). The demographic and biochemical profiles of compensated (n=210) and decompensated (n=140) cirrhosis are presented in Table I. Serum protein, albumin and calcium (values being similar to corrected calcium) were significantly lower, whereas bilirubin, aspartate aminotransferase (AST) and alkaline phosphatase were significantly higher in the decompensated group as compared to compensated cirrhosis.

Vitamin D deficiency (VDD): The mean serum 25(OH)D level was 8.75, 9.45, and 7.25 ng/ml in all the participants, compensated and decompensated groups, respectively (Table I). No significant difference was noted in the mean serum 25 (OH)D level in the compensated and decompensated groups (P=0.07). VDD was observed in 313/350, 89.4 per cent [95% confidence interval (CI): 85-92%] of the participants and VDI was found in 8.6 per cent (95% CI: 5-12%) of the participants. VDD and VDI were found in 86.7 and 11.9 per cent, respectively, in patients with compensated cirrhosis; whereas in patients with decompensated cirrhosis, VDD and VDI were found in 93.6 and 3.6 per cent, respectively. On grouping patients into normal and insufficiency (≥20 ng/ml) and deficiency (<20 ng/ml) vitamin D levels, a higher number of patients had lower vitamin D levels with decompensated liver disease (Table I).VDD was also assessed using the Institute of medicine cut-off and it was observed in 225/350 (64.3%) of the patients and VDI was found in 25.1 per cent of patients.

Bone mineral density (BMD) in cirrhotic patients and its predictors: BMD was similar in both compensated and decompensated cirrhosis at any site, *i.e*. lumbar spine (P=0.22), left hip neck (P=0.52) and total forearm (P=0.09) (Table II). Overall, osteoporosis and osteopenia were found in 36.3 per cent (95% CI: 31-41%) and 49.7 per cent (95% CI: 44-55%) of patients, respectively, with no difference between compensated and decompensated groups (Table III). There was no association between serum 25(OH)D

Table I. Comparison of demographics, clinical and biochemical parameters between individuals with compensated and decompensated cirrhosis

Parameters	Total (n=350)	Compensated cirrhosis (n=210)	Decompensated cirrhosis (n=140)
Age (yr)[$]	43.7±11.8	44.3±11.9	42.9±11.8
Gender (male:female)	278:72	160:50	118:22
Aetiology[***]			
Viral[@]	160 (45.7)	104 (49.5)	56 (40)
Alcohol[@]	71 (20.3)	28 (13.3)	43 (30.7)
Cryptogenic[@]	95 (27.1)	60 (28.6)	35 (25)
Others[@]	24 (6.9)	17 (8.1)	7 (5)
Duration of disease (months)[#]	32 (1-312)	33 (1-312)	25 (1-219)
BMI (kg/m^2)[$]	22.7±4.1	22.9±4.1	22.4±4.2
Bilirubin (mg/dl)[#]	1.2 (0.19-11.7)	0.9 (0.2-6.9)	1.2 (0.19-11.7)[***]
Total protein (g/dl)[$]	7.3±0.6	7.4±0.5	7.1±0.8[***]
Albumin (g/l)[$]	3.8±0.7	4.2±0.56	3.3±0.71[***]
AST (IU)[#]	48 (12-286)	43 (15-227)	62 (12-286)[***]
ALT (IU)[#]	38 (9-219)	38 (9-168)	40 (9-219)
ALP (IU)[#]	265 (12-1288)	260 (12-943)	283 (61-1288)[***]
Blood urea (mg/dl)[#]	23 (3.1-129)	23 (10-98)	22 (3.1-129)
Creatinine (mg/dl)[#]	0.8 (0.1-5)	0.8 (0.1-3.1)	0.8 (0.4-5)
Calcium (mg/dl)[$]	8.5±0.8	8.7±0.8	8.2±0.8[***]
Phosphorous (mg/dl)[$]	3.4±0.7	3.4±1	3.4±0.7
Vitamin D status[δ,**]			
Serum 25(OH) D (ng/ml)[#]	8.75 (2-59.9)	9.45 (2-59.9)	7.25 (2-55.2)
Deficiency (<20 ng/ml)[@]	313 (89.4)	182 (86.7)	131 (93.6)
Insufficiency (21-29) ng/ml[@]	30 (8.6)	25 (11.9)	5 (3.6)
Normal (30-100 ng/ml)[@]	7 (2)	3 (1.4)	4 (2.9)

P [**]<0.01, [***]<0.001. Data expressed as [@]n (%), [$]mean±SD and [#]median (minimum-maximum). [δ]*P* value when patients were grouped into two groups [Normal and Insufficiency serum 25(OH) D (≥20 ng/ml) *vs*. 25(OH) D deficiency (<20 ng/ml)]. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index

Table II. Bone mineral density (g/cm^2) at different sites in individuals with cirrhosis

Site	Total (n=350)	Compensated cirrhosis (n=210)	Decompensated cirrhosis (n=140)
Lumbar spine [total (L1-L4)]	0.859±0.138	0.866±0.144	0.848±0.129
Left hip neck	0.708±0.121	0.706±0.123	0.712±0.119
Total forearm	0.549±0.079	0.544±0.079	0.555±0.079

and low-BMD at any site, *i.e*. lumbar spine (*P*=0.38) and left hip (*P*=0.36). In univariate analysis, BMI and serum albumin was associated with the presence of low BMD (Table IV). On multivariable logistic regression analysis, BMI>25 kg/m^2 was found to be protective for low BMD in patients with cirrhosis. Age was a confounder between the BMI and low bone health, however, in the stepwise logistic regression model including age; it was not an independently associated factor. No factors are responsible for the prediction of VDD in this cohort.

Discussion

This study shows the prevalence of VDD (89.4%) and low BMD (86%) in individuals with cirrhosis in India. This study gains significance firstly, because of

Table III. Prevalence of low bone mineral density in individuals with cirrhosis (n=350)

DEXA scan (T score)*	Total (n=350), n (%)	Compensated cirrhosis (n=210), n (%)	Decompensated cirrhosis (n=140), n (%)
Normal (+2.5 to−1)	49 (14)	31 (14.8)	18 (12.9)
Osteopenia (−1 to−2.5)	174 (49.7)	108 (51.4)	66 (47.1)
Osteoporosis (>−2.5)	127 (36.3)	71 (33.8)	56 (40)

*Worst value at the lumbar spine [total (L1- L4)] or left hip neck was taken to define osteopenia/osteoporosis. DEXA, dual-energy X-ray absorptiometry

the large number of study participants included; and secondly inclusion of varied aetiology of the cirrhosis, which is a common scenario seen in most of the gastroenterology OPDs. All the three studies included different etiological groups; however, had a small sample size. The prevalence of VDD (89.4%) in the present study is comparable with the prevalence of VDD (70 to 91%) in the Indian healthy population[3,4]. Our results are similar to other studies, where high prevalence of VDD was reported in individuals with cirrhosis[13-16]. VDD was found in 35 and 92 per cent of individuals with cirrhosis from western and northern India, respectively[7,8]. Another Indian study showed 80 per cent of cirrhotics had some form of vitamin D inadequacy and it is more common in cirrhotics as compared to their healthy relatives[17]. Studies have shown that VDD is more common in cirrhotics *vs.* non-cirrhotics, and in cirrhosis, as CTP increases there is more chance of VDD[13,14,18]. In the present study also decompensated cirrhosis had significantly lower vitamin D levels as compared to compensated cirrhosis. VDD also impacts mortality in cirrhotics as compared to non-cirrhotics in critically ill individuals[19] and is associated with increased mortality in individuals with VDD as compared to no VDD in cirrhotics[18]. VDD can be multifactorial in cirrhosis. Liver produces 25-hydroxy vitamin D which is a precursor to metabolically active vitamin D, *i.e.* 1,25, dihydroxyvitamin D. Those with impaired liver function will also have impaired synthesis of vitamin D, leading to VDD. Cirrhotic patients have low appetite, decreased oral intake and impaired absorption due to portal hypertension and ascites, leading to VDD in cirrhosis.

The prevalence of MBD and low BMD varied across different studies due to diverse population groups and varied selection criteria of the study participants. In cirrhotic individuals, the prevalence of osteoporosis ranged from 11.5 to 55 per cent, varying in different aetiological subgroups[5,20]. A study by Gallego-Rojo *et al*[20] included only viral aetiology with only 32 participants and osteoporosis was measured with Z score, whereas the study by Sokhi *et al*[5] included mixed etiological cirrhosis with 104 patients, awaiting liver transplant. In a large study of 406 cirrhotic individuals, 56 per cent of participants had hepatic osteodystrophy and 80 per cent had some form of vitamin D inadequacy[21]. Initially, it was opined that only cholestatic liver disease has a risk of developing MBD; however, subsequent studies showed that MBD is equally prevalent in non-cholestatic cirrhosis, too[7,9,22]. Our study showed osteoporosis in 36 per cent and osteopenia in 49 per cent, and BMD being similar in compensated and decompensated cirrhosis, which is in concordance with other studies which show that the severity of liver disease does not affect the MBD[7,21]. Nevertheless, other studies have shown that the severity of liver disease affects the MBD[5,20]. In another study from north India, osteopenia and osteoporosis were found in 57 and 38 per cent participants respectively[7], which is similar to our study. This study has an importance bearing that more than two-thirds of all patients have some form of MBD.

Various studies have shown that age, previous fragility fracture, oral glucocorticoid therapy (>5 mg for three months), BMI (<19 kg/m^2), alcohol intake (>3 units/day), maternal history of hip fracture, poor nutrition, smoking history, hypogonadism are the risk factors for MBD[22,23]. Other important factors which play a role in low BMD in cirrhosis is increased inflammatory mediators TNF-alpha and IL-6 and decreased level of IGF-1, which prevent bone loss[8,24]. The possible factors for the high prevalence for VDD and MBD are usually multifactorial in Indian patients: dusky skin colour, more indoor activity, poor nutritional status, poor calcium intake, malabsorption, high ambient air pollution[3,25-27].

In univariate analysis, low albumin was a risk factor for low BMD, but in multivariable logistic regression analysis, it was not predictive of low BMD in our study. However, in multivariable logistic regression analysis, high BMI was shown

Table IV. Variables associated with low bone mineral density

Parameter	Normal, n (%)	Low BMD, n (%)	OR (95% CI)	
			Univariate analysis	Multivariate analysis
Gender				
Male	43 (15.46)	235 (84.53)	1	-
Female	6 (8.33)	66 (91.66)	1.99 (0.81-4.89)	-
BMI (kg/m^2)				
<18.5	6 (8.45)	65 (91.55)	1.40 (0.54-3.61)	1.35 (0.52-3.5)
18.5-25	22 (11.46)	170 (88.54)	1	1
>25	21 (24.71)	64 (75.29)***	0.39 (0.2-0.76)	0.38 (0.19-0.75)***
Duration of illness (yr)				
<5	40 (16.26)	206 (83.74)	1	-
5-10	6 (7.59)	73 (92.41)	2.36 (0.96-5.8)	-
>10	3 (12)	22 (88)	1.42 (0.4-4.98)	-
Aetiology				
Viral	21 (13.13)	139 (86.88)	1	-
Alcohol	14 (19.72)	57 (80.28)	0.61 (0.29-1.29)	-
Cryptogenic	9 (9.47)	86 (90.53)	1.44 (0.63-3.29)	-
Others	5 (20.83)	19 (79.16)	0.60 (0.2-1.78)	-
CTP class				
A	31 (14.76)	179 (85.24)	1	-
B	15 (12.5)	105 (87.5)	1.29 (0.62-2.34)	-
C	3 (15)	17 (85)	1.03 (0.28-3.73)	-
MELD				
<15	41 (14.34)	245 (85.66)	1	-
≥15	8 (12.5)	56 (87.5)	1.19 (0.53-2.68)	-
Protein (g/dl)				
≥6.6	44 (14.38)	262 (85.62)	1	-
<6.6	5 (11.36)	39 (88.64)	1.30 (0.48-3.5)	-
Albumin (g/dl)				
≥4.0	27 (18.12)	122 (81.87)	1	-
<4.0	22 (10.94)	179 (89.05)	1.79 (0.97-3.29)	1.84 (0.99-3.42)
AST (IU)				
Up to 50	31 (16.66)	155 (83.33)	1	-
>50	18 (10.98)	146 (89.02)	1.61 (0.86-3)	-
ALT (IU)				
Up to 50	33 (13.31)	215 (86.69)	1	-
>50	16 (15.69)	86 (84.31)	0.82 (0.43-1.57)	-
ALP (IU)				
Up to 240	25 (18.38)	111 (81.61)	1	-
>240	24 (11.21)	190 (88.79)	1.76 (0.96-3.24)	-
Calcium (mg/dl)				
≥8.1	36 (14.63)	210 (85.36)	1	-

Contd...

Parameter	Normal, n (%)	Low BMD, n (%)	OR (95% CI)	
			Univariate analysis	Multivariate analysis
<8.1	13 (12.5)	91 (87.5)	1.19 (0.6-2.35)	-
Phosphorous (mg/dl)				
≥2.5	45 (14.15)	273 (85.84)	1	-
<2.5	4 (12.5)	28 (87.5)	1.14 (0.38-3.43)	-
25(OH) D (ng/ml)				
≥20	4 (10.81)	33 (89.19)	1	-
<20	44 (14.05)	269 (85.94)	0.72 (0.24-2.15)	-

$^{***}P<0.001$. CI, confidence interval; CTP, Child-Turcotte-Pugh; MELD, model for end stage liver disease; OR, odds ratio

to be protective, and similar results have also been reported in a meta-analysis[28]. VDD did not emerge as a risk factor predicting low BMD in our study, possibly due to the high prevalence of vitamin D in the general population and the multifactorial mechanism of low BMD in cirrhosis. Several studies reported no significant correlation between serum vitamin D level and MBD[7,20,21]. Another study had shown that female gender and VDD as risk predictors of low-BMD[29]. A recent randomized control trial did not show the benefit of vitamin D supplementation for one year in improving BMD even though vitamin D levels improved[30]. A few limitations of this study included (*i*) signs and symptoms of specific vitamin deficiency were not specifically looked into because of masking of many signs and symptoms due to ascites and malnutrition, (*ii*) there were no matched controls, and (*iii*) endocrine society cut-offs were used for diagnosing VDD, which might have overestimated the VDD, as compared to Institute of Medicine cut-off.

Overall, this study shows that VDD is prevalent in individuals with cirrhosis and hence individuals with cirrhosis should be screened for VDD and MBD. In clinical settings, vitamin D should be supplemented in deficient patients with cirrhosis. Rather, other antiresorptive therapy for improving BMD should be explored in future clinical trials. However, the extraskeletal benefit of vitamin D supplementation should not be discounted and should be looked at in further studies in a patient with cirrhosis. In conclusion, VDD and low BMD are prevalent in patients with cirrhosis and should be looked for in patients with cirrhosis for its prevention.

***Acknowledgment*:** The authors acknowledge Dr Ravinder Goswami, Professor, Department of Endocrinology and Metabolism, AIIMS, New Delhi, for his continuous intellectual input in conducting this study.

***Financial support & sponsorship*:** This study was financially supported by the Indian Council of Medical Research, New Delhi, India (Grant no. 5/9/1074/2012-NUT) .

***Conflicts of Interest*:** None.

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