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An Observational Study on the Influence of Chronic Liver Disease on Bone and Calcium Metabolism in Indian Patients

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ABSTRACT
Chronic liver disease (CLD) impacts the metabolism of other organs such as bones. The prevalence of hepatic osteodystrophy varies from 13% to 70% in Western countries and is even higher, ranging from 68% to 95%, in India. Studies on serum 25(OH)D concentrations and their correlation with liver disease progression have yielded inconsistent results. Limited studies in Central India have explored the impact of CLD on bone mineral homeostasis. Against this backdrop, this study aims to elucidate the effects of CLD and its severity on various bone mineral metabolism parameters. A cross-sectional study was conducted at a tertiary care hospital in Central India. The study included 123 cases with confirmed CLD and 123 age- and sex-matched controls selected from the OPD patients. Serum levels of calcium, inorganic phosphate, 25(OH) vitamin D and intact parathyroid hormone (iPTH) were measured. The severity of the disease was graded using the Child-Pugh-Turcotte score. Patients with CLD exhibited significantly lower serum calcium and 25(OH)D levels, while serum iPTH levels were significantly higher compared to controls. Regular monitoring of serum calcium, inorganic phosphate and 25(OH)D levels should be integral in CLD patients to facilitate timely interventions for optimal management.

INTRODUCTION

Chronic liver disease (CLD) is characterized by the gradual deterioration of essential liver functions, including the synthesis of clotting factors and proteins, detoxification of metabolites and bile excretion, persisting for >6 months. This process involves a continuum of inflammation, tissue destruction, regeneration of liver cells, ultimately leading to fibrosis and cirrhosis of the liver. Cirrhosis, the most severe consequence of CLD, resulted in over a million deaths in 2010, contributing significantly to the estimated 1.03 million deaths globally attributed to liver disease each year[1,2].

CLD significantly impacts the Calcium-parathyroid hormone (PTH)-vitamin D axis, leading to abnormalities in bone metabolism. Hepatic osteodystrophy prevalence rates range widely, from 13% to 70% in Western populations, with higher rates of 68% to 95% reported in India[3-6]. However, previous studies have provided inconsistent data on the prevalence of abnormal serum concentrations of 25-hydroxyvitamin D (25(OH)D) and its correlation with liver disease progression. Some studies have observed a decline in 25(OH)D levels as liver disease advances[7-12], while others have found no significant differences among cirrhotic patients, non-cirrhotic patients, or different Child-Pugh groups[8,13,14]. Additionally, there is a lack of research in Central India regarding the impact of CLD on bone mineral homeostasis.

Against this backdrop, our study aimed to assess serum calcium, inorganic phosphate (PO4), as well as regulatory hormones of bone metabolism such as intact parathyroid hormone (iPTH) and 25(OH)D levels in patients with diverse etiologies of chronic liver disorders treated at a tertiary care hospital in Central India. Furthermore, we aimed to elucidate the effects of CLD severity based on the Child-Pugh Turcotte (CTP) score on bone mineral metabolism.

MATERIALS AND METHODS

An observational cross-sectional study was conducted at a tertiary care hospital in Central India. The study included 123 participants with CLD and 123 age and sex-matched volunteers with similar demographic and socioeconomic status were chosen as controls. Participants aged 21-70 years who provided consent were included. They had diverse CLD etiologies such as autoimmune hepatitis, cryptogenic cirrhosis, hepatitis B, hepatitis C, NAFLD (non-alcoholic fatty liver disease), primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease. The Child-Pugh score, ranging from 5-15, was determined using five parameters (albumin, ascites, bilirubin, encephalopathy, prothrombin time).

Patients who refused consent, had acute exacerbations of CLD, recent gastrointestinal bleeding or intestinal resection, acute renal failure, chronic disorders affecting mineral metabolism, or were on medications affecting bone turnover were excluded. Control group participants with metabolic bone disease, current medications influencing bone turnover, or recent fractures were also excluded.

Blood samples were collected aseptically after a 12-hour overnight fast and centrifuged for serum extraction. Biochemical analyses included serum bilirubin, liver enzymes, albumin, alkaline phosphatase, prothrombin time, calcium, phosphorus, parathyroid hormone (assayed using chemiluminescence immunoassay) and vitamin D (assayed using ELISA).

RESULTS AND DISCUSSIONS

Comparison between cases and controls based on basic demographic characteristics showed that they were age and sex-matched to the best extent possible. However, significant differences were observed in serum calcium, serum 25(OH) vitamin D and serum intact parathyroid hormone (iPTH) levels between CLD patients and controls (Table 1). Further categorization of cases based on disease severity using the Child-Pugh-Turcotte score (mild: Class A, moderate: Class B, severe: Class C) revealed a progressive decrease in serum calcium and serum 25(OH) vitamin D levels as CLD severity increased. Conversely, serum iPTH levels showed a significant increase with worsening liver disease severity (Table 2).

Correlation analysis between these parameters yielded varying results. Strong positive correlations were observed among serum calcium, phosphate and 25(OH) vitamin D levels. In contrast, serum iPTH exhibited a negative correlation with serum calcium, phosphate and 25(OH) vitamin D levels (see Table 3).

The study findings revealed a notable prevalence of hypocalcemia and Vitamin D deficiency among patients with CLD. Further analysis demonstrated a strong correlation between the severity of hypovitaminosis D and hypocalcemia with higher CTP scores, indicating a significant dysregulation of the Calcium-PTH-Vitamin D axis. Additionally, elevated levels of serum intact parathyroid hormone (iPTH) were observed in patients with hypovitaminosis D, further emphasizing the dysregulation of this axis[8-10].

The impairment in alpha hydroxylation of Vitamin D by the kidney in CLD is attributed to a decline in the primary substrate for this enzyme, 25-hydroxy Vitamin D, produced by the liver. The liver plays a crucial role in synthesizing Vitamin D carrier proteins and is fundamental in Vitamin D metabolism. Studies, such as the one by Bikle *et al*., suggest that while low levels of total vitamin D may not affect biological activity when normal levels of unbound Vitamin D are maintained, Vitamin D-binding protein (DBP) has excess capacity to bind with Vitamin D, even with a 50% reduction in DBP

Table 1: Demographic and baseline parameters in cases and controls

Parameter	Cases (123) Mean±SD	Controls (123) Mean±SD	p-value
Age	54.3±5.4	52.7±5.6	0.12
Gender Ratio(female:male)	1.53:1	1.74:1	0.62
Total protein (mg/dL)	5.0±0.85	7.2±0.78	<0.05
Albumin (mg/dL)	2.95±0.81	4.02±0.35	<0.05
Total bilirubin (mg/dL)	2.93±1.55	0.47±0.11	<0.05
ALP	374.8±24.3	85.8±13.2	<0.05
SGPT	156.5±34.2	27.5±2.5	<0.05
SGOT	131.8±10.4	25.5±2.7	<0.05
PR-INR	2.04±0.56	0.81±0.16	<0.05
25(OH)Vit D	16.66±6.43	53.9±7.5	<0.05
iPTH	92.0±30.81	34.1±5.2	<0.05
Calcium (mg/dL)	8.2±0.27	9.5±0.25	<0.05
Inorganic phosphorus (mg/dL)	2.56±0.47	3.4±0.39	<0.05

Table 2: Comparison of bone mineral metabolism variables

Parameters	CPT A (n=41)	CPT B (n=41)	CPT C (n=41)	p-value
25(OH)Vit D (ng/mL)	23.8±1.05	17.9±2.21	9.10±2.59	<0.05
iPTH (pg/mL)	55.45±13.63	93.02±9.08	125.6±9.78	<0.05
Calcium (mg/dL)	8.28±0.15	8.06±0.17	7.75±0.18	<0.05
Inorganic phosphorus (mg/dL)	3.10±0.20	2.44±0.21	2.01±0.23	<0.05

Table 3: Pearson correlation (r values) between biochemical parameters in cases

Parameters	Calcium (mg/dL)	Phosphorus (mg/dL)	25(OH)Vit D (ng/mL)	iPTH (pg/mL)
Calcium (mg/dL)	-	0.75	0.78	-0.82
Phosphorus (mg/dL)	0.75	-	0.84	-0.85
25(OH)Vit D (ng/mL)	0.78	0.84	-	-0.89
iPTH (pg/mL)	0.82	-0.85	-0.89	-

levels not significantly reducing Vitamin D levels[13]. This may explain why decreasing serum 25(OH)D levels are predominantly seen in advanced liver disease when this capacity is fully depleted.

The study's findings align with recent research by Narayanasamy *et al*., reporting hypocalcemia in 85.59% of CLD patients and a prevalence of 69.3% in Vitamin D deficient patients[7]. Similar results were observed in studies by Jamil *et al*., which showed a negative correlation between Vitamin D levels and CTP scores, as well as higher iPTH levels in CLD patients[14]. Interventional studies providing Vitamin D/Calcium supplements to CLD patients have yielded conflicting results, with some studies showing no delay in osteoporosis progression or increase in bone mineral density (BMD), while others observed an increase in BMD after Vitamin D supplementation[15-20].

Besides musculoskeletal manifestations like hepatic osteodystrophy, Vitamin D deficiency contributes to early decompensation and increased mortality rates in CLD patients[21]. Proper Vitamin D replacement has shown potential in improving functional status, prognosis and long-term morbidity in liver disease patients[22]. Therefore, addressing this deficiency promptly is crucial for the benefit of CLD patients. In summary, Vitamin D deficiency and hypocalcemia are prevalent in the CLD population, with hypovitaminosis D correlating with higher CTP scores. These findings underscore significant dysregulation in the Calcium-PTH-Vitamin D axis in CLD and highlight the importance of addressing these imbalances in patient management.

CONCLUSION

The study findings reveal that a significant proportion of CLD patients exhibit hypovitaminosis D, with declining levels as the disease progresses. This is particularly significant in regions like ours, where Vitamin D deficiency is prevalent. Insufficient calcium and Vitamin D in CLD patients contribute to secondary hyperparathyroidism, often leading to osteoporosis development. Based on these results, routine measurement of serum 25-hydroxyvitamin D (25(OH)D) and calcium levels is recommended for CLD patients. Adequate Vitamin D supplementation should be initiated as part of the therapeutic approach to manage these patients effectively.

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