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Original Article

Impact of Chronic Liver Disease on Serum Vitamin D and Calcium Levels: A Comparative Study

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Abstr act

Background: Chronic liver disease (CLD) is associated with various metabolic disturbances, including abnormalities in vitamin D and calcium homeostasis. The impairment of liver in CLD can lead to significant deficiencies. This study evaluates the serum levels of vitamin D and calcium in CLD patients and their association with disease severity.

Methods: This observational cross-sectional study was carried out from November 2012 to November 2013 at the Department of Gastroenterology, in BSMMU, Dhaka, with a sample size of 60 participants in each group. Data were entered into statistical software (SPSS version 22) for analysis, with categorical variables analyzed using the Chi-square test and a p-value of <0.05 considered statistically significant.

Results: The study assessed 30 CLD patients and 30 healthy individuals, revealing that 70% had decompensated cirrhosis (CTP B/C), with hepatitis B as the leading cause (43.3%). CLD patients had significantly lower serum albumin, calcium, and platelet counts (p<0.05), with 63.3% showing vitamin D deficiency (p=0.007) and 83.3% having low calcium levels (p<0.001). Vitamin D levels declined with worsening liver disease (p=0.009), while calcium levels were lower in advanced CTP classes but not statistically significant (p=0.276).

Conclusion: This study showed a high prevalence of vitamin D deficiency in patients with advanced chronic liver disease. Vitamin D levels inversely correlate with the Child-Turcotte-Pugh classes. Serum calcium level is also found to be low in these patients.

Keywords: Chronic Liver Disease, Vitamin D, Calcium, Child-Turcotte-Pugh Class

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Introduction

CLD is the process of long-term progressive destruction and regeneration of the liver. CLD leads to hepatic fibrosis (scarring) and cirrhosis.[1] Cirrhosis is the final stage of chronic inflammation in the liver. Liver cirrhosis is responsible for portal hypertension and complications such as bleeding oesophageal varices, ascites, and encephalopathy. A child´s grade is used to evaluate hepato-cellular function in cirrhosis based on these factors.[2] CLD is progressive, indolent, and has many complications. However, with the development of modern treatment modalities for cirrhosis of liver life span is increased. With the effective treatment long-term complications are now encountered. Metabolic bone disease occurring in patients with cirrhosis, known as hepatic osteodystrophy, covers both osteomalacia and osteoporosis.[3] It is a common complication among individuals with long-standing hepatic disease. Vitamin D has a role in the regulation of cell proliferation and differentiation.[4] Vitamin D from the skin and diet is hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D]. 25-(OH)D is the major circulating form of vitamin D. It is used to determine a patient's vitamin D status.[5] There are several causes for the deficiency of vitamin D in chronic liver disease. The important potential mechanisms are reduced exogenous exposure, intestinal malabsorption, reduced endogenous production of vitamin D binding protein and albumin in the liver, impaired hepatic hydroxylation of vitamin D to 25(OH) D, and increased catabolic removal of 25(OH) D .[6] Vitamin D is a fat-soluble vitamin and helps in the absorption of calcium from the renal tubule and intestine. Up to 93% of patients with chronic liver disease have insufficient vitamin D levels, with nearly one-third of them exhibiting severe deficiency .[7] Vitamin D3 is primarily acquired endogenously through the photochemical conversion of 7-dehydrocholesterol to pre-vitamin D3 in the skin. Then it is transported to the liver and bound to vitamin D- binding protein. Vitamin D2, following ingestion incorporated into micelles. Then, it is further incorporated into chylomicrons via enterocyte absorption. After that, vitamin D2 reaches the liver via portal circulation for hydroxylation. After hydroxylation, it is converted to 25- hydroxyvitamin D (25(OH) D) and secreted in the circulation again mostly bound to DBP. Further hydroxylation to 1, 25-dihydroxivitamin D in the kidney converts the vitamin into its active form.[8] 25(OH) D is the only vitamin D metabolite that is used to determine whether a patient is vitamin D deficient, sufficient or intoxicated. 25(OH) D is the major circulating form of vitamin D that has a half-life of approximately 2-3 weeks [9]. This study intended to compare the level of serum vitamin D and calcium among patients with CLD with healthy individuals.

Methods

This observational cross-sectional study was carried out from November 2012 to November 2013 at the Department of Gastroenterology, in BSMMU, Dhaka, with a sample size of 60 participants in each group. The sampling technique used in this study was non-probability consecutive sampling. The study aimed to assess the vitamin D and calcium levels in patients with (CLD) (n=30) and compare them with a healthy control group (n=30). Non-probability consecutive sampling was adopted for participant selection, with CLD patients diagnosed based on clinical, laboratory, and ultrasonographic findings. The diagnosis of cirrhosis was confirmed using the Child-Pugh scoring system. The control group consisted of healthy subjects with no known renal, endocrine, or liver disease. Serum 25(OH)D levels were categorized into deficiency (<20 ng/ml), insufficiency (21-29 ng/ml), and sufficiency (≥30 ng/ml), while serum calcium levels below 2.12 mmol/L were considered low. Ethical clearance was taken from the concerned authority and written informed consent was obtained from all participants. Blood samples were collected under aseptic conditions and analyzed for 25(OH)D and calcium levels using an automated analyzer. Data were entered into statistical software (SPSS version 22) for analysis, with categorical variables analyzed using the Chi-square test and a p-value of <0.05 considered statistically significant.

Inclusion criteria

Age ≥ 18 years
Patients with CLD diagnosed by clinical, biochemical & ultrasonographic evidence
Patients who provided consent

Exclusion criteria

Patients with acute liver failure and hepatocellular carcinoma
Pregnant women
Patients with severe life-threatening infections and acute emergency condition
Patients who have deformity or fracture in any part of the body
Patients having secondary cause associated with osteoporosis
Patients not willing to take part in the study

Results

Table 1: Distribution of subjects according to demography (N=60)

	CLD (n=30)	Healthy individual (n=30)	p-value
Age (years)			
≤30	2 (6.7)	11 (36.7)	
31 – 40	6 (20.0)	9 (30.0)	
41 – 50	8 (26.7)	5 (16.7)	
>50	14 (46.7)	5 (16.7)	
Mean ± SD	49.76 ± 12.02	37.96 ± 12.35	<0.001
Gender			
Male	21 (70.0)	14 (46.7)	0.042
Female	9 (30.0)	16 (53.3)	

t-test and Chi-Square test were done

Table 1 shows that among 30 patients with chronic liver disease (CLD), 21 (70%) were males and 9 (30%) were females. The patients' ages ranged from 18 to 70 years, with a mean age of 49.76 ± 12.02 years.

Table 2: Distribution of variables of the study subjects with chronic liver disease (n=30)

	Frequency (n)	Percentage (%)
Bedridden	12	40.0
Exposure to sunlight (>1hr)	15	50.0
Positive family history	14	46.7
Ascites	14	46.7
CTP		
CTP A (<7)	9	30.0
CTP B (7-9)	12	40.0
CTP C (≥10)	9	30.0

Table 2 shows among the 30 patients with CLD, 21 (70%) had decompensated cirrhosis having CTP class B (40%) and CTP class C (30%). 9 patients (30%) had compensated cirrhosis of the liver with CTP class A. Family history and ascites were present in 46.6% of patients with CLD.

Table 3: Etiology of chronic liver disease among patients with CLD (n=30)

	Frequency (n)	Percentage (%)
HBV infection	13	43.3
HCV infection	5	16.7
Cryptogenic	11	36.7
Wilson disease	1	3.3

Table 3 demonstrates among the 30 patients with CLD, 13 (43.3%) were affected by hepatitis B infection. Other causes of CLD were cryptogenic 11 (36.7%), hepatitis C infection affecting 5 (16.7%) patients, and 1 (3.3%) patient had Wilson disease.

Table 4: Biochemical findings (N=60)

	CLD (n=30)	Healthy individual (n=30)	p-value
Serum albumin (g/dl)	2.83 ± 0.60	4.03 ± 0.23	<0.001
Serum calcium (mg/dl)	8.05 ± 0.76	8.81 ± 0.49	<0.001
Serum creatinine (mg/dl)	1.05 ± 0.36	0.81 ± 0.16	0.001
Serum bilirubin (mg/dl)	2.09 ± 1.82		
Prothrombin time (sec)	15.74 ± 2.45		
INR	1.33 ± 0.21		
Platelet (/cmm)	135233 ± 74483	325000±35355	0.001

An unpaired t-test was done

Table 4 shows the distribution of some baseline variables among the study group. It was observed that serum albumin, serum calcium, and platelet count were significantly lower among patients in comparison to healthy individuals (p= <0.05).

Table 5: Serum 25(OH)D level in patients with CLD and healthy individuals (N=60)

Serum 25(OH)D level	CLD (n=30)	Healthy individual (n=30)	p-value
Deficient	19 (63.4)	7 (23.3)	0.007
Insufficient	10 (33.3)	20 (66.7)	
Sufficient	1 (3.3)	3 (10.0)	

A chi-square test was done

Table 5 shows that a significant proportion of patients with chronic liver disease had either deficient or insufficient vitamin D levels. The majority of patients with chronic liver disease (63.3%) had deficient vitamin D levels, compared to 23.3% in the comparison group.

Table 6: Serum calcium level in patients with CLD and healthy individuals (N=60)

Serum Calcium	CLD (n=30)	Comparison group (n=30)	p-value
Low	25 (83.3)	4 (13.3)	<0.001
Normal	5 (16.7)	26 (86.7)	

A chi-square test was done

Serum calcium levels were significantly lower in CLD patients (8.05 ± 0.76 mg/dL) compared to the healthy group (8.81 ± 0.49 mg/dL), with a p-value of <0.001, indicating a statistically significant difference.

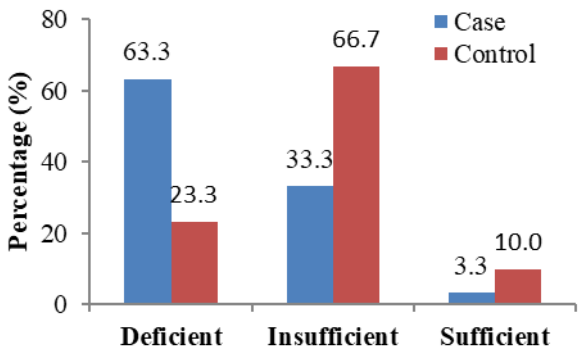

Figure 1: Patients with chronic liver disease and controls according to vitamin D categories

Figure 1 presents three categories of vitamin D levels in the patients and comparison groups in the bar diagram. Three categories are: deficient, insufficient, and sufficient. Vitamin D deficiency was much higher in patients with CLD than in healthy individuals. However, healthy individuals were also insufficient in vitamin D levels.

Table 7: Association of serum 25(OH)D level with CTP class of liver cirrhosis (n=30)

	CTP-A (n=9)	CTP-B (n=12)	CTP-C (n=9)	p-value
Deficient	2 (22.2)	11 (91.7)	6 (66.7)	0.021
Insufficient	6 (66.7)	1 (8.3)	3 (33.3)	
Sufficient	1 (11.1)	0 (0.0)	0 (0.0)	

The majority of patients in CTP class C were vitamin D deficient, with none having sufficient vitamin D stores. In contrast, only 2 (22.2%) patients in CTP class A exhibited vitamin D deficiency. These findings suggest a significant association between vitamin D levels and CTP classification ($p < 0.05$).

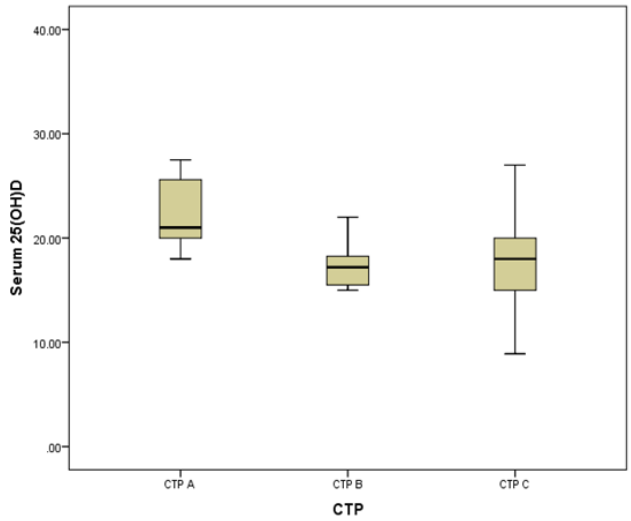

Figure 2: Serum 25(OH)D levels in different CTP classes of patients with chronic liver disease

Figure 2 illustrates serum 25(OH)D levels across different Child-Turcotte-Pugh (CTP) classes in patients with chronic liver disease. It demonstrates that patients in CTP class A have relatively higher serum vitamin D levels compared to those in CTP classes B and C.

Discussion

In this study, 21 (70%) had decompensated cirrhosis having Child-Turcotte-Pugh class B (40%) and Child-Turcotte-Pugh class C (30%). Nine patients (30%) had compensated cirrhosis of liver with Child-Turcotte-Pugh class A. Family history and ascites were present in 46.6% of patients with CLD. It was observed that serum albumin, serum calcium levels, and platelet count were significantly lower among patients in comparison to healthy persons ($p= <0.05$). Among the 30 patients, 13 (43.3%) were affected by hepatitis B infection. Others were cryptogenic 11 (36.7%), hepatitis C infection affecting 5 (16.7%) patients, and 1 (3.3%) patient had Wilson disease. Many comprehensive studies have been conducted to assess vitamin D deficiency among cirrhotic patients. In a study of cirrhotic patients, 93% had deficient levels of vitamin D (7). The majority of patients (n = 19) had deficient vitamin D levels (patients: 63.3% vs. controls: 23.3%). This difference was statistically significant (p-value = 0.007). These data suggest that many patients with CLD are suffering from insufficient stores of vitamin D and it can be responsible for hepatic osteodystrophy and other musculoskeletal manifestations. Vitamin D levels were inversely correlated to Child-Turcotte-Pugh classes. Most patients with Child-Turcotte-Pugh class C were vitamin D deficient. Only 2 (22.2%) patients having Child-Turcotte-Pugh class A had deficient vitamin D levels. However, serum calcium levels were not significantly related to CTP classes. Vitamin D deficiency was much higher in patients with chronic liver disease than in healthy individuals. This finding corresponds to other studies. Another study has also observed lower serum calcium in cirrhotic patients than non-cirrhotic.[10] In this study, we found serum calcium level was lower (<8.4 mg/dl) among patients with CLD than the healthy individuals (patients: 8.05 ± 0.76 mg/dl vs. healthy individuals: 8.81 ± 0.49 mg/dl; p-value = <0.001). Serum calcium levels in these patients (CLD) are often altered due to several factors, including impaired vitamin D metabolism, hypoalbuminemia, and liver dysfunction. Hypocalcemia is commonly observed in CLD patients, often resulting from vitamin D deficiency, as liver dysfunction impairs the conversion of vitamin D to its active form.[11] In 2012, Al-Othman A. et al noticed that sunlight exposure and physical activity influence vitamin D levels. Serum vitamin D level had a significant association with serum albumin (p =0.002). But, other variables like age, platelet count, prothrombin time, and serum bilirubin have no significant association (p = >0.05) with serum vitamin D levels .[12] The cause of low vitamin D in cirrhotic patients is multifactorial. The main mechanism through which cirrhosis of the liver causes vitamin D deficiency is the inhibition of vitamin D hydroxylation. Other mechanisms are intestinal malabsorption, reduced endogenous production of vitamin D binding protein and albumin in the liver and increased removal of 25(OH) D.[13] The etiology of vitamin D deficiency in healthy populations may be female sex, smoking, limited sun exposure (<30 min), dietary, environmental, and genetic causes.[14] Many studies have also suggested that adequate replacement of vitamin D by using vitamin D supplements can improve the functional status, prognosis, Child-Turcotte-Pugh score, and overall morbidity of these patients.[15]

Limitations

The sample size was small. All investigations (like a parathyroid hormone, and thyroid profile) to exclude secondary causes of low vitamin D could not be done due to economic constraints. All patients were enrolled in this study from a single tertiary level hospital which does not reflect the whole country. The cross-sectional nature of the study precludes cause and effect interpretations.

Conclusion

This study showed a high incidence of vitamin D deficiency in population with advanced chronic liver disease. Vitamin D levels inversely correlate with the Child-Turcotte-Pugh classes. Serum calcium level is also found to be low in patients with CLD. So, serum vitamin D and calcium levels may be routinely checked in every patient with advanced CLD. Finally, vitamin D supplements might be an adjunct to improve the patient's quality of life in this cohort with vitamin D deficiency or insufficiency.

Recommendation

A further multi-centric case-control study with a large sample size might be carried out to find out the associated factors of vitamin D deficiency and low serum calcium. A randomized controlled trial can be done to observe the effect of vitamin D supplements in this cohort. Vitamin D levels can be routinely checked in every patient suffering from advanced CLD. Finally, vitamin D supplements might be an adjunct to improve the patient's quality of life.

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