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Association of Serum Vitamin D and Calcium with Different Stages of Chronic Liver Diseases

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Abstract **Original Research Article**

Introduction: Chronic liver disease (CLD) is a progressive condition characterized by liver tissue destruction, leading to complications such as cirrhosis. Vitamin D deficiency is highly prevalent in patients with CLD and is associated with skeletal and immune system impairments. This brief focuses on the impact of vitamin D deficiency in CLD and the significance of assessing vitamin D status and calcium levels for effective interventions and improved patient outcomes. ***Aim of the Study:*** The aim of this study was to investigate the association between the serum vitamin D and calcium with different stages of chronic liver diseases. ***Methods:*** This observational cross-sectional study was conducted in the Department of Gastroenterology at BSMMU in Dhaka, Bangladesh, over a period from April 2019 to March 2020. The study included 60 patients, of them 30 patients had chronic liver disease and a comparison group comprising 30 healthy attendants from the same department. Data were collected without interventions, cleaned, and analyzed using SPSS version 22.0. Ethical clearance of this study was obtained from the Institutional Review Board (IRB) of BSMMU, Dhaka, Bangladesh. ***Results:*** The study examined the association between serum vitamin D and calcium levels with different stages of chronic liver disease (CLD). Among the CLD patients, a significant proportion (63.4%) had deficient vitamin D levels compared to the healthy individuals (23.3%), and only 3.3% had sufficient levels ($p = 0.007$). Serum calcium levels were significantly lower in CLD patients (8.05 ± 0.76 mg/dl) compared to healthy individuals (8.81 ± 0.49 mg/dl) ($p < 0.001$). Furthermore, vitamin D levels were associated with the severity of liver cirrhosis, as higher Child-Turcotte-Pugh (CTP) classes had lower vitamin D levels ($p = 0.009$). These results indicate a potential link between vitamin D deficiency and advanced stages of chronic liver disease, emphasizing the importance of monitoring vitamin D and calcium levels in CLD patients. ***Conclusion:*** This study reveals a strong link between vitamin D deficiency, low calcium levels, and the severity of chronic liver disease. Monitoring and addressing vitamin D and calcium levels in CLD patients are crucial for improving outcomes. Further research with larger samples is necessary to validate these findings and explore potential interventions to optimize vitamin D status in CLD.

Keywords*:* Vitamin-D, Calcium-Levels, Chronic, Liver.

INTRODUCTION

Chronic liver disease (CLD) is a progressive condition characterized by liver tissue destruction, leading to hepatic fibrosis and cirrhosis [1]. Cirrhosis is the advanced stage of chronic liver inflammation, associated with complications such as portal hypertension, bleeding varices, ascites, and encephalopathy [2]. Hepatocellular failure in cirrhosis results in elevated bilirubin, hypoalbuminemia, and prolonged prothrombin time [3]. The Child-Pugh grade is commonly used to assess hepato-cellular function in cirrhosis [4]. Despite improvements in treatment modalities, chronic liver disease still presents complications, including metabolic bone disease. Hepatic osteodystrophy, encompassing osteomalacia and osteoporosis, is common in CLD patients [5]. Vitamin D has essential roles in cell proliferation, differentiation, and exhibits immunomodulatory, anti-inflammatory, and anti-fibrotic properties [6]. The liver plays a crucial role in vitamin D metabolism, hydroxylating vitamin D and

synthesizing vitamin D binding protein (DBP). The major circulating form, 25-hydroxyvitamin D [25(OH)D], is used to assess vitamin D status [7]. Multiple factors contribute to vitamin D deficiency in chronic liver disease, including reduced exposure to sunlight, malabsorption, impaired production of DBP and albumin, impaired hepatic hydroxylation, and increased catabolic removal of 25(OH)D [8]. Vitamin D deficiency prevalence is high in CLD, with up to 93% of patients having insufficient levels, and approximately one-third classified as severely deficient [9]. Vitamin D is crucial for calcium absorption, maintaining skeletal health, and modulating immune function. In liver disease, it activates and regulates innate and adaptive immunity, aiding in pathogen elimination and immune responses [10]. The reliable measure for assessing vitamin D deficiency and serum calcium levels in chronic liver disease is 25(OH)D, with a longer half-life compared to the biologically active form, 1,25(OH)D3 [11]. Measuring 1, 25(OH) D3 levels is less suitable due to its rapid turnover and potential elevation in response to increased parathyroid hormone (PTH) levels in vitamin D-deficient patients. Studies worldwide have investigated the prevalence of vitamin D deficiency and serum calcium levels in chronic liver disease. A study found significantly higher vitamin D deficiency prevalence in cirrhotic patients compared to non-cirrhotic patients in Iran. Additionally, patients classified as Child-Pugh class B and C exhibited lower vitamin D levels than those in class A [12]. Ultimately, chronic liver disease is associated with a high prevalence of vitamin D deficiency, impacting skeletal health and immune function. 25(OH) D levels reliably indicate vitamin D status and reveal significant deficiency, particularly in cirrhotic patients. Understanding the relationship between vitamin D and calcium levels in different stages of liver disease is crucial for guiding interventions and improving patient outcomes. Therefore, the aimed to investigate the relationship between the level of serum vitamin D and calcium with different stages of chronic liver diseases.

METHODS

This observational cross-sectional study was conducted in the Department of Gastroenterology at BSMMU in Dhaka, Bangladesh, over a period from April 2019 to March 2020. The study included 60 patients of them 30 had chronic liver disease and a comparison group comprising 30 healthy attendants from the same department. Non-probability consecutive sampling was used to select participants. Data collection involved obtaining relevant information from the participants, and no interventions or additional procedures were performed. The collected data were cleaned, entered into a computer, and analyzed using SPSS version 22. Descriptive statistics, such as means and standard deviations for numerical variables, and counts with percentages for categorical variables, were used for data presentation. Chi-square tests, unpaired t test, and ANNOVA tests were performed to determine the association between serum vitamin D and serum calcium with the chronic liver diseases , where $p<0.05$ considered as the level of significance. Ethical considerations were followed, including obtaining approval from the institutional review board, providing clear explanations to participants, obtaining informed consent, and ensuring confidentiality of the study information. The inclusion and exclusion criteria of this study were as follows:

Inclusion Criteria:

- Age ≥ 18 years
- Patients with chronic liver disease evidenced by clinical, biochemical &ultrasonographic evidences
- Patients who gave informed written consent

Exclusion Criteria:

- Patients with acute liver failure and hepatocellular carcinoma
- Patients with severe life-threatening infection and acute emergency condition
- Patients who had any secondary cause associated with osteoporosis
- Patients with chronic kidney disease, diabetes mellitus, history of endocrine disease, metastatic bone disease or other malignancies

RESULTS

Table 1: Demographic profile of the study subjects (N=60)

Variable	CLD (n=30)	Comparison group (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)	<0.001
Mean ± SD	49.76 ± 12.02	37.96 ± 12.35	
Gender			
Male	21 (70.0)	14 (46.7)	
Female	9 (30.0)	16 (53.3)	0.042

Unpaired t test and Chi-Square test was done to measure the level of significance

Among the participants, 30 patients with chronic liver disease (CLD), 21 (70%) were males and 9 (30%) were females. The minimum age of the patients was 18 years and the maximum was 70 years, with mean age of 49.76 (± SD, ± 12.02) years which is statistically significant (p-value= <0.001).

Table 2: Serum 25(OH) D level in patients with CLD and healthy individuals (N=60).

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

*Chi-Square test was done to measure the level of significance

According to this table patients were categorized into three groups according to vitamin D levels: patients with deficient (<20 ng/mL), insufficient (20–30 ng/mL) and sufficient (>30 ng/mL) vitamin D levels. The majority of patients with chronic liver disease (n = 19) had deficient vitamin D levels (patients: 63.3% vs. comparison group: 23.3%). This difference was statistically significant (p value = 0.007). Sufficient levels of vitamin D were found in only 1 patient with chronic liver disease (patients: 3.3% vs. comparison group: 10%).

Table 3: 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)	

*Chi-Square test was done to measure the level of significance

Among these cases, serum calcium level was significantly lower in patient with CLD than the healthy individual (patients: 8.05 ± 0.76 mg/dl vs. comparison groups: 8.81 ± 0.49 mg/dl; p value = <0.001).

Table 4: Serum 25(OH) D and serum calcium level at different CTP classes (n=30).

	CTP (n=9)	CTP-B (n=12)	CTP-C (n=9)	p-value
Serum 25(OH)D	23.67 ± 6.29	16.26 ± 4.10	17.80 ± 5.22	0.009
Serum calcium	8.38 ± 0.98	7.97 ± 0.55	7.82 ± 0.72	0.276

* ANOVA test was done to measure the level of significance.

In this table shows serum 25(OH) D and serum calcium level at different CTP classes. Serum 25(OH)D level was significantly lower among patient groups (p= <0.05). Serum calcium level was also lower in patients with CLD, but statistically not significant.

Table 5: Association of serum 25(OH) D level with CTP class of cirrhosis of the liver (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)	

* Chi-Square test was done to measure the level of significance

Association of serum 25(OH) D level with Child-Turcotte-Pugh (CTP) class of cirrhosis of the liver. Most patients with CTP class C were vitamin D deficient, while none had sufficient vitamin D stores. In contrast to this, 2 (22.2%) patients having CTP class A had deficient vitamin D levels. The results indicated that vitamin D levels in cirrhotic patients are associated with CTP classification (p <0.05). Vitamin D levels were strongly related to CTP classification of liver cirrhosis.

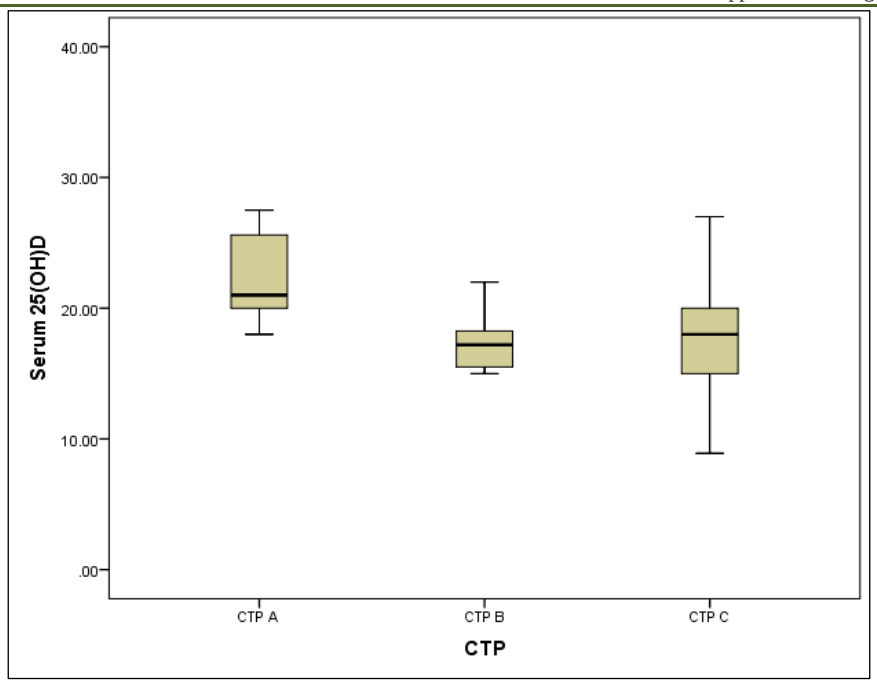

Figure 1: Serum 25(OH) D levels in different CTP classes of patients with chronic liver disease

Fig. 1: shows serum 25(OH) D levels in different Child-Turcotte-Pugh classes of patients with chronic liver disease. It shows relatively higher serum vitamin D in patient with CTP class A than CTP class B and CTP class C. This indicates as the CTP class advances, vitamin D levels decrease.

DISCUSSION

The present study aimed to investigate the relationship between the level of serum vitamin D and calcium with different stages of chronic liver disease (CLD). The results revealed significant associations between serum vitamin D, calcium levels, and the severity of CLD as assessed by the Child-Turcotte-Pugh (CTP) classification. The results of this study demonstrated a strong correlation between vitamin D deficiency and CLD. The majority of patients with CLD had deficient vitamin D levels (63.4%), compared to the comparison group (23.3%) (p-value = 0.007). Only a small percentage of patients had insufficient (33.3%) or sufficient (3.3%) levels. These findings are consistent with several previous studies that have reported a high prevalence of vitamin D deficiency in patients with liver diseases, including CLD [9], [13]. The association between vitamin D deficiency and CLD is statistically significant (p-value < 0.05). Vitamin D deficiency in CLD has been linked to various complications, such as bone loss, muscle weakness, immune dysfunction, and increased mortality rates [14]. Regarding the association between serum calcium levels and CLD, this study found significantly lower serum calcium levels in patients with CLD (83.3%) compared to healthy individuals (13.3%) (p-value < 0.001). Another study found that significantly lower serum calcium levels in patients with CLD compared to healthy individuals($P<0.05$) [15]. Similar studies indicating that hepatic dysfunction can disrupt calcium homeostasis, leading to decreased serum calcium levels [16], [17]. The liver is involved in the production of vitamin D-binding protein, which is responsible for transporting vitamin D and its metabolites, including calcium, in the blood. Liver disease can impair this process, resulting in decreased calcium levels. Hypocalcemia in CLD has been associated with an increased risk of hepatic encephalopathy, coagulopathy, and other complications [18]. The study also examined the relationship between serum vitamin D and calcium levels with different stages of CLD based on the CTP classification. The results showed that serum vitamin D levels significantly decreased as the CTP class advanced from A to C (p-value = 0.009).Another study found that lower in CTP class B than in CTP class C with no significant different [19]. Similar previous studies reporting lower vitamin D levels in patients with more severe liver disease [13], [20]. However, no significant difference was observed in serum calcium levels across different CTP classes (p-value = 0.276), indicating that calcium homeostasis may not be directly affected by the severity of liver disease. The findings of this study have important clinical implications. Vitamin D deficiency and hypocalcemia are prevalent in patients with CLD and may contribute to disease progression and associated complications. Therefore, regular monitoring of vitamin D and calcium levels and appropriate supplementation, when necessary, could potentially improve outcomes and quality of life for individuals with CLD. Moreover, the strong association between vitamin D levels and the CTP classification suggests that vitamin D status could serve

as a potential prognostic marker in CLD. Further research is warranted to explore the underlying mechanisms linking vitamin D deficiency, impaired calcium homeostasis, and liver disease progression.

Limitation of the Study

The study is the relatively small sample size (N=60), which may limit the generalizability of the findings.

CONCLUSION

In conclusion, this study highlights a significant association between vitamin D deficiency, hypocalcemia, and the severity of chronic liver disease. The findings underscore the importance of monitoring and addressing vitamin D and calcium levels in patients with CLD to mitigate complications and improve patient outcomes. Further research with larger sample sizes is needed to confirm these findings and explore potential therapeutic interventions for optimizing vitamin D status in CLD.

RECOMMENDATION

Considering the study findings, it is recommended to routinely evaluate the vitamin D and calcium status of patients diagnosed with chronic liver disease. Further investigation should be conducted to explore the effectiveness and potential benefits of implementing vitamin D supplementation as a preventive and therapeutic intervention for managing vitamin D deficiency and associated complications in this specific patient population.

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