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FREQUENCY OF HYPOCALCEMIA IN PATIENTS WITH CHRONIC LIVER DISEASE

Original Research

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ABSTRACT

Background: Chronic liver disease is characterized by persistent hepatic inflammation, fibrosis, and architectural distortion, leading to progressive hepatic dysfunction. The impairment of liver function disrupts multiple metabolic pathways, including vitamin D metabolism, which plays a crucial role in calcium homeostasis. Electrolyte imbalances, particularly hypocalcemia, are common but often overlooked in patients with chronic liver disease. Despite its clinical significance, limited data exist on the burden of calcium deficiency in this population, particularly in local settings. This study aimed to assess the prevalence of asymptomatic hypocalcemia in patients with chronic liver disease and its association with demographic and disease-related factors.

Objective: To determine the frequency of hypocalcemia and its association with gender, age, and severity of liver disease in patients with chronic liver disease.

Methods: This cross-sectional study was conducted at the Department of Gastroenterology, Hayatabad Medical Complex, Peshawar, from June 1, 2024, to November 30, 2024. A total of 159 male and female patients aged 20 to 70 years, diagnosed with chronic liver disease on ultrasound, were enrolled. Hypocalcemia was defined as a serum calcium level below 8.5 mg/dL. Relevant demographic, clinical, and biochemical data were recorded. Data analysis was performed using SPSS version 25, and statistical significance was set at $p \leq 0.05$.

Results: The mean age of participants was 54.12 ± 7.189 years, with 144 (90.6%) patients older than 45 years. Males constituted 111 (69.8%) of the sample. A BMI greater than 24.0 kg/m² was recorded in 85 (53.5%) patients. The mean duration of chronic liver disease was 14.57 ± 7.533 years, with 103 (64.8%) patients having the disease for more than 10 years. Cirrhosis severity assessment showed that 61 (38.4%) patients had Child-Pugh Class C cirrhosis. Hypocalcemia was detected in 110 (69.2%) patients, with a significantly higher prevalence in females (89.6%) compared to males (60.4%) ($p < 0.001$). Advanced cirrhosis was strongly associated with hypocalcemia, as 52 (85.2%) patients in Child-Pugh Class C had low calcium levels ($p = 0.001$).

Conclusion: Hypocalcemia is highly prevalent in patients with chronic liver disease, particularly among females and those with advanced cirrhosis. The findings underscore the importance of routine calcium monitoring and early intervention in this vulnerable population.

Keywords: Calcium deficiency, Chronic liver disease, Cirrhosis, Electrolyte imbalance, Hepatic dysfunction, Hypocalcemia, Vitamin D metabolism.

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INTRODUCTION

Chronic liver disease is a progressive condition characterized by persistent hepatic parenchymal inflammation, damage, and attempts at regeneration, ultimately culminating in fibrosis (1). In its advanced stage, liver cirrhosis develops, wherein extensive fibrosis and scar tissue replace the normal liver parenchyma, leading to significant architectural distortion and the formation of regenerative nodules (2,3). The etiological spectrum of chronic liver disease is broad, encompassing chronic viral hepatitis, excessive alcohol consumption, metabolic disorders such as Wilson disease and hemochromatosis, and autoimmune conditions including autoimmune hepatitis, alpha-1 antitrypsin deficiency, primary biliary cholangitis, and primary sclerosing cholangitis (4,5). Complications associated with chronic liver disease are diverse, with electrolyte imbalances, including disturbances in macro- and micronutrient levels, being a common occurrence (6). Among these, alterations in serum calcium levels are frequently observed (7). The precise pathophysiological mechanisms underlying hypocalcemia in these patients remain unclear; however, it is hypothesized that impaired vitamin D metabolism plays a key role (8). Ineffective hepatic hydroxylation of vitamin D disrupts calcium homeostasis, thereby leading to decreased calcium absorption and eventual deficiency (9). Studies have reported a high prevalence of vitamin D deficiency in patients with chronic liver disease, with rates as high as 84.8% in one study and 66.4% in another (10).

Despite the well-recognized nutritional derangements in chronic liver disease, limited research has specifically addressed asymptomatic hypocalcemia in this population, particularly in local settings. Given that chronic liver disease is associated with a state of multi-nutrient deficiency, the clinical implications of low calcium levels can range from an asymptomatic biochemical abnormality to severe manifestations requiring urgent medical intervention. There remains a lack of comprehensive data on the burden of hypocalcemia in these patients, both nationally and globally (11). This study aims to assess the prevalence of asymptomatic hypocalcemia in patients with chronic liver disease within our local population. By identifying the magnitude of this electrolyte imbalance, the findings may contribute to a better understanding of its clinical significance, ultimately guiding future diagnostic and management strategies.

METHODS

This cross-sectional study was conducted to determine the prevalence of asymptomatic hypocalcemia in patients with chronic liver disease. A total of 177 male and female patients, aged between 20 and 70 years, diagnosed with chronic liver disease were enrolled from the Department of Gastroenterology, Hayatabad Medical Complex, Peshawar, between June 1, 2024, and November 30, 2024. The study utilized a non-probability convenience sampling technique, which may introduce selection bias and limit the generalizability of the findings. To mitigate this, an attempt was made to include a diverse patient population representative of the broader spectrum of chronic liver disease cases presenting to the facility. Patients with chronic kidney disease, hormonal disorders, recent intake of calcium supplements within the past two months, malabsorptive enteropathies, malignancies, or a history of gastrointestinal resection were excluded to minimize confounding variables. The diagnosis of chronic liver disease was confirmed radiologically based on ultrasound findings demonstrating a coarse, shrunken liver with irregular margins. Hypocalcemia was defined as a serum calcium level of less than 8.5 mg/dL, measured through standard laboratory techniques. Given that total serum calcium levels can be influenced by hypoalbuminemia, which is common in chronic liver disease, adjustments for albumin levels were made where required to enhance diagnostic accuracy.

Ethical approval for the study was obtained from the hospital's research review board. Written informed consent was obtained from all participants before enrollment, ensuring adherence to ethical guidelines. Demographic details and baseline clinical information were recorded, followed by a detailed medical history and thorough clinical examination. Symptoms potentially associated with hypocalcemia, including generalized weakness, fatigue, numbness, dental erosions, and bone fractures, were assessed. Clinical signs such as Trousseau's and Chvostek's signs were specifically examined to evaluate neuromuscular excitability. Blood samples were drawn aseptically from a superficial vein and immediately sent to the hospital laboratory for analysis. Serum calcium levels were measured using standard biochemical methods, with appropriate quality control measures in place. Hypocalcemia was documented as per the operational definition. The data were systematically recorded and analyzed using SPSS version 25. Continuous variables were expressed as means and standard deviations, while categorical data were presented as frequencies and percentages. To control for confounders and

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effect modifiers, stratification was performed. Statistical significance was assessed using the chi-square test and Fisher's exact test, with a p-value of ≤0.05 considered statistically significant.

RESULTS

The study included 177 participants diagnosed with chronic liver disease, with a mean age of 54.12 ± 7.189 years. The mean BMI of the study population was recorded at 24.842 ± 2.702 kg/m², while the mean duration of chronic liver disease was 14.57 ± 7.533 years. The mean weight and height of the participants were 71.91 ± 6.489 kg and 170.45 ± 7.935 cm, respectively. Among the enrolled patients, 111 (69.8%) were male, while 48 (30.2%) were female. A significant majority, 144 (90.6%), were above 45 years of age. BMI less than 24.0 kg/m² was observed in 74 (46.5%) patients, while 85 (53.5%) had a BMI greater than 24.0 kg/m². The duration of chronic liver disease exceeded 10 years in 103 (64.8%) patients. Cirrhosis severity was classified using the Child-Pugh score, with 52 (32.7%) classified as Class A, 46 (28.9%) as Class B, and 61 (38.4%) as Class C. Hypocalcemia was observed in 110 (69.2%) of the patients, whereas 49 (30.8%) had normal calcium levels. The prevalence of hypocalcemia was analyzed in relation to various demographic and clinical parameters. Among patients above 45 years of age, hypocalcemia was present in 102 (70.8%) individuals, while it was recorded in 8 (53.3%) patients aged 45 years or below (p = 0.162). Male patients had a lower frequency of hypocalcemia at 67 (60.4%) compared to females, where 43 (89.6%) were affected (p < 0.001). The occurrence of hypocalcemia did not show a statistically significant association with BMI, as 52 (70.3%) patients with a BMI ≤24.0 kg/m² and 58 (68.2%) with a BMI >24.0 kg/m² were affected (p = 0.782). Similarly, the duration of chronic liver disease did not have a statistically significant impact on hypocalcemia, with 41 (73.2%) cases among those with a disease duration ≤10 years and 69 (67.0%) among those with a duration exceeding 10 years (p = 0.417).

A significant association was found between the severity of liver disease and the presence of hypocalcemia. Among Child-Pugh Class A patients, 27 (51.9%) had hypocalcemia, while it was present in 31 (67.4%) patients in Class B. The highest prevalence of hypocalcemia was observed in Class C patients, where 52 (85.2%) were affected (p = 0.001). The mean serum calcium levels varied across different patient subgroups, highlighting differences in calcium homeostasis among individuals with chronic liver disease. Males had a higher mean calcium level (8.7 ± 0.4 mg/dL) compared to females (8.3 ± 0.5 mg/dL), aligning with the observed higher prevalence of hypocalcemia among female patients. Patients aged 45 years or below demonstrated slightly higher calcium levels (8.8 ± 0.3 mg/dL) compared to those above 45 years (8.5 ± 0.4 mg/dL), though the difference was not statistically significant. Calcium levels did not show a marked variation based on BMI, with individuals having a BMI ≤24.0 kg/m² showing a mean calcium level of 8.6 ± 0.4 mg/dL, while those with a BMI >24.0 kg/m² had a mean of 8.5 ± 0.3 mg/dL. Patients with a chronic liver disease duration of 10 years or less exhibited slightly higher calcium levels (8.7 ± 0.3 mg/dL) compared to those with a disease duration of more than 10 years (8.4 ± 0.4 mg/dL), suggesting progressive metabolic derangements over time. The most significant decline in calcium levels was observed in patients classified under Child-Pugh Class C, with a mean serum calcium level of 8.2 ± 0.5 mg/dL, compared to 8.6 ± 0.4 mg/dL in Class B and 8.9 ± 0.5 mg/dL in Class A, reinforcing the strong association between worsening liver function and calcium deficiency.

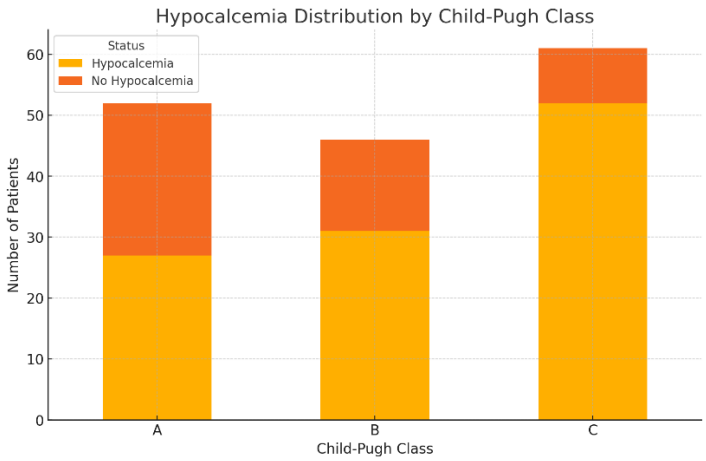


Figure 2 Hypocalcemia Distribution by Child-Pugh Class

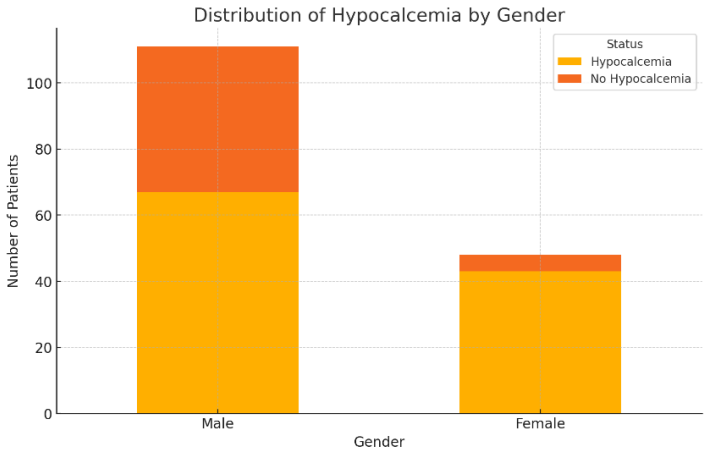


Figure 1 Distribution of Hypocalcemia by Gender

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Table 1: Means and standard deviation of patients according to baseline parameters (n = 159)

Parameters	Minimum	Maximum	Mean	Std. Deviation
Patient Age (years)	41	74	54.12	7.189
Patient Weight (kg)	56	88	71.91	6.489
Patient Height (cm)	155	183	170.45	7.935
Patient BMI (kg/m^2)	21.3	32.5	24.842	2.7029
CLD duration (years)	4	36	14.57	7.533

Table 2: Frequencies and percentages of patients according to various baseline parameters and Hypocalcemia (n = 159)

Parameters		Frequency	Percent
Gender	Male	111	69.8
	Female	48	30.2
Age (years)	45 or below	15	9.4
	More than 45	144	90.6
BMI (kg/m^2)	24.0 or below	74	46.5
	More than 24.0	85	53.5
	Total	159	100.0
CLD duration (years)	10 or below	56	35.2
	More than 10	103	64.8
CP Class	A	52	32.7
	B	46	28.9
	C	61	38.4
Hypocalcemia	Yes	110	69.2
	No	49	30.8

Table 3: Contingency table analysis of Hypocalcemia with various parameters (n = 159)

Parameters		Hypocalcaemia		Total	Chi square p value
		Yes (n =110)	No (n = 49)		
Age (years)	45 or below	8	7	15	0.162
		53.3%	46.7%	100.0%	
	More than 45	102	42	144	
		70.8%	29.2%	100.0%	
Gender	Male	67	44	111	0.000
		60.4%	39.6%	100.0%	
	Female	43	5	48	
		89.6%	10.4%	100.0%	

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Parameters		Hypocalcaemia		Total	Chi square p value
		Yes (n =110)	No (n = 49)		
BMI (kg/m^2)	24.0 or below	52	22	74	0.782
		70.3%	29.7%	100.0%	
	More than 24.0	58	27	85	
		68.2%	31.8%	100.0%	
CLD duration (years)	10 or below	41	15	56	0.417
		73.2%	26.8%	100.0%	
	More than 10	69	34	103	
		67.0%	33.0%	100.0%	
Child Class	A	27	25	52	0.001
		51.9%	48.1%	100.0%	
	B	31	15	46	
		67.4%	32.6%	100.0%	
	C	52	9	61	
		85.2%	14.8%	100.0%	

DISCUSSION

The findings of this study demonstrated that the majority of patients with chronic liver disease were above 45 years of age, with a mean age of 54.12 ± 7.189 years. The male population constituted a higher proportion of the study participants, accounting for 69.8%. These demographic patterns align with previously reported literature, where chronic liver disease has been predominantly observed in middle-aged and older individuals. Some studies, however, have reported a lower mean age, which may be attributed to differences in age selection criteria, geographic variations, and genetic predisposition. The observed male predominance in this study is consistent with prior research, which has largely reported a higher prevalence of chronic liver disease in males (12). However, contrasting reports exist where female participants outnumbered males, highlighting the potential influence of regional, environmental, and lifestyle factors. The mean serum calcium level in the study population was 7.90 ± 0.89 mg/dL, with hypocalcemia observed in 69.2% of the patients. These findings suggest a substantial burden of calcium deficiency in individuals with chronic liver disease, reinforcing the hypothesis that hepatic dysfunction interferes with calcium homeostasis. When compared to previous research, variations in mean serum calcium levels and hypocalcemia prevalence were noted. Studies from different populations have reported slightly higher mean calcium levels and lower hypocalcemia prevalence, which may be explained by differences in nutritional status, ethnicity, sample size, and vitamin D sufficiency (13). Western populations tend to exhibit better nutritional profiles and greater sun exposure, which facilitates adequate vitamin D synthesis and consequently better calcium homeostasis. In contrast, regions with limited sun exposure and sociocultural restrictions on outdoor activities, particularly among females, may contribute to lower vitamin D and calcium levels (14).

Hypocalcemia was significantly more prevalent in female patients (89.6%) compared to males (60.4%), a finding consistent with the majority of published literature. The increased susceptibility of females to hypocalcemia may be attributed to hormonal influences, dietary patterns, and limited sun exposure due to sociocultural and religious practices, all of which contribute to vitamin D insufficiency and impaired calcium absorption. Some studies, however, have reported a non-significant gender difference in hypocalcemia prevalence, indicating that additional factors such as disease severity, duration of hepatic impairment, and metabolic variations may play a role (15). A strong association was observed between advanced liver disease and hypocalcemia, with Child-Pugh Class C cirrhosis patients showing the highest prevalence of hypocalcemia (85.2%, p = 0.001). This finding aligns with existing research, where lower calcium

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levels have been consistently recorded in patients with advanced fibrosis and hepatic dysfunction. The decline in liver synthetic function in cirrhosis results in impaired vitamin D metabolism, leading to reduced intestinal calcium absorption and an overall state of calcium deficiency (16). The progression of fibrosis further compounds this imbalance, explaining the higher prevalence of hypocalcemia in severe liver disease. Some reports have documented a similar trend, although variations in cut-off values for hypocalcemia and study methodologies may account for minor discrepancies (17).

The strengths of this study lie in its focused assessment of asymptomatic hypocalcemia in chronic liver disease patients, contributing to the existing body of knowledge on hepatic dysfunction and electrolyte imbalances. The use of a well-defined operational definition for hypocalcemia and stratified analysis enhances the reliability of findings (18,19). However, several limitations must be acknowledged. The use of a convenience sampling method introduces selection bias, limiting the generalizability of results. Additionally, total serum calcium levels were used for defining hypocalcemia without adjusting for albumin levels, which could lead to an overestimation or underestimation of true calcium deficiency (20). Future research should incorporate albumin-adjusted calcium and ionized calcium measurements to provide a more precise assessment. Moreover, longitudinal studies are warranted to evaluate the long-term impact of hypocalcemia on disease progression and patient outcomes. Despite these limitations, the findings emphasize the clinical significance of hypocalcemia in chronic liver disease and highlight the need for routine monitoring and early intervention. Addressing underlying vitamin D deficiencies, optimizing calcium intake, and considering supplementation strategies could potentially improve calcium homeostasis and prevent complications associated with chronic liver disease. Further research exploring the molecular mechanisms linking hepatic dysfunction with calcium metabolism may provide deeper insights into potential therapeutic targets.

CONCLUSION

This study highlights the high prevalence of hypocalcemia among patients with chronic liver disease, emphasizing its strong association with disease severity and gender. Female patients and those with advanced liver fibrosis were more frequently affected, indicating that progressive hepatic dysfunction plays a critical role in calcium homeostasis. The findings underscore the importance of early detection and management of calcium imbalances in this population to prevent potential complications. Given the significant correlation between hypocalcemia, gender, and liver disease progression, routine monitoring and appropriate interventions should be considered as part of comprehensive patient care.

AUTHOR CONTRIBUTIONS

Author	Contribution
Fida Muhammad Khan	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Salman Afridi	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Younas*	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Syed Hira Hassan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Asif Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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