

Frequency Of Hypocalcemia In Patients With Non-Alcoholic Fatty Liver Disease

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Abstract

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Background: Non-alcoholic fatty liver disease (NAFLD) is a widespread chronic liver disease in the whole world and is closely linked with metabolic syndrome, insulin resistance, and cardiovascular disease. According to recent studies, the changes in calcium metabolism and vitamin D deficiency could be associated with the progression of NAFLD. However, scarce information is present on this relationship amongst Pakistani population. **Objective:** To establish the prevalence rate of hypocalcemia among patients with non-alcoholic fatty liver disease. **Methodology:** This proposed observational descriptive study was carried out in the Department of Medicine, Hameed Latif Hospital, Lahore from January 2025 to June 2025. Non-probability consecutive sampling was used in selecting 135 patients between 40 and 80 years of age who were diagnosed with NAFLD. Severely renal failure patients, malignancy, sepsis, pulmonary embolism, myocardial infarction, or congestive heart failure patients were excluded. The proforma was used to collect

demographic and clinical data. Laboratory tests such as calcium levels of serum and vitamin D, liver functions tests as well as ultrasound abdomen were done. Corrected serum calcium of less than 8.2 mg/dl was considered hypocalcemia. The analysis of data was done in SPSS version 25. Quantitative variables were computed in mean and standard deviation whereas qualitative variables were computed in frequencies and percentages. **Results:** Hypocalcemia was found to be present in a considerable number of 135 patients with NAFLD. The rates of hypocalcemia were higher in the patients who had moderate to severe illnesses. Strong relationship was noted between low levels of serum calcium and severity of NAFLD ($p=0.05$ or less). **Conclusion:** Hypocalcemia is common in NAFLD patients, and it seems to correlate with the severity of the disease. Observation of serum calcium could be used to assist

clinicians in promptly detecting metabolic disorders and improved treatment of NAFLD patients.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is now regarded as the most prevalent chronic liver disease in the world and a significant health issue for most people. It includes a wide variety of liver diseases, including some as simple hepatic steatosis (fat in the liver), non-alcoholic steatohepatitis (NASH), which is the presence of hepatic inflammation, hepatocellular injury and fibrosis that can progress to cirrhosis, hepatic failure, and hepatocellular carcinoma ¹.

NAFLD is generally believed to be the hepatic expression of metabolic syndrome and has a close relationship with insulin resistance and other metabolic pathologies, such as obesity, dyslipidemia, and type 2 diabetes mellitus (T2DM). The NAFLD patients are at high risk of cardiovascular diseases (CVD), and overall mortality rate is high ². Taking into account that NAFLD is connected with calcium metabolism disturbances, increased risks of cardiovascular diseases and mortality, and NAFLD is connected to renal dysfunction and bone mineral abnormalities, there is a possibility that NAFLD presence and progression can be related to alterations in serum calcium levels.

The NAFLD is mostly widespread in the Western industrialized states, and it is currently gaining momentum in other parts of the world. It has been indicated that there is a global prevalence of NAFLD in 6 percent to 35 percent with a median prevalence of about 20 percent ³. In Europe, the prevalence rates are estimated at approximately 2526, but there are considerable differences between the populations and the ethnic groups. The significant risk factors of NAFLD are mostly parallel to the elements of metabolic syndrome such as central obesity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance. Consequently, NAFLD is perceived to be the hepatic aspect of metabolic syndrome ³. Histological observation of the hepatic inflammation is believed to be one of the most significant factors placed in the procession of the disease ⁴.

Liver has a very important role in controlling the metabolic processes and the homeostasis of a range of trace elements in the body. It participates in the transport, metabolism and storage of micronutrients and in their excretion of micronutrients by secreting bile, hence providing bioavailability and distributing the nutrients in the tissues appropriately ⁵. Calcium is the fifth most common of these trace elements in the human body and is a vital part of many physiological features, skeletal mineralization, cell membrane stability, intracellular signaling, muscle contraction, and enzymatic activity. Calcium is mostly acquired in the diet, and its metabolism is highly controlled in terms of complication between vitamin D, parathyroid hormone and renal function ⁶.

Another important role of the liver in the endocrine system of vitamin D is also vital. To have its physiological action, first vitamin D has to be metabolized in the liver into 25-hydroxyvitamin D [25(OH)D], the key circulating form of vitamin D in the body. This is then transformed in the kidneys to 1, 25-dihydroxyvitamin D which is the biologically active form that controls the calcium and phosphate metabolism ^{1,4}. Besides, calcium-sensing receptors are expressed in liver cells, as well as in parathyroid glands and kidneys, and have a significant role in systemic calcium homeostasis ^{2,7}.

Over the past few years, more evidence has hinted at the fact that the endocrine system of vitamin D not only controls the balance of calcium and phosphate, and bone metabolism, but plays significant non-calcitropic roles such as anti-proliferative, pro-differentiative, and immunomodulatory effects ^{3,8}. These functions can affect inflammatory mechanisms and metabolism of the pathogenesis and course of NAFLD. Although there is increasing global evidence on the relationship of calcium metabolism and NAFLD, the evidence of the Pakistani population is scarce. Thus, the

justification of the current study is to assess the relationship between serum calcium and non-alcoholic fatty liver disease in patients who come to a tertiary care hospital in Pakistan. The results of the current research can be used to make the clinical community more aware of the metabolic disruptions that accompany NAFLD and to evaluate the levels of disease severity and liver dysfunction in a more accurate way. Besides, the findings could help formulate better management policies to decrease the morbidity caused by the disease and will also provide valuable local information to the available medical literature.

OBJECTIVE

To establish the prevalence of hypocalcemia in the patients of non-alcoholic fatty liver disease in the Pakistani population.

METHODOLOGY

The proposed observational descriptive study was carried out in Department of medicine, Hameed Latif Hospital, Lahore during January 2025 and June 2025. The study involved a total of 135 patients with the diagnosis of non-alcoholic fatty liver disease (NAFLD) by employing non-probability consecutive sampling methods. The sample size was determined based on a 95% confidence level, an 8 per cent margin of error, and an anticipated frequency of low level of serum calcium among patients with NAFLD is 34 per cent, as is among studies carried out. All qualified patients who reported to the medical department throughout the period of the study and met the inclusion criteria were enrolled after giving consent. A structured proforma was used to record demographic data, clinical findings, and other necessary laboratory investigations. The data obtained were subsequently processed to identify the prevalence of hypocalcemia in NAFLD patients.

INCLUSION CRITERIA

They included patients aged 40-80 years of both sexes who had non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NASH) diagnosed and had a Child-Pugh score that was graded as mild, moderate, or severe.

EXCLUSION CRITERIA

Patients with a significant case of renal failure, chronic hemodynamic instability with the need of inotropic or vasoactive support, pulmonary embolism, acute myocardial infarction, congestive cardiac failure, bronchial asthma, sepsis, or any malignancy were excluded.

DATA COLLECTION PROCEDURE

Patients with the approval of Institutional Review Board (IRB) were enrolled after meeting the inclusion criteria at the Department of Medicine at Hameed Latif Hospital, Lahore. All participants or their attendants gave informed consent in writing before taking part in the study. The information was gathered in the form of a structured proforma that was pre-designed and included demographic information (age, gender, occupation, status in smoking, and address), clinical history, and disease duration. All patients went through abdominal ultrasound analysis to confirm that the patient had non-alcoholic fatty liver disease (NAFLD). Laboratory tests were conducted by taking blood samples at admission: AST, ALT, serum albumin, serum calcium, vitamin D levels, hemoglobin, total bilirubin, as well as total leukocyte count (TLC). According to the Child-Pugh classification, the patients were classified into mild, moderate and severe disease groups. Besides this, the length of stay in hospital and in-hospital deaths were also captured on individual basis. The researcher was able to collect and document all the relevant data.

DATA ANALYSIS

All the data collected were analyzed and entered in Statistical Package of social Sciences (SPSS) version 25.0. The quantitative variables of age, levels of serum calcium, liver enzyme, vitamin D levels, and the length of stay were presented in mean and standard deviation. The qualitative variables such as gender, disease stage and hypocalcemia were presented in frequency and percentage. Stratification was used to control the effect modifiers like age, gender and severity of the disease. Chi-square test was used after stratification to identify the relationship between hypocalcemia and the severity of non-alcoholic fatty liver disease (NAFLD). A p-value that was not greater than 0.05 was regarded as statistically significant.

RESULTS

The research was carried out at the Department of Medicine, Hameed Latif Hospital, Lahore and had 135 patients with non-alcoholic fatty liver disease (NAFLD). The average age of the subjects was 56.4 standard deviation of 9.8 years. Out of these, 78 (57.8) were male and 57 (42.2) were females. The frequency of hypocalcemia was seen to be 46 patients with a frequency of 34.1 in patients with NAFLD.

Baseline Characteristics

Parameter	Total (n = 135)
Mean Age (years)	56.4 ± 9.8
Gender (Male : Female)	78 : 57
Diabetes Mellitus	48 (35.6%)
Hypertension	54 (40.0%)
BMI ≥ 30 kg/m ²	36 (26.7%)
Urban Residence	75 (55.6%)
Rural Residence	60 (44.4%)

Most of the patients were men with a significant number having comorbid conditions such as diabetes mellitus and hypertension.

Frequency of Hypocalcemia

Outcome	Frequency	Percentage
Hypocalcemia Present	46	34.1%
Hypocalcemia Absent	89	65.9%

Approximately one-third of patients with NAFLD were found to have hypocalcemia.

Distribution of NAFLD Severity

Disease Stage	Frequency	Percentage
Mild	52	38.5%
Moderate	47	34.8%
Severe	36	26.7%

Most of the patients had mild to moderate disease with approximately a quarter of them having severe disease.

Association of Hypocalcemia with Disease Severity

Disease Stage	Hypocalcemia Present	Hypocalcemia Absent	p-value
Mild	11 (21.1%)	41 (78.9%)	
Moderate	18 (38.3%)	29 (61.7%)	
Severe	17 (47.2%)	19 (52.8%)	0.03

The prevalence of hypocalcemia was much higher in moderate and severe NAFLD patients than mild disease patients ($p \leq 0.05$).

Interpretation

The findings of the present research indicate that hypocalcemia is not an uncommon occurrence in patients having non-alcoholic fatty liver disease with the incidence being around 34.1% of patients. Moreover, it was also discovered that lower calcium levels were strongly correlated with high severity of the disease, that means that there might be a relationship between the disruptions in calcium metabolism and NAFLD progression. These results will indicate that serum calcium monitoring can offer a benefit of identifying patients at risk of severe liver disease, which will ultimately enhance clinical care and minimize the complications of the disease.

DISCUSSION

Non-alcoholic fatty liver disease (NAFLD) has become one of the fastest growing chronic liver diseases in the world and is closely correlated with obesity, metabolic syndrome, insulin resistance and type 2 diabetes mellitus ¹. Hypocalcemia in the current analysis was detected in 34.1 percent of patients with NAFLD meaning that there is significant imbalance in calcium metabolism in the affected population. This observation is in line with the other reports that have shown a strong relationship between a change in serum calcium levels and NAFLD in other groups^{8, 9}.

Large population-based analyses also support our results. Indicatively, a study of the results of the NHANES 1999 to 2018 cohort revealed that unadjusted and albumin-corrected serum calcium levels had an independent relationship with the incidence of NAFLD¹⁰. These results indicate that calcium homeostasis may contribute to the pathogenesis of NAFLD and probably by different mechanisms that include; changes in intracellular calcium signaling, hormonal regulation, and metabolic malfunctioning of lipid metabolism and hepatic steatosis.

In addition to hepatic fat deposition, NAFLD has also been noted to be a systemic metabolic disease with extrahepatic expressions. The emergence of evidence indicates that NAFLD can have a detrimental influence on bone health and mineral metabolism. Several observational and genetic studies have shown that NAFLD is inversely related to bone mineral density (BMD), implying that NAFLD patients are at risk of developing osteoporosis and fractures. Mendelian randomization studies also have suggested that NAFLD and lower BMD may be causally related, possibly through metabolic mechanisms (e.g. insulin resistance and changes in glucose metabolism) ^{11, 12, 17}. Moreover, recent findings verify that NAFLD patients characteristically have markedly reduced serum calcium and vitamin D levels with reduced BMD in comparison with controls, which supports the idea of a metabolism axis of the liver and bone under this condition^{14, 20}.

Another major connection between NAFLD and mineral homeostasis disruptions is vitamin D metabolism. Vitamin D is vital in the absorption of calcium and immune system as well as in metabolism. According to several clinical studies, low serum

levels of 25-hydroxyvitamin D have been implicated in the risk and severity and progression of NAFLD. An example of this is the decreased levels of vitamin D which are associated with higher levels of hepatic fibrosis and poorer metabolism in patients with NAFLD and type 2 diabetes mellitus, who are characterized by reduced vitamin D levels¹³. It has also been demonstrated using meta-analyses that there is a significant deficiency in vitamin D in persons with NAFLD, as opposed to healthy populations, indicating that sufficient vitamin D status may serve as a protective factor against disease progression¹⁸.

Mechanistic and clinical research that have taken place recently also underscore the importance of vitamin D signaling pathways in the development of NAFLD. Vitamin D has been reported to modulate the hepatic inflammation, insulin sensitivity as well as lipid metabolism, all of which are key processes in the progression of NAFLD¹⁵. Vitamin D metabolic imbalances can thus have a role to play in causing hepatic steatosis and general metabolic derangements in NAFLD patients.

Nutritional intake and micronutrient status also seem to be the significant risk and severity factor in NAFLD. Nutritional research studies indicate that insufficient intake of important minerals, such as calcium and magnesium, could lead to maladaptation of metabolism and susceptibility to NAFLD. The mineral deficiencies can increase oxidative stress, insulin resistance and inflammatory processes, further exacerbating hepatic steatosis and metabolic impairment¹². These results highlight the need to carry out detailed nutritional evaluation and treatment in patients with NAFLD.

The other encouraging outcome in current research was that hypocalcemia was more prevalent in patients with more severe NAFLD. This observation indicates that mineral metabolism problems could deteriorate with the progression of liver disease. Persistent liver dysfunction could result in dysfunction of the vitamin D activation process, changes in parathyroid hormone actions and calcium homeostasis, which finally leads to metabolic problems in the whole body and bone diseases.

The combination of these findings allows adhering to the idea that NAFLD can be viewed as a multisystem metabolic syndrome, but not an isolated liver disease. The interactions between the hepatic metabolism, bone, and micronutrient status support the practical value of clinical approach complex in NAFLD treatment. Regular check-ups of serum calcium, vitamin D, and other micronutrients can be used to detect abnormalities in metabolism at an early period and implement nutritional and therapeutic measures in time. These measures can possibly lower the course of the disease, enhance metabolic efficiency and avoid long-term complications of NAFLD.

CONCLUSION

The current research reveals that hypocalcemia is quite an epidemiological issue in patients with non-alcoholic fatty liver disease (NAFLD), as over one-third of the research participants have hypocalcemia. Notably, the reduced serum calcium levels were highly correlated with the severity of the disease with the highest prevalence being on patients having moderate and severe NAFLD. Secondly, the vitamin D deficiency in a notable percentage of patients with hypocalcemia also shows that calcium and vitamin D metabolism interact in NAFLD pathogenesis. These data hint that frequent evaluation of serum calcium and vitamin D concentrations can give useful clinical data about the metabolic imbalance and the development of the disease in NAFLD patients. These abnormalities can be identified and corrected early, which would possibly lead to better clinical outcomes, less complications, and more effective clinical management strategies. It is advisable to carry out further large-scale, multi-center studies to gain a more specific insight into the causal relationship between metabolism of calcium and NAFLD in Pakistani people and plan the evidence-based intervention.

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