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Original Research Article

# Comparative Observational Hospital Based Study of Vitamin D Levels in Healthy Controls and Non-Cholestatic Chronic Liver Disease

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**Conflict of interest: Nil**

**Abstract**

**Background:** Chronic liver disease (CLD) is defined as the long-term, ongoing destruction and regeneration of the liver; cirrhosis and hepatic fibrosis (scarring) frequently appear as the disease advances. Given that the liver is involved in the production of bile salts, the absorption of vitamin D, and the 25-hydroxylation of vitamin D, it seems sense that vitamin D deficiency would be common in individuals with chronic liver disease (CLD).

**Methods:** From March 2025 to August 2025, 60 patients participated in the present hospital-based observational comparison analysis, which was carried out in the Department of Medicine at SKMCH, Muzaffarpur, Bihar. In order to confirm the anticipated difference of 58.6% in the proportion of cases with vitamin D deficiency in the non-cholestatic chronic liver disease group with age and sex matched control group (hospital staff and patient attendants) (76.5% vs. 17.96%), a minimum sample size of 30 was needed in each group at 95% confidence interval and 80% power.

**Results:** 30 study participants were cases and 30 study participants were controls. Out of the total study participants 23 (38.3%) were female and 37 (61.7%) patients were male and the male to female sex ratio was 1.6 : 1. The mean age of 30 cases in our study was 39.1 ± 8.69 years and the mean age of 30 controls was 38.4 ± 8.02 years and no significant difference was observed. Mean serum Vitamin D3 was lower in CLD cases (23.4 ± 6.44 ng / L) as compared to controls (43.8 ± 5.18 ng/ L). This difference was statistically significant with a p value <0.001. In univariate analysis in patients with non-cholestatic CLD, significant (P<0.05) positive correlations were found between serum level of vitamin D and serum bilirubin, serum albumin, platelet count, & haemoglobin. Also, there were significant (P<0.05) negative correlations between vitamin D concentration and serum bilirubin, INR & MELD score. No significant correlation was seen between vitamin D and age, serum level of PTH, calcium, phosphate, ALT, AST, ALP, urea, or creatinine.

**Conclusion:** In non-cholestatic CLD patients, vitamin D deficiency is quite prevalent and is correlated with the disease's severity. Therefore, we advise that the evaluation of each patient's vitamin D level be included of clinical guidelines for the management of non-cholestatic CLD. More research is needed to evaluate and replace vitamin D in the treatment of patients with non-cholestatic CLD.

Keywords: Chronic Liver Disease, Vitamin D Inadequacy, Non-Cholestatic CLD.

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## Introduction

Hepatic fibrosis (scarring) and cirrhosis are common as the condition progresses. Chronic Liver condition (CLD) is the process of the liver's long-term progressive destruction and regeneration.[1] Hepatocellular carcinoma (HCC), infections, and chronic liver failure are among the hepatic consequences linked to the advancement of CLD and decline in liver function. Hepatic osteodystrophy is a significant extrahepatic sign of severe liver illness that resembles the symptoms of traditional osteoporosis and increases the risk of fractures.[2] The metabolism of vitamin D and

bone is significantly influenced by the liver. The liver hydroxylates vitamin D to its primary circulating form, 25-hydroxy vitamin D, which the kidneys then transform into the active form 1, 25-dihydroxyvitamin D.[3] It is reasonable to assume that vitamin D deficiency would be prevalent in people with chronic liver disease (CLD) as the liver is involved in the formation of bile salts, vitamin D absorption, and 25-hydroxylation of vitamin D.[4] As a secosteroid hormone, vitamin D is primarily recognized for its ability to regulate the metabolism of calcium and bone. Nonetheless, vitamin D has a variety of pleiotropic effects, such as immunomodulation, cellular differentiation, and proliferation. The pathophysiology and management of infections, cardiovascular, autoimmune, degenerative, and various cancers have all been linked to these extra-skeletal consequences.

Conflicting findings have been found in earlier research examining the relationship between vitamin D, blood PTH level, and the degree of hepatic dysfunction. According to a study, over 90% of patients who are candidates for liver transplantation and over two-thirds of patients with end-stage liver disease do have low vitamin D levels without osteomalacia.[4] However, some other investigations have produced contradictory findings.[5]

Notably, vitamin D is also thought to have qualities that include collagen production, fibroblast stimulation, and the regulation of metalloproteinase and its inhibitors' synthesis. These findings support the theory that vitamin D may play a part in the development of CLD and hepatic damage. The purpose of this study was to assess the patterns of vitamin D disruption and correlate it in a group of patients with non-cholestatic CLD, given the paucity of research on vitamin D status in these patients.

## Material and Methods

The Department of Medicine at Sri Krishna Medical College and Hospital in Muzaffarpur, Bihar, carried out the current hospital-based observational comparison investigation between March and August of 2025. The minimum sample size required was 14 in each group at 95% confidence interval and 80% power to verify the expected difference of 58.6% in proportion of cases with vitamin D deficiency in Non cholestatic chronic liver disease group with age and sex matched control group (hospital staff and attendants of patients) (76.5% vs 17.96%). We enhanced the sample size to 30 in each group. Venous blood samples were obtained after an overnight 10–12 h of fasting. All patients with non-cholestatic CLD (Hepatitis B, Hepatitis C, Autoimmune Hepatitis and Cryptogenic cause) attending department of Medicine were included in the study. Patient on medication with vitamin D or calcium supplement, bisphosphonates, calcitonin, hormone replacement therapy, corticosteroids or anti-viral drugs were excluded from the study.

The diagnosis of CLD was based on consistent clinical findings, serologic markers of hepatitis B and C, hepatitis B virus DNA, and hepatitis C virus RNA measurements by polymerase chain reaction method, auto antibodies (anti- nuclear antibody, anti-smooth muscle antibody), bio- chemical features (including iron studies, ceruloplasmin, and urinary copper), endoscopic and imaging (including abdominal ultrasonography) evidence, and histological examinations (liver biopsy examination). The diagnosis of cirrhosis was established by liver biopsy or definitive clinical or bio- chemical evidence of hepatocellular failure and / or portal hypertension. Liver biopsy was performed for patients who did not have contraindication and samples were studied for fibrosis and inflammation. The Model for End-Stage Liver Disease (MELD) score was also calculated. The resulting study groups were subjected to detailed history and examination followed by vitamin D and PTH and other relevant tests.

Data were analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, USA). Variables were expressed as percentage or mean ± standard deviation (SD). Patients with and without cirrhosis were compared using Chi-square analysis for categorical variables and independent sample t test for continuous variables. Comparison of variables between categories of vitamin D was performed using analysis of variance (ANOVA). Pearson correlation coefficients were calculated between vitamin-D and other variables. p value $<0.05$ was considered significant.

## Results

A total of sixty study participants were included in this investigation. Thirty of the study participants were controls, and thirty were cases. The male to female sex ratio was 1.6:1, with 37 (61.7%) patients being male and 23 (38.3%) female of the total study participants. In our investigation, there was no discernible difference between the mean age of 30 cases (39.1 ± 8.69 years) and 30 controls (38.4 ± 8.02 years). Table 1 makes clear that there were 19 males and 11 females in the case group and 18 males and 12 females in the control group. The sex composition of the case and control groups did not differ significantly. (Table 1)

**Table 1: Distribution of Patients according to age and sex**

| Parameters | Case | Control | P value |
|---|---|---|---|
| Mean age (years) | 39.1±8.69 | 38.4±8.02 | 0.724 |
| Female | 11(36.7%) | 12(40%) | 0.791 |
| Male | 19(63.3%) | 18(60%) | |

**Table 2: Comparison of Mean Serum Vitamin $D_3$ (ng/dl) in the study groups**

| Group | Number | Mean | Std. Deviation |
|---|---|---|---|
| Case | 30 | 23.4 | 6.44 |
| Control | 30 | 43.8 | 5.18 |

**t= -13.592; at 58 degree of freedom; p<0.001 (S)**

Table 2 indicates that mean serum Vitamin-D3 was lower in CLD cases (23.4 ± 6.44 ng / L) as compared to controls (43.8 ± 5.18 ng / L). This difference was statistically significant with p value <0.001.

**Table 3: Correlation of Vitamin D3 with Different Parameters among CLD Cases**

| Variable | Correlation Co-efficient | P-value |
|---|---|---|
| Age | -0.118 | 0.535 |
| Bilirubin | -0.507 | 0.004 (S) |
| ALP | -0.161 | 0.396 |
| SGOT | -0.129 | 0.496 |
| SGPT | -0.098 | 0.608 |
| Albumin | 0.384 | 0.036(S) |
| INR | -0.472 | 0.009(S) |
| Platelet | 0.373 | 0.043(S) |
| Hemoglobin | 0.418 | 0.002(S) |
| Calcium | 0.303 | 0.104 |
| Phosphorus | -0.076 | 0.689 |
| PTH | 0.015 | 0.937 |
| Urea | 0.110 | 0.561 |
| Creatinine | 0.006 | 0.976 |
| MELD score | -0.671 | 0.002(S) |

In univariate analysis in patients with non-cholestatic CLD, significant (P<0.05) positive correlations were found between serum level of vitamin D and serum bilirubin, serum albumin, platelet count & haemoglobin. Also, there were significant (P<0.05) negative correlations between vitamin D concentration and serum bilirubin, INR &MELD score. No significant correlation was seen between vitamin D and age, serum level of PTH, calcium, phosphate, ALT, AST, ALP, urea, or creatinine. (Table3)

**Discussion**

In this study, we assessed the relationship between clinically useful parameters in cirrhotic and noncirrhotic patients with non-cholestatic CLD (ALT, AST, ALP, bilirubin, albumin, INR, Child–Pugh score, and MELD score) and calcium–phosphate metabolism parameters (vitamin D, PTH, calcium, and phosphate). In the current investigation, the mean age of CLD patients was 39.1 ± 8.69 years, whereas the mean age of controls was 38.4 ± 8.02 years. No discernible difference was found between the two groups. The study conducted by Miroliaee et al. [6] found that the mean age of the control group was 40.98 ± 9.29 years, whereas the mean age of the case group was 42.39 ± 13.02 years. Age and sex did not significantly differ between patients and healthy controls. The causes of CLD were viral hepatitis C (n=11), viral hepatitis B (n=6), autoimmune hepatitis (n=3), and cryptogenic (n=10). Cirrhosis was evident in 19 patients. The main causative factor for cirrhosis was viral hepatitis C (36.8%), whereas in the non-cirrhotic group cryptogenic (36.4%) and viral hepatitis C (36.4%) were more prevalent. Similar study was done by Miroliaeeet al[6] enrolled 90 consecutive patients with evidence of non-cholestatic CLD due to hepatitis C (n=28), hepatitis B (n=26), autoimmune hepatitis (n=19), and cryptogenic causes (n=17). Cirrhosis was evident in 51 patients. The main causative factor for cirrhosis was viral hepatitis C (31.4%), whereas in the noncirrhotic group viral hepatitis B (33.3%) and C (30.8%) were moreprevalent.

We demonstrated that the majority of non-cholestatic CLD patients (86.6%) had insufficient serum vitamin D concentrations. In present study mean serum Vitamin D3 of 30 cases was 23.4 ng / mL and mean serum Vitamin D3 of 30 controls was 43.8 ng / mL. Standard deviation was 6.44 in case group and 5.18 in control groups. Mean serum Vitamin D3 was lower in cases (23.4 ± 6.44 ng /

mL) as compared to controls (43.8±5.18ng/mL). This difference was significant as p value was <0.001. Although we found a strong association between serum 25 (OH) D concentration and liver injury, this does not establish the relationship as causal. One would expect older patients to have lowered25 (OH) D levels. However, there was no age difference in our series. Other possible factors contributing to vitamin D insufficiency in CLD may include the following: (1) reduced exposure to sunlight (patients with CLD and greater liver function abnormalities possibly spend less time outdoors), (2) dietary insufficiency, (3) malabsorption, (4) low levels of serum proteins that bind with vitamin D, (5) impaired cutaneous synthesis of vitamin D in jaundiced patients, (6) decrease hepatic hydroxylation of vitamin D to 25 (OH)D,(7) increase catabolism and removal of 25 (OH)D. One could speculate that in individual CLD patients, inadequacy in vitamin D status is determined by different pathogenic factors.

Similar results obtained in study done by Miroliaee et al[6] in which the mean value of serum Vitamin D3 (nmol / L) in controls and cases were found to be 95.28 ± 29.41 and 40.721 ± 22.43 nmol / L respectively (p< 0.001). Zhao et al found that serum 25 (OH)D levels in chronic hepatitis B patients (7.83±3.47ng/mL) were significantly lower than that in healthy controls (9.76 ± 4.36 ng / mL, P<0.001). Similar study done by Fisher et al.[8] obtained that serum 25 (OH) D levels were inadequate in 91 patients: vitamin D deficiency (<50 nmol / L) was found in 68 patients and vitamin D insufficiency (50-80 nmol / L) was found in 23 patients.(P<0.05).

In univariate analysis in patients with non-cholestatic CLD, significant (P<0.05) positive correlations were found between serum level of vitamin D and serum bilirubin, serum albumin, platelet count and haemoglobin. Also, there were significant (P<0.05) negative correlations between vitamin D concentration and serum bilirubin, INR & MELD score. No significant correlation was seen between vitamin D and age, serum level of PTH, calcium, phosphate, ALT, AST, ALP, urea, or creatinine. Fisher et al. [8] showed that serum vitamin D levels less than 25 nmol / l would be a reliable predictor of higher INR and serum bilirubin as well as lower serum albumin and platelet count. Hen et al. [9] reported a positive correlation of serum 25 (OH) D concentrations with albumin levels (r = 0.655, P < 0.0001). Christos Konstantakis et al[10] showed that there is evidence of a significant relation of 25(OH) D levels with the degree of liver dysfunction, considering that an inverse correlation of 25 (OH) D levels with both Child-Pugh score and Model for End-Stage Liver Disease has been reported. Our results, demonstrating the high rate of vitamin D deficiency in CLD patients, could possibly suggest that screening and treatment of vitamin D deficiency should be considered in the management of patients with CLD. It should be noted that vitamin D insufficiency is not only a causative factor for bone diseases in the general population but also a risk factor for a wide range of chronic inflammatory and autoimmune diseases (inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis and diabetes mellitus), cancers (colon, prostate and breast), and metabolic disorders (metabolic syndrome and hypertension).[9] Vitamin D can influence hepatic injury, fibrosis, and tissue remodelling by different mechanisms. Vitamin D and its derivates are potent regulators of cell proliferation, differentiation, and immunomodulation. These effects include inhibition of certain matrix metalloproteinases (MMPs) and induction of their inhibitors, suppression of proliferation of fibroblasts, and increased collagen production. Vitamin D insufficiency is associated within creased circulating MMP -2 and -9, which is correctable by supplementation. Hepatocytes produce the major MMPs and tissue inhibitors involved in liver extracellular matrix remodelling. MMP-2 and -9 are of particular relevance to the liver because they are critically involved in the degradation of components of the basement membrane such as collagen IV and fibronectin, 2 main components of the space of Disse. Inhibition of MMPs protects from hepatic ischemic injury.[10]

Therefore, determination and treatment of vitamin D deficiency may represent an important therapeutic target in the follow-up of CLD patients. Vitamin D deficiency may present with bone pain, proximal muscle weakness, and bone fracture, but many patients are asymptomatic. After liver transplantation and corticosteroid therapy, many patients will be symptomatic. Our results, demonstrating the high rate of vitamin D deficiency in CLD patients, could possibly suggest that screening and treatment of vitamin D deficiency should be considered in the management of patients with CLD.

The study demonstrated that the majority of non-cholestatic CLD patients had significant insufficient serum vitamin D concentrations. Serum Parathyroid Hormone was significantly higher in CLD cases and serum levels of calcium and phosphate were normal in many patients with vitamin D deficiency.

This can be explained by reabsorption of minerals from bones. So, osteopenia and osteomalacia could be expected in these patients. Our study also showed a significant correlation between low serum vitamin D level and markers of liver function insufficiency including coagulopathy, hypoalbuminemia, hyperbilirubinemia, and

thrombocytopenia.

In our study univariate analysis in patients with non- cholestatic CLD, significant positive correlations were found between serum level of vitamin D and serumbilirubin, serum albumin, platelet count & haemoglobin. Also, there were significant negative correlations between vitamin D concentration and serum bilirubin, INR & MELD score. No significant correlation was seen between vitamin D and age, serum level of PTH, calcium, phosphate, ALT, AST, ALP, urea, or creatinine.

## Conclusion

In conclusion, vitamin D deficiency is quite prevalent in non-cholestatic CLD patients and is associated with the severity of the illness. Therefore, we advise that the evaluation of each patient's vitamin D level be included of clinical guidelines for the management of non-cholestatic CLD. More research is needed on vitamin D replacement in the treatment of patients with non-cholestatic CLD.

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