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ORIGINAL ARTICLE

# Prevalence of Vitamin D Deficiency in Chronic Liver Disease

**J. Arteh · S. Narra · S. Nair**

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**Abstract** Vitamin D deficiency has been associated with cholestatic liver disease such as primary biliary cirrhosis. Some studies have suggested that cirrhosis can predispose patients to development of osteoporosis because of altered calcium and vitamin D homeostasis. The aim of this study was to determine the prevalence of vitamin D deficiency in patients with chronic liver disease.

*Methods* One hundred and eighteen consecutive patients (43 with hepatitis C cirrhosis, 57 with hepatitis C but no cirrhosis, 18 with nonhepatitis C-related cirrhosis) attending the University of Tennessee Hepatology Clinic had their 25-hydroxyvitamin D level measured. Severity of vitamin D deficiency was graded as mild (20–32 ng/ml), moderate (7–19 ng/ml) or severe (<7 ng/ml), normal being >32 ng/ml.

*Results* Of patients, 109/118 (92.4%) had some degree of vitamin D deficiency. In the hepatitis C cirrhosis group, 16.3% (7/43) had mild, 48.8% (21/43) had moderate, and 30.2% (13/43) had severe vitamin D deficiency. In the hepatitis C noncirrhotic group, 22.8% (19/57) had mild, 52.6% (30/57) had moderate, and 14% (8/57) had severe vitamin D deficiency. In the nonhepatitis C-related cirrhosis group, 38.9% (7/18) had mild, 27.8% (5/18) had moderate, and 27.8% (5/18) had severe vitamin D deficiency. Severe vitamin D deficiency (<7 ng/ml) was more common among patients with cirrhosis compared with noncirrhotics (29.5% versus 14.1%, $P$ value = 0.05). Female gender, African American race, and cirrhosis were independent predictors of severe vitamin D deficiency in chronic liver disease.

*Conclusion* Vitamin D deficiency is universal (92%) among patients with chronic liver disease, and at least one-third of them suffer from severe vitamin D deficiency. African American females are at highest risk of vitamin D deficiency.

**Keywords** Vitamin D deficiency · Chronic liver disease · Cirrhosis

**Abbreviations**

| | |
|---|---|
| BMI | Body mass index |
| CLD | Chronic liver disease |
| HCV | Hepatitis C virus |
| MMP | Matrix metalloproteinase |
| 25(OH)D | 25-hydroxyvitamin D |

## Introduction

The liver plays an important role in metabolism of vitamin D. Vitamin D from the skin and diet is hydroxylated in the liver into 25-hydroxyvitamin D [25(OH)D]. 25(OH)D,

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Study Highlights

High prevalence of severe vitamin D deficiency in patients with chronic liver disease.

Severe vitamin D deficiency correlated with severity of liver disease.

African Americans and women are at highest risk for severe vitamin D deficiency.

J. Arteh
Department of Internal Medicine, University of Tennessee Health Science Center, Memphis, TN, USA

S. Narra · S. Nair (✉)
Division of Gastroenterology and Hepatology, University of Tennessee Health Science Center, Memphis, TN 38163, USA
e-mail: snair@utmem.edu

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the major circulating form of vitamin D, is used to determine a patient's vitamin D status [1]. 25(OH)D, in turn, is transported to the kidney, undergoes a second hydroxylation, and is converted into 1,25(OH)D, the active form [1]. Consequently, diseases of the liver interfere with production of the active metabolites of vitamin D, thus resulting in abnormal calcium and bone metabolism [2].

Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture [3, 4]. There is also an increasing body of evidence that shows association of vitamin D deficiency with various types of cancer (e.g., colon, prostate, breast), autoimmune, inflammatory, and metabolic disease processes [5].

Previous studies have reported inconsistent results with respect to serum concentrations of 25(OH)D and its relationship with the severity of liver disease. Some studies suggested that 25(OH)D levels decrease with progression of liver disease [6–10]; others did not find a difference between cirrhotic and noncirrhotic patients [11] or between various Child-Pugh groups [12]. However, much of the focus has been given to vitamin D deficiency in cholestatic liver disease and alcoholics. Thus, the main objective of our study was to determine the prevalence of vitamin D deficiency in patients with chronic liver disease of varying etiologies and its relationship to the severity of liver dysfunction.

## Methods

The study group consisted of 118 consecutive patients with chronic liver disease seen at a tertiary care Hepatology Clinic at the University of Tennessee Health Science Center. The demographics and clinical profile of the patients are summarized in Table 1. The group consisted of 59 males and 59 females, with mean age of 53.2 ± 8.9 years (range 23–72 years). Forty-three had hepatitis C cirrhosis, 57 had hepatitis C without cirrhosis, and 18 had nonhepatitis C cirrhosis. The latter group consisted of six patients with nonalcoholic fatty liver disease, four patients with autoimmune hepatitis, three patients with hemochromatosis, two with alcoholic cirrhosis, one with chronic hepatitis B, one with overlap syndrome, and one for whom etiology was unknown. The diagnosis of cirrhosis was established by liver biopsy or by definitive clinical or biochemical evidence of hepatocellular failure and/or portal hypertension. Sixteen patients (13%) had ascites or diuretic controlled ascites at the time of the evaluation. The presence of hepatitis C infection was established by documentation of hepatitis C virus (HCV) RNA. None of the patients were taking vitamin D or calcium supplements at the time of the study. No patient had alcohol use during the last 6 months of the visit, even though alcohol might have contributed to cirrhosis in six patients.

Vitamin D status was assessed by measuring serum concentration of 25(OH) vitamin D. The test was performed using automated chemiluminescence immunoassay (DiaSorin Liaison, Stillwater, MN, USA) with a laboratory reference range of 32–100 ng/ml (commercial assay multiply by 2.496 for nmol/L). According to the assay, the normal 25(OH)D level is ≥32 ng/ml. Degree of vitamin D level was arbitrarily categorized as mild (20–31 ng/ml), moderate (7–19 ng/ml) or severe (<7 ng/ml).

### Statistical Analysis

Univariate analysis was performed to identify whether age, gender, race, body mass index (BMI), diabetes, severity of liver disease (cirrhosis versus noncirrhosis) or etiology (HCV versus non-HCV) was associated with severe vitamin D deficiency (<7 ng/ml). Categorical variables were compared using chi-square test, and continuous variables were analyzed by Student's *t*-test. A *P* value of <0.05 was considered statistically significant. A multiple logistic regression (stepwise forward conditional) model was used to identify any risk factors for severe vitamin D deficiency (<7 ng/ml).

## Results

Demographics and clinical profile of patients are presented in Table 1. Vitamin D deficiency, defined as 25(OH)D < 32 ng/ml, was seen in 109 out of 118 patients (92.4%). In

**Table 1** Patient ($n = 118$) demographics and clinical profile

| | |
|---|---|
| Age (years) | 53 ± 9 |
| Gender (female) | 50% |
| Race (Caucasians/African Americans) | 55%/45% |
| BMI (kg/m$^2$) | 29.4 ± 7.6 |
| HCV (%) | 100 (84%) |
| Cirrhosis | |
| HCV cirrhosis | 43(36%) |
| Non-HCV cirrhosis | 18 (15%) |
| Ascites | 16 (13%) |
| AST (IU/L) | 2 ± 65 |
| ALT (IU/L) | 60 ± 69 |
| Alkaline phosphatase (IU/L) | 106 ± 51 |
| Total bilirubin (mg/dL) | 1.1 ± 4.8 |
| S. albumin (gm/dL) | 3.8 ± 0.6 |
| INR | 1.14 ± 0.34 |
| Serum calcium (mg/dL) | 8.2 ± 1.4 |
| S. creatinine (mg/dL) | 1.0 ± 0.7 |

*HCV* hepatitis C virus

the HCV cirrhosis group, 16.3% (7/43) had mild, 48.8% (21/43) had moderate, and 30.2% (13/43) had severe vitamin D deficiency (Table 2). In the hepatitis C noncirrhotic group, 22.8% (19/57) had mild, 52.6% (30/57) had moderate, and 14% (8/57) had severe vitamin D deficiency. In the nonhepatitis C cirrhosis group, 38.9% (7/18) had mild, 27.8% (5/18) had moderate, and 27.8% (5/18) had severe vitamin D deficiency (Table 2). A total of 61 patients had cirrhosis, the main etiology being hepatitis C (70.5%). Only three had normal 25(OH)D levels, defined as >32 ng/ml.

Table 3 presents the results of univariate analysis of risk factors for severe vitamin D deficiency (<7 ng/ml) in all patients; severe vitamin D deficiency (<7 ng/ml) was more common in cirrhotic (29.5%) than in noncirrhotic patients (14%; $P$ value = 0.05), in African American (35.2%) than in Caucasian patients (10.1%, $P$ value = 0.001), and in female (29.7%) than in male patients (13.1%, $P$ value = 0.03). There was no difference in prevalence of severe vitamin D deficiency between diabetic and nondiabetic patients, HCV and non-HCV patients, obese (BMI ≥30 kg/m$^2$) and nonobese patients (BMI <30 kg/m$^2$) or older (>55 years) and younger patients (≤55 years). Mean age and BMI were not statistically different between patients with severe vitamin D deficiency and those without the deficiency (Mann–Whitney $U$ test). Similarly, liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and bilirubin were not statistically significant between those with severe deficiency and those without. Serum creatinine and calcium were also not statistically different in patients with severe vitamin deficiency. In a logistic regression model (stepwise forward conditional, Table 4), only female gender, African American race, and presence of cirrhosis were independent risk factors for severe vitamin D deficiency. In a similar model to assess the risk factors for severe vitamin D deficiency in cirrhotics, only female gender and African American race were independent predictors (Table 5).

## Discussion

In addition to its role in calcium metabolism, vitamin D derivatives may be involved in cell proliferation, differentiation, and immunomodulation [13]. Vitamin D inhibits certain types of matrix metalloproteinases (MMP, a family of zinc-dependent endoproteinases that are involved in degradation of extracellular matrix components) and induces their inhibitors [14]. Consequently, vitamin D

**Table 3** Univariate analysis of variables associated with severe vitamin deficiency (<7 ng/ml) in patients with severe vitamin D deficiency

| | Vitamin D <7 ng/ml | Vitamin D >7 ng/ml | $P$ value |
|---|---|---|---|
| Race | | | |
| AA | 35% | 65% | 0.001 |
| White | 10% | 90% | |
| Gender | | | |
| Male | 13% | 87% | 0.03 |
| Female | 30% | 70% | |
| Severity of liver disease | | | |
| Cirrhosis | 29% | 71% | 0.03 |
| Noncirrhosis | 14% | 86% | |
| BMI (kg/m$^2$) | 30.9 ± 8.7 | 29 ± 7.2 | NS |
| AST (IU/L) | 48 ± 33 | 66 ± 66 | NS |
| Alkaline phosphatase (IU/L) | 121 ± 67 | 103 ± 46 | NS |
| Albumin (gm/dL) | 3.6 ± 0.7 | 3.9 ± 0.6 | NS |
| INR | 1.13 ± 0.13 | 1.15 ± 0.42 | NS |
| S. bilirubin (total; mg/dL) | 0.8 ± 0.5 | 1.2 ± 1.0 | NS |
| S. creatinine (mg/dL) | 1.05 ± 0.4 | 0.99 ± 0.7 | NS |
| S. calcium (mg/dL) | 8.7 ± 1.2 | 8.3 ± 1.4 | NS |

Fisher exact test for categorical variables and Mann–Whitney $U$ test for continuous variable

All percentage values are rounded off to the nearest whole number

*NS* not significant

**Table 2** Vitamin D status in chronic liver disease ($N$ = 118)

| Group | Serum 25(OH)D, ng/ml | | | | Total ($n$ = 118) |
|---|---|---|---|---|---|
| | >32 ng/ml $n$ (%) | 20–32 ng/ml $n$ (%) | 7–19 ng/ml $n$ (%) | <7 ng/ml $n$ (%) | |
| HCV cirrhosis | 2 (4.7) | 7 (16.3) | 21 (48.8) | 13 (30.2) | 43 |
| HCV without cirrhosis | 6 (10.5) | 13 (22.8) | 30 (52.6) | 8 (14.0) | 57 |
| Non-HCV cirrhosis | 1 (5.6) | 7 (38.9) | 5 (27.8) | 5 (27.8) | 18 |
| All groups | 9 (7.6) | 27 (22.9) | 56 (47.5) | 26 (22.0) | 118 |

Conversion factor for 25(OH) vitamin D for SI units (nmol/L) is 2.496

*HCV* hepatitis C virus, *25(OH)D* 25-hydroxyvitamin D in ng/ml

**Table 4** Logistic regression model for independent risk factors (stepwise forward conditional entry) for severe vitamin D deficiency (<7 ng/ml) in chronic liver disease ($n = 118$)

| | Odds ratio (95% CI) | *P* value |
|---|---|---|
| Gender (female) | 3.8 (1.23–11.7) | 0.02 |
| Race (African American) | 8.43 (2.5–27.8) | 0.0001 |
| Cirrhosis | 4.7 (1.5–15.53) | 0.01 |

Factors entered into the model were age (≤55 versus >55 years), gender, race, diabetes, BMI (<30 versus ≥30 kg/m$^2$), HCV versus non-HCV, and cirrhosis versus noncirrhosis

**Table 5** Logistic regression model for independent risk factors (stepwise forward conditional entry) for severe vitamin D deficiency (<7 ng/ml) in cirrhosis only ($n = 61$)

| | Odds ratio (95% CI) | *P* value |
|---|---|---|
| Gender (female) | 4.54 (1.01–20.7) | 0.02 |
| Race (African American) | 9.75 (2.2–42.8) | 0.0001 |

Factors entered into the model were age (≤55 versus >55 years), gender, race, diabetes, BMI (<30 versus ≥30 kg/m$^2$), HCV versus non-HCV, and cirrhosis versus noncirrhosis

deficiency has been associated with increased circulating MMP2,9, a situation that can be corrected with vitamin D supplementation [15]. Other effects of vitamin D include suppression of proliferation of fibroblasts and increased collagen production [16]. These data are relevant to chronic liver disease. Even though hepatocytes are the major source of MMPs and tissue inhibitors, their production is not affected by the presence of cirrhosis [17]. Therefore, vitamin D deficiency in patients with chronic liver disease (CLD) can lead to progression of hepatic fibrosis. Moreover, inhibition of MMPs has been shown to provide protection from hepatic ischemic injury [18, 19].

Our study showed high prevalence (92.4%) of vitamin D deficiency in 118 patients with chronic liver disease primarily due to noncholestatic causes. In addition, we observed that severe vitamin D deficiency, defined as 25(OH)D <7 ng/ml, was more common among patients with cirrhosis than among noncirrhotic patients (29.5% versus 14%). Our results are similar to the findings of a recent study [20] that analyzed 100 outpatients with noncholestatic CLD and showed that 91% of these subjects had vitamin D deficiency (<80 nmol/L). One mechanism for the higher prevalence of vitamin D deficiency in cirrhotics is impairment in the 25-hydroxylation of vitamin D [2, 10, 12, 21], which occurs in cholestatic forms of liver disease and alcoholic cirrhosis and leads to low serum levels of 25(OH)D in relation to the degree of liver dysfunction. In one study [22], deficient hepatic hydroxylation was observed only in patients with advanced CLD, whereas others found no impediment to the production of vitamin D metabolites even in the advanced stages of liver disease [23, 24]. The fact that cirrhosis was an independent risk factor for vitamin D deficiency in our study raises the question of whether impaired synthetic function of liver was responsible for low levels of vitamin D in some of our patients. However, the biochemical tests for liver dysfunction such as serum albumin, bilirubin, and international normalized ratio (INR) did not correlate with severe deficiency (Table 3). Several other factors could contribute to the development of vitamin D deficiency in patients with CLD, including inadequate exposure to the sun, insufficient dietary intake, corticosteroid use, and impaired cutaneous synthesis of vitamin D in the presence of jaundice.

One of the limitations of the study is that we did not measure parathyroid hormone (PTH) levels and hence we could not further explore the interaction between PTH levels and vitamin D calcium levels in liver disease, especially in those with advanced liver disease.

In conclusion, vitamin D deficiency is universal in patients with CLD, at least one-third of whom suffer from severe vitamin D deficiency. In view of the increasingly recognized beneficial effects of adequate levels of vitamin D, measurement of 25(OH)D levels and replacement may be considered as part of the overall management of patients with CLD.

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