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The correlation of vitamin D level with the disease etiology and disease level in patients with chronic liver disease

The correlation of vitamin D level with the disease etiology in with chronic liver disease

Ece Ulukal Karancı[1], Dinç Dinçer[2], Yusuf Karancı[3], Cihan Bedel[3]
[1] Department of Internal Medicine, Health Science University, Antalya Training and Research Hospital
[2] Division of Gastroenterology, Department of Internal Medicine, Akdeniz University Medical School
[3] Department of Emergency Medicine, Health Science University, Antalya Training and Research Hospital, Antalya, Turkey

Abstract

Aim: Although vitamin D (VD) deficiency or insufficiency is demonstrated to exist in the majority of patients with chronic liver disease (CLD), there are also studies that prove otherwise or show that this may only be related to VD deficiency at severe levels. Therefore, we aimed to evaluate 25-(OH)VD (25-OHD) level in patients with various type of CLD and the clinical significance of its deficiency or insufficiency.

Material and Methods: The 25-OHD levels measured in patients diagnosed with CLD were retrospectively recorded. According to their VD levels, patients were categorized into four groups as normal (≥30 ng/ml), insufficient (20-29.9 ng/ml), deficient (10-19.9 mg/ml) and severely deficient (<10 ng/ml).

Results: One hundred seventy-eight (52.4%) of 340 patients were females, and the mean age of the patients was 52.8±13.77 years. The mean 25-OHD level of the patients was 19.43±9.71. Patients with Hepatitis C Virus had significantly higher 25-OHD levels than patients with cirrhosis, non-alcoholic fatty liver disease (NAFLD) and Hepatitis B Virus (p=0.014). When the patients were divided into groups according to their 25-OHD levels, 47 patients (13.8%) were found to have a sufficient level, 113 (33.2%) an insufficient level, 120 (35.3%) a deficient level, and 60 (17.6%) a severely deficient level. In regression analysis, albumin and direct bilirubin are independent predictors of the VD level severity (odds ratio [OR]: 0.477, 95% confidence interval [CI]: 0.234-0.720, p <0.001; OR: 0.74, 95% CI: 0.135-1.609, p=0.021, respectively).

Discussion: High levels of VD deficiency can be seen in patients with CLD, especially in women. Awareness of VD level in patients with CLD, which can be detected through periodic screenings, may be beneficial

Keywords

Vitamin D, Chronic Liver Disease, Child-Pugh Score, MELD Score

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Corresponding Author: Cihan Bedel, Health Science University Antalya Training And Research Hospital, Kazım Karabekir Street, postal zip code: 07100, Muratpaşa, Antalya, Turkey.
E-mail: cihanbedel@hotmail.com P: +90 507 564 12 54 F: +90 242 249 44 87
Corresponding Author ORCID ID: https://orcid.org/0000-0002-3823-2929

Introduction

Vitamin D (VD) is among the fat-soluble vitamins and a group of sterols with hormones and hormone precursors, since they can also be synthesized endogenously in the appropriate biological medium. Its effect on calcium, phosphorus metabolism and bone mineralization is most important [1,2]. Over recent years, VD deficiency and insufficiency have been found to be correlated with many chronic and common diseases, including cancers, cardiovascular diseases, metabolic syndrome, infectious and autoimmune diseases. VD deficiency is currently considered a global pandemic [3,4].

VD synthesis in humans mainly results from the exposure of the skin to sunlight. For further activation, vitamin D is hydroxylated in liver to create 25-(OH) vitamin D (25-OHD) and transformed into 1,25 (OH)2 VD [1,25(OH)2 D], which is an active metabolite in the kidneys [5]. For this reason, severe VD deficiency can be foreseen in people with chronic liver disease (CLD). Studies have shown that VD deficiency or insufficiency is observed in most of the patients with CLD due to mainly alcohol, secondarily chronic hepatitis C (HCV) [6]. However, there are also studies suggesting that no significant correlation could be found between the VD level and CLD, or if there is a significant correlation, this may only be related to VD deficiency at severe levels [7,8]. Moreover, there are few studies that examine the correlation between cirrhosis and chronic hepatitis stages and VD level in the literature. The primary goal of this study was to document vitamin D deficiency in patients with CLD and find its association with the liver cirrhosis.

Therefore, in this study, it was aimed to compare the diseases leading to cirrhosis and chronic hepatitis, stage of cirrhosis, grade of hepatosteatosis, stage of chronic hepatitis, and activation level with 25-OHD that can be measured in blood.

Material and Methods

This study included 502 patients suffering from CLD, who applied to the gastroenterology department of a tertiary university hospital between August 2016 and February 2017. Primary inclusion criteria were as follows: (1) Patients with CLD; (2) patient's age ≥18 years; Exclusion criteria were as follows: (1) Patients suffering from other comorbid conditions such as ischemic heart disease, malignity or other chronic conditions (n=48), (2) Patients still receiving VD treatment (n=12), (3) Patients with missing laboratory data (n=102). Consequently, 340 patients complying with these criteria were selected for this study.

The diagnosis history of CLD was based on physical examination, biochemical abnormalities suggestive of CLD, such as impaired liver function tests, ultrasonography (US) signs of CLD, chronic liver parenchymal changes in liver biopsy, medical records suggesting. The diagnosis of alcoholic liver disease was established as more than one positive response in the (CAGE (Cut down, Annoy, Guilt, Eye opener) questionnaire based on the medical history of the patients. In this scoring, item responses in CAGE questions receive 0 points for "no" and 1 point for "yes" answers. A high score is an indicator of alcohol-related problems. A total score of two or more is considered clinically significant. However, there was no single laboratory and imaging study to confirm the diagnosis, we had to use CAGE to diagnose alcoholic liver disease. The diagnosis of chronic hepatitis B (HBC) and HCV was based on serologic markers (HBV surface antigen with ELISA, anti-HCV antibody with third-generation ELISA, anti-HIV antibodies) and liver function tests, including assessment of alanine transaminase (ALT) and aspartate transaminase (AST) enzyme levels, alpha fetoprotein, platelet count, total and direct bilirubin, albumin and prothrombin were tested. Autoimmune hepatitis markers were also evaluated for the diagnosis of autoimmune hepatitis. The diagnosis of non-alcoholic fatty liver disease was based on the typical (US) findings of hepatosteatosis without the history of significant alcohol consumption. Cirrhosis patients without any reason were determined to have cryptogenic cirrhosis.

The demographic profile and history of the patients were examined in full. From the samples taken during the admission of the patients, serum bilirubin, serum albumin, international normalized ratio (INR) and blood platelet counts were recorded. Hepatitis serology and autoimmune markers were examined for the diagnosis of CLD. Blood samples were taken in a dark room for the prediction of 25 (OH) VD, and its levels were checked in the serum using the UV detector and immuChrom brand kit (ImmuChrom GmbH, Tiergartenstr 7, Heppenheim Germany) in high-performance liquid chromatography (HPLC) (LC 20AT, Shimadzu, Japan). VD levels were categorized into four groups as normal (≥30 ng / ml), insufficient (20-29.9 ng / ml), deficient (10-19.9 mg / ml) and severely deficient (<10 ng / ml). According to the Child-Pugh classification, the cirrhosis patients were divided into 3 stages as Group A, B and C. Five parameters were used to calculate these scores. The parameters were ascites, hepatic encephalopathy, serum bilirubin, INR, and serum albumin. Each parameter was scored as 1, 2 or 3. The total score was interpreted as Child-Pugh A if it was 5-6, Child-Pugh B if it was 7-9 and Child-Pugh C if it was 10-15. The model for end-stage liver disease (MELD) score of the patients was calculated with the logarithmic formula of the patients' values of the INR, bilirubin and creatinine. The fibrosis score and HAI score were calculated according to the presence of fibrosis in CLD patients. Fibrosis was staged with the Ishak scale (ranging from 0=no fibrosis to 6=cirrhosis). Non-alcoholic fatty liver disease (NAFLD) is semi-quantitatively scored between 0-3 in US. The grading is as follows: 0-not available, 1-slight, 2-mild, 3-severe. All patients were informed about the details of the study and written consent was obtained. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. Permission was obtained from the Akdeniz University clinical research ethics committee (2017-184).

Statistical analysis

Data analysis was performed using the IBM Statistical Package for Social Sciences-20 (SPSS-20) packaged software. Descriptive statistics were demonstrated as mean ± standard deviation for continuous variables. Chi-square test, Kruskal-Wallis test, and Mann-Whitney-Wilcoxon test were used to compare differences between groups for qualitative or quantitative variables, where appropriate. P <0.05 was accepted as statistical significance.

Results

Three hundred forty patients who met the inclusion criteria were analyzed in the study. Among these patients, 178 (52.4%)

Table 1. Demographic Characteristics of Chronic Liver Patients and their Relationship with Vitamin D

Characteristics	n (%)	25-OHD (ng/mL)	P value
Gender			0.10
Male	162 (47.6)	20.33±9.12	
Female	178 (52.4)	18.60±10.17	
Aetiology CLD			0.014
Cirrhosis	77 (22.6)	17.89±10.16	
NAFLD	74 (21.8)	17.42±9.42	
HCV	117 (34.4)	21.51±9.07	
HBV	72 (21.2)	19.75±10.00	
Aetiology Cirrhosis			0.871
Alcoholic	9 (11.7)	18.77±8.87	
HCV	20 (26)	17.30±9.95	
HBV	25 (32.5)	17.39±10.87	
PBC	7 (9.1)	20.48±13.6	
AIH	2 (2.6)	26.95±8.78	
Cryptogenic	13 (16.9)	16.67±9.74	
Others	1 (1.3)	14.03±7.02	
NAFLD stage			0.022
Grade 1	20 (27.1)	21.87±11.77	
Grade 2	42 (56.7)	18.26±9.09	
Grade 3	12 (16.2)	12.70±5.08	
Liver cirrhosis stage			0.063
Child-Pugh A	58 (75.3)	18.11±9.55	
Child-Pugh B	14 (18.2)	20.44±12.52	
Child-Pugh C	5 (6.5)	8.17±3.07	
Fibrosis Score (1≥ vs ≤4)			0.648
HBV Fibrosis Score	71 (93.43)	21.89±9.80	
HCV Fibrosis Score	5 (6.57)	19.51±15.17	
25-OHD Classification			0.512
Severely deficient (<10 ng/ml)	60 (17.6)		
Deficient (10–19.9 ng/ml)	120 (35.4)		
Insufficient (20–29.9 ng/ml)	113 (33.2)		
Normal (≥30 ng/ml)	47 (13.8)		

CLD: Chronic liver disease; NAFLD: Nonalcoholic fatty liver disease; HBV: Chronic Hepatitis B HCV: Chronic Hepatitis C 25-OHD: 25-hydroxy vitamin D PBC: Primary biliary cholangitis AIH: Autoimmune Hepatitis

Table 2. Relationship between Demographic Data, Laboratory Results and Fibrosis Scores with Vitamin D Level

	Mean±SD	Min	Max	Percentiles			P
				25	50	75	
25-OHD (ng/mL)	19.43±9.71	4.20	53.89	11.85	19.00	25.00	-
Age	52.80±13.77	18	84	44	57	63	0.895
HBV Fibrosis Score	2.73±1.21	1	6	2	2	4	0.19
HBV HAI Score	8.53±2.70	1	15	7	8	10	0.47
HCV Fibrosis Score	2.20±1.30	1	4	1.00	2.00	3.50	0.71
HCV HAI Score	5.20±2.77	1	8	2.50	6.00	7.50	0.95
MELD	10.17±4.52	5	29	7.00	9.00	11.50	0.38
Albumin (g/mL)	4.37±2.17	1.70	43.00	4.10	4.40	4.52	0.77
Total Bilirubin (mg/mL)	0.78±0.75	0.10	5.60	0.40	0.60	0.90	0.85
Direct Bilirubin (mg/mL)	0.25±0.42	0.01	5.30	0.10	0.16	0.26	0.40
Platelet (x109/L)	224.94±91.61	27000	681000	169750	232000	268000	0.91

HBV: Chronic Hepatitis B HCV: Chronic Hepatitis C 25-OHD: 25-hydroxy vitamin D; MELD: Model for end-stage liver disease

were females and 162 (47.6%) were males. The mean age of the patients was 52.8±.13.77 years. When the etiology of CLD patients and cirrhosis patients was examined in terms of CLD, 77 (22.6%) were determined as cirrhosis patients, 74 (21.8%) as NAFLD patients, 117 (34.4%) as HBV patients, 72 (21.2%) as HCV patients. In terms of the etiology of cirrhosis, the most frequently observed were 25 (32.5%) cases of HBV and 20 (26%) cases of HCV. According to the NAFLD staging, 42 patients (56.7%) were at Grade 2, 20 patients (27.1%) at Grade 1, and 12 (16.2%) were at Grade 3. When the Child-Pugh staging of the patients diagnosed with cirrhosis was examined, 58 of them were determined to be 75.3% A, 14 (18.2%) B, and 5 (6.5%) C. According to the fibrosis score, 71 patients (93.43%) of the patients had a score of ≤4, while only 5 (6.57%) had a score of 5 and above. The mean 25-OHD level of the patients was 19.43±9.71. In our study, a statistically significant correlation was found in terms of the CLD and VD classification. Patients with HCV had significantly higher 25-OHD levels than patients

Table 3. The Relationship of Demographic, Laboratory Results, Fibrosis Scores and Vitamin D Level Classification in Chronic Liver Patients

	Severely deficient (<10 mg/ml)	Deficient (10–19.9mg/ml)	Insufficient (20–29.9 ng/ml)	Normal (≥30 ng/ml)	P
Age	53.02±14.28	53.45±13.08	51.37±13.78	54.30±14.92	0.56
HBV Fibrosis Score	3.00±1.50	2.79±1.06	2.78±1.26	2.30±1.18	0.55
HBV HAİ Score	8.55±2.87	8.91±2.53	8.24±2.96	8.58±2.31	0.83
HCV Fibrosis Score	1.00±0.00	3.00±1.00	0.00±0.00	1.00±0.00	0.29
HCV HAİ Score	7.00±0.00	4.33±3.51	0.00±0.00	6.00±0.00	0.80
Meld score	10.63±5.69	10.45±4.37	9.05±3.84	11.00±4.50	0.60
Albumin	4.15±0.57	4.58±3.61	4.33±0.41	4.20±0.51	0.58
Total Bilirubin	0.75±0.64	0.89±0.84	0.68±0.45	1.00±0.92	0.21
Direct Bilirubin	0.23±0.30	0.25±0.35	0.20±0.15	0.40±0.26	0.06
Platelet	229.73±108.71	221.90±99.98	231.91±80.07	209.93±66.68	0.53

HBV: Chronic Hepatitis B HCV: Chronic Hepatitis C 25-OHD: 25-hydroxy vitamin D; MELD: Model for end-stage liver disease

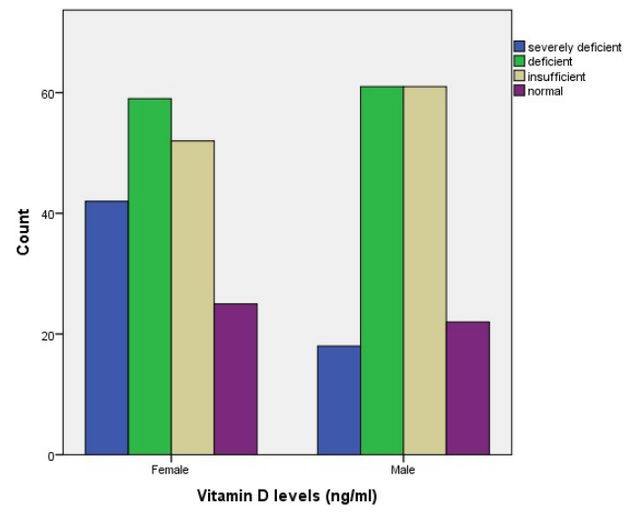

Figure 1. Patients with chronic liver disease according to vitamin D categories

with cirrhosis, NAFLD and HBV (P=0.014). When 25-OHD levels were compared according to the NAFLD staging, a significant difference was observed. Grade 1 patients had significantly higher 25-OHD levels compared to Grade 2 and 3 (21.87±11.77, 18.26±9.09, 12.70±5.08; p=0.022). There was no significant difference between gender, etiology and stage of cirrhosis and fibrosis score groups in terms of 25-OHD levels. The correlation between demographic, etiologic characteristics and VD od CLD patients is shown in Table 1.

In our study, the mean fibrosis score of patients with HBV was 2.73±1.21, the mean HAI score was 8.53±2.70, whereas the mean fibrosis score of the patients with HCV was 2.20±1.30, and the mean HAI score was 5.20±2.77. The mean MELD score of the patients was 10.17±4.52. The mean albumin level was 4.37±2.17 g/dL, the total bilirubin level was 0.78±0.75 mg/dL, the direct bilirubin level was 0.25±0.42 and the platelet level was 224.94±91.61 x109/L. There was no significant difference between these parameters in terms of 25-OHD levels. The correlation between the demographic, laboratory results, fibrosis scores and the VD level are shown in Table 2.

Among the 178 female patients, 42 (23.6%) had VD levels at a severely deficient level (<10), 59 (33.1%) had VD levels at a deficient level (between 10-20), 52 (29.2%) had VD levels at an insufficient level (20-30) and 25 (14.0%) had VD levels at a sufficient level (>30). Among the 162 male patients, 18 (11.1%) had VD levels at a severely deficient level (<10), 61 (37.7%) had VD levels at a deficient level (between 10-20), 61 (37.7%) had VD levels at an insufficient level (20-30) and 22 (13.6%) had VD levels at a sufficient level (>30). In our study, a statistically significant correlation was found between gender and VD level classification (p=0.020; Figure 1). Accordingly, the VD level can be said to be lower in female patients with CLD than male patients.

When the patients were grouped according to their 25-OHD levels, 47 patients (13.8%) were found to have it at a sufficient level, 113 (33.2%) at an insufficient level, 120 (35.3%) at a deficient level, and 60 (17.6%) at a severely deficient level. The correlation between demographic, laboratory, and fibrosis scores and 25-OHD level classification of the CLD patients is presented in Table 3. There was no significant correlation between age, fibrosis scores of the patients with HBV and HBC, MELD score and 25-OHD level classification of the laboratory parameters (albumin, total-direct bilirubin, platelet). In multivariate analysis, albumin and direct bilirubin are the independent predictors of the VD level severity (odds ratio [OR]: 0.477, 95% confidence interval [CI]: 0.234-0.720, p<0.001; OR: 0.74, 95% CI: 0.135-1.609, p=0.021, respectively).

Discussion

VD is a hormone that plays a significant role in the regulation of calcium metabolism and bone health. Recently, it has been shown to have significant effects on the immune system, insulin secretion, cell proliferation and cell differentiation by inhibiting matrix metalloproteinases, and several others [9,10]. Studies have reported that VD levels may be low in patients since those with a chronic disease spend their lives more at home and they are less exposed to sunlight [11]. Other causes of low VD levels in patients with CLD are a decrease in hepatic hydroxylation, an increase in extrahepatic involvement of VD together with adipose tissue, impairment of intestinal absorption and a decrease in its intake via the diet [12,13]. In our study, it was aimed to document the VD deficiency in patients with CLD. The mean 25-OHD level, which was found as 19.43±9.71 ng/mL in our patients, supports this purpose. When we grouped the patients according to their 25-OHD levels, more than half of the patients were found to have deficient or severely deficient levels of 25-OHD.

Obesity and insulin resistance have an inverse correlation with serum VD levels [14,15]. Current data suggest a correlation between VD insufficiency/deficiency and NAFLD, and this correlation can partially be explained with VD sequestration in the adipose tissue. VD sequestration in the body fat leads to a decrease in the hydroxylation possibility. Weight loss after the bariatric surgery had controversial effects on serum 25-OHD levels, and some studies reported increased levels whereas others put forward decreased levels [16-18]. In a study conducted by Targher et al. [19], patients with NAFLD had significantly low 25-OHD levels compared to the control groups. Nakano et al. [20] discovered in a rat model that rats receiving phototherapy had higher VD metabolite levels, increased adiponectin levels, decreased transforming growth factor beta, and decreased α-smooth muscle actin than the control groups. Lee et al. [21] conducted a study that provided nutritional recommendations to help with weight loss and examined 82 patients with NAFLD for two months. The authors found out that weight loss increased serum VD levels and developed metabolic parameters in NAFLD [21]. These studies suggest that a low VD might be correlated with a higher suspected NAFLD prevalence and possibly higher disease severity. In our study, similar to the literature, patients with NAFLD were found to have low 25-OHD levels. Besides, in our study, a significant difference was observed when the 25-OHD levels were compared according to the NAFLD staging. Grade 1 patients were found to have significantly higher 25-OHD levels compared to Grade 2 and 3.

In a study by Malham et al. [22], VD deficiency was found to be more frequent in patients with alcoholic cirrhosis compared to patients with primary biliary cholangitis (PBC). These data were contrary to the assumption that VD deficiency might be more frequent in PBC than other cirrhosis etiologies, since the lipid metabolism is impaired. This is an important study showing that there are also other factors for VD metabolism apart from lipid metabolism regarding bile acid. According to our data, no significant correlation could be found between the etiology of cirrhosis and VD level.

The decompensation rate of the cirrhosis patients is about 10% per year. The most important objective parameter used in the determination of the prognosis in patients is the Child-Pugh classification. The Child-Pugh stage is correlated with the prognosis of the patient and is used clinically very often, but it is insufficient to evaluate some patients [23]. For this reason, MELD scores, which are created with the logarithmic transformation of some parameters, are used [24]. In a study, by Paternostro et al. [7], they observed a decrease in the VD level as the Child-Pugh score increased. Again, in the same study, VD deficiency was found to be a prediction factor in cirrhosis mortality. In a study conducted by Bankuti et al. [25],

the correlation between MELD and Child-Pugh scores and VD deficiency was found to be significant. Studies indicated that the VD level was lower in the Child C, and this is an expected finding, since the liver is involved in the synthesis and storage in VD metabolism. As a result of these studies, it can be concluded that cirrhosis progresses more aggressively and quickly in the patient groups with low VD levels. In our study, similar to the literature, the lowest VD level was detected in the Child C, and although the MELD score decreased as VD deficiency increased, this was not statistically significant, unlike other studies.

This study has some limitations. The first limitation is the monocenter structure of the study, and that it was conducted on a partially low number of people. Secondly, treatment options may vary among the cases, even though the hospital where the study was carried out had standard clinic treatment protocols, and moreover, drugs and some patient-related factors may affect the VD level. Based on the results of our study, 25-OHD levels were found to be low in patients with CLD, and it seems to be associated with negative clinical outcomes in these patients. In this patient group, it can be thought that VD may provide potential benefit in addition to their treatment. Prospective and extensive studies are needed in order to better understand the mechanism of the correlation between the patients with CLD and VD.

Conclusion

High levels of VD deficiency can be seen in patients with CLD, especially in women. Awareness of VD level in patients with CLD, which can be detected with periodic screenings, may be beneficial. There was no significant correlation between age, fibrosis scores of the patients with HBV and HBC, MELD score and 25-OHD level classification

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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