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PREVALENCE OF VITAMIN D DEFICIENCY AND THERAPEUTIC ROLE OF VITAMIN D SUPPLEMENTS IN CHRONIC LIVER DISEASE

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Abstract:

Introduction: *Vitamin D, along with its beneficial effects on bone, has many other advantages. There is rising concern in surveying the association between plasma vitamin D levels and chronic liver disease.*

Objectives: *To ascertain the prevalence of vitamin D deficiency in patients suffering from chronic liver disease as well as to evaluate liver functionality and plasma vitamin D levels after vitamin D administration.*

Material and Methods: *This was a two stage study. The first stage included evaluation of demographic and clinical data in 87 patients having chronic liver disease. The second stage included administration of various doses of vitamin D to patients having either insufficient or deficient plasma vitamin D levels. Post-experimental liver function tests and grades of liver functionality were assessed and compared with pre-experimental data.*

Results: *88% of the patients had either VD insufficiency or deficiency with a mean vitamin D level of 18.6 ± 9.28 ng/ml. Alcohol consumption contributed to a greater deficiency of vitamin D ($p = 0.002$). Mean vitamin D levels in patients with cirrhosis was 15.3 ng/ml, while non-cirrhotic patients had a mean level of 20.7 ng/ml. Liver functionality was found to be inversely correlated with plasma levels of vitamin D, Child A (16.17 ± 3.94 ng/mL) vs Child C (6.96 ± 5.64 ng/ mL). Normal values of VD levels were achieved in 92.7% of patients who did not have liver cirrhosis as compared to 88.4% of patients having liver cirrhosis. Serum Albumin levels ($p < 0.05$) and liver functionality grade ($p < 0.05$) also showed significant results.*

Keywords: *Vitamin D, Chronic liver disease, CLD, Cirrhosis, Child-pugh, MELD*

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INTRODUCTION:

Vitamin D (VD), an important lipid soluble vitamin, is also called regulator of mineral homeostasis and bone metabolism. [1] Besides playing a role as an important micronutrient in the body, it also acts as a vital hormone involved in an intricate and multifaceted system affecting skeletal muscle integrity, immunomodulation , cellular proliferation and differentiation. [2] VD rich foods such as fish and eggs etc. provide vitamin D_2 and D_3 which enter the circulation after being absorbed form the intestine with the help of bile. [3] The primary source of VD in the body in through exposure of sunlight, which triggers the biogenesis of VD within the epidermal cells. Regardless of the source, VD in the body can be stored in fat cells (lipocytes/adipocytes) or it can be transferred to liver, via being bound to vitamin D-binding protein (DBP), also known as group-specific component (Gcglobulin), for hepatic 25-hydroxylation. [4] 25(OH)D is ultimately carried to the kidneys where it is converted to form the activated form of VD, calcitriol ($1,25(OH)D_3$). [4] The steps of the process are given in Fig 1.

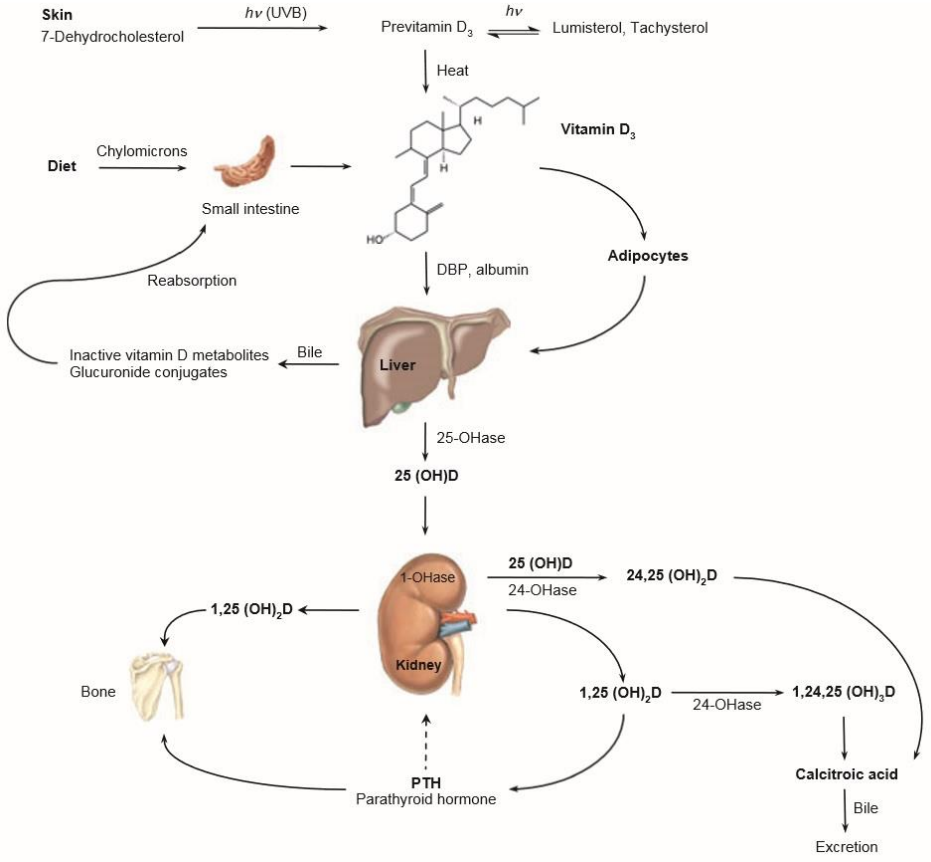

Fig. 1. Metabolism of vitamin D. UVB, ultraviolet B light; DBP: vitamin D-binding protein; 25(OH)D: 25-hydroxyvitamin D; 1,25(OH)2D: 1,25- dihydroxyvitamin D; 24,25(OH) 2D: 24,25-dihydroxyvitamin D; 1,24,25(OH)3D: 1,24,25-trihydroxyvitamin D; 25-OHase: 25-hydroxylase; 24- OHase: 24-hydroxylase.[(D)]

In the published Endocrine Society's Practice Guidelines, serum VD levels (25(OH)D) levels less than 20 ng/mL were categorized as deficient, levels between 21 ng/mL to 29 ng/mL were categorized as insufficient while levels of 30 ng/mL or more were categorized as sufficient for optimum musculoskeletal health. [10] On the basis of these guidelines, 1 billion people all over the world have been estimated to have either insufficient or deficient VD levels. [11] In patients with chronic liver diseases (CLD), defined as a disease state of the liver involving damage and regeneration of liver leading to hepatic fibrosis and cirrhosis with the advancement of disease, the prevalence of VD insufficiency and deficiency is much higher than normal individuals and practically universal, ranging between 64% and

92% respectively. [7,12,5] Additionally, the incidence of VD deficiency has been reported to be directly linked to liver disease progression. [8,6,13]
The possible suggested mechanisms for hypovitaminosis in CLD are: a) decreased sunlight exposure, b) impairment of VD absorption from the intestine, c) compromise of the hepatic protein synthesizing mechanisms secondary to cirrhosis leading to reduced amounts of vitamin DBP and albumin, d) impaired hepatic hydroxylation of VD to 25(OH)D and e) increased catabolic removal of 25 (OH)D. [4] Moreover, decreased plasma VD concentrations have also been, reportedly, linked with higher incidence of infections, portal hypertension related complications and even increased risk of death. [9] Thus, an exploration of VD levels in CLD patients seems appropriate based on this vital relationship between VD and liver disease.

The objectives of this study were to assess the serum levels of VD in CLD patients and to see whether these levels differed based on the etiology of the underlying liver disease. This study also examined whether VD supplementation had an effect on patient VD levels and disease progression.

MATERIAL AND METHODS:

In the first part of the study, CLD patients seen or admitted in the Medicine ward of our tertiary care hospital (Liaquat University Hospital, Jamshoro) during the months of July and August 2018 were registered to be included in the study. The exclusion criteria were patients receiving VD supplements or Calcium therapy. The sample size comprised of 87 CLD patients which were recruited to be a part of the study. All of them were counseled about the details of the study and the potential benefits.

Liver function tests, serum creatinine, albumin and baseline VD concentration were determined. Additionally, epidemiological data pertaining to etiology of CLD, disease stage and cirrhosis was recorded.

The patients who had VD insufficiency or deficiency were then given different doses of VD supplements (General Nutrition Corporation, USA) depending upon their existing baseline VD levels for three consecutive months. Patients who had insufficient plasma levels of VD were given 2000 IU/day, while those having deficient plasma levels of VD were given 5000 IU/day. At the end of the study period, blood samples were collected and analyzed for plasma VD concentration, liver function test (LFT) and prognostic variables of liver disease (Child-Pugh score and model for end-stage liver disease [MELD] score). The study participants were regularly followed up for routine checkups to confirm VD therapy compliance. During that period, there were 2 deaths recorded due to complications related to cirrhosis.

The data was analyzed using SPSS (Statistical Package for Social Sciences) version 22. The expression of quantitative variables was done in terms of mean and standard deviation while the expression of qualitative variables was done in terms of percentage. The proportions related to qualitative variables were compared using Chi-Square test whereas the difference in mean of quantitative variables was assessed using Student-t test. Statistical significance was considered at a p value of ≤ 0.05.

RESULTS:

Baseline data of study population

Out of the total 87 CLD patients that took part in the study, 68% were males with a mean age of 61±14.72 years. The baseline data of the study population is shown in Table 1. Out of total 87 CLD patients 47% were positive for liver cirrhosis 88% of which were males. On the basis of Child-Pugh score, 65%, 27% and 8% were class A, class B and class C respectively. While on the basis of MELD score, a score >20 was seen in 11% and a score <10 was seen in 89% of patients. Of the patients who were suffering from cirrhosis, 34% had no varices whereas 27%, 22% and 17% had varices grade 1, 2 and 3 respectively as shown in Table 2. 78% cirrhotic patients had grade 1 ascites. Portal vein thrombosis (PVT) was seen in 7 patients while hepatocellular carcinoma was observed in 3 patients.

Table 1 – Baseline characteristics of study population.

Variables	Patients
Age (mean ± SD)	**61±14.72**
Sex (male %)	**59 (68%)**
Cirrhosis	**41 (47%)**
Etiology	
- HCV	**47 (54%)**
- Alcoholic	**22 (25%)**
- AIH	**8 (9%)**
- PBC	**6 (7%)**
- NAFLD	**4 (5%)**
Vitamin D (mean ± SD)	**18.6 ± 9.28**

AIH, autoimmune hepatitis; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cirrhosis; SD, standard deviation.

Table 2 – Baseline characteristics of the cirrhotic population.

Variables	Patients
Cirrhosis	**41 (47%)**
Sex (male %)	**36 (88%)**
Child – Pugh A (%)	**27 (65%)**
Child – Pugh B (%)	**11 (27%)**
Child – Pugh C (%)	**3 (8%)**
Etiology	
- HCV	**25 (61%)**
- Alcoholic	**9 (22%)**
- AIH	**2 (5%)**
- PBC	**4 (10%)**
- NAFLD	**1 (2%)**
Vitamin D (mean ± SD)	**15.3 ± 5.82 ng/mL**
- Child – Pugh A (%)	**16.17 ± 3.94 ng/mL**
- Child – Pugh B (%)	**15.73 ± 3.42 ng/mL**
- Child – Pugh C (%)	**6.96 ± 5.64 ng/mL**
Ascites (%)	
None, or with response to diuretics	**32 (78%)**
Moderate or under tension	**9 (22%)**
Portal Vein Thrombosis	**7 (17%)**
Hepatocellular Carcinoma	**3 (7%)**
Varices	
- No Varices	**14 (34%)**
- Grade I	**11 (27%)**
- Grade II	**9 (22%)**
- Grade III	**7 (17%)**

AIH, autoimmune hepatitis; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; SD, standard deviation.

Etiology of CLD

In terms of origin of CLD, 54% of the cases were caused as a result of Hepatitis C virus (HCV), 25% were a consequence of alcohol consumption, 9% of the cases occurred due to autoimmune hepatitis and 7% were caused by primary biliary cirrhosis. The remainders of the cases were caused by non-alcoholic fatty liver disease as shown in Table 1. Similarly, in patients with liver cirrhosis, the causative factor in 61% of cases was found to be HCV while 22% was

secondary to alcohol consumption; the details are given in Table 2.

Vitamin D levels

Out of the total 87 CLD patients that took part in the study, 88% had either VD insufficiency or deficiency. The mean baseline VD levels in the study participants were found to be 18.6 ± 9.28 ng/ml. In patients with liver cirrhosis, the mean VD levels were found to be 15.3 ng/ml, which was lower than the mean VD levels of patients who did not have liver cirrhosis who had a mean of 20.7 ng/ml; the difference was found to be statistically significant ($p = 0.002$), as shown in Fig 2. Amongst the cirrhotic patients, alcohol consumption contributed to a greater deficiency of VD levels with a mean of 13.9 ng/ml ($p = 0.002$).

Vitamin D correlation with liver function

A direct correlation was established between plasma VD levels and grade of liver function as the mean VD level was found to be lower in patients with Child-Pugh class C ($p = 0.014$). In addition, VD levels were found to be directly correlated with platelet count and albumin levels and inversely correlated with plasma bilirubin levels and levels of international normalized ratio (INR) ($p < 0.005$).

Patient response to vitamin D therapy

This study also ascertained the extent of response to VD therapy in individuals suffering from either VD insufficiency or deficiency. After VD supplement therapy for 90 days at the previously mentioned doses the plasma VD levels were assessed and compared with the initial baseline concentrations. After treatment, normal VD levels of > 30ng/ml were achieved in 91.3% of patients. Normal values of VD levels were achieved in 92.7% of patients who did not have liver cirrhosis as compared to 88.4% of patients having liver cirrhosis, despite the use of lower doses in those patients. Post treatment VD levels were significantly higher in non-cirrhotic patients ($p < 0.05$). Lowest serum VD levels were seen in patients suffering from CLD caused by HCV and consumption of alcohol. The extent or grade of liver injury as measured by the Child-Pugh score was seen to improve significantly in patients as the VD levels rose and reached near physiological values ($p = 0.05$). However, a significant change was not observed in the MELD scores which was seen to decrease from a value of 10.09 to a value of 8.74 ($p = 0.09$). The one single laboratory test which showed significant improvement post VD therapy was albumin. Serum levels of albumin > 3.5g/dL were found in 91.4% of study participants at the conclusion of the study duration ($p = 0.001$).

DISCUSSION:

The importance of VD is based on its diverse functions playing a vital role in processes such as angiogenesis, immunomodulation, cell differentiation and cell proliferation. [14] Based on these facts, a strong association has been established between deficient levels of VD and an increased risk of development of chronic diseases like different types of autoimmune disorders, various cancers, diabetes mellitus and even certain infections. [15]

As mentioned earlier, VD deficiency is a worldwide epidemic with around 1 billion people having inadequate VD levels. [16] In developed countries such as the United States of America (USA) around 25% to 50% of the adults have been estimated to have either VD insufficiency or deficiency. [17] Similarly, a high variation is seen in the VD status of different countries of Europe, where VD levels less than 25 nmol/L were found in 2% to 30% of adults and in 75% of older adults. [17,18] As mentioned earlier, the main source of VD in the body is through proper exposure to sunlight but even in the presence of more than enough sunlight exposure, regions such as Africa and the Middle East have the reported the highest global incidence rates of rickets. [19] In the Middle East, this is probably due to the inadequate sunshine exposure owing to the cultural attires and extended duration of breast feeding without aid of calcium supplements, while in Africa it can be attributed to the dark skin colour which alters the baseline plasma calcium levels in individuals. [20,21] Deficiency of VD in patients suffering from CLD has been found to be prevalent in an average of 64% to 92% of people. [7] 66.3% of HCV infected patients in Brazil, Europe and America, 71% in North America, 46.4 to 73% in Italy and 86% in France have been found to have low VD levels. [24]

According to previous studies, deficient levels of VD were considered to occur in cholestatic liver disorders owing to impaired or diminished gastro-intestinal absorption. Recent studies, however, suggest multifactorial origin and widespread presence of hypovitaminosis in CLD, regardless of its etiology. [4] This is attributed not only to intestinal malabsorption, but also to dysfunction of liver cells leading to compromise in their ability to hydroxylate VD, increased renal secretion, disruption in the normal enterohepatic circulation, low intake/high breakdown and reduced exposure to sunlight. [25]

In CLD patients, an inverse relation has been established between deficient plasma VD levels and progression of disease, with decreased VD levels

being associated with increased liver fibrosis, elevated hepatic dysfunction, higher risk of developing non-alcoholic liver disease and hepatic cancer. [12] In addition, reduced plasma levels of VD, in CLD patients, have also been associated with poor response to antiviral therapies such as Ribavarin and Interferon. [23]

In this study, it was observed the majority of the patients with CLD had inadequate VD levels; with 84% of the patients showing insufficient levels of plasma VD, irrespective of the underlying etiology. However, the decrease in plasma VD concentration was more pronounced in patients who had cirrhosis of liver as compared to those who were cirrhosis free. These findings are similar to the findings of Arteh et al. (2010), who observed the prevalence of deficient plasma VD levels in 92% of CLD patients and also that this number was significantly higher in patients having cirrhosis of liver. [7] Similarly, Miroli-aee et al. (2010). found decreased VD levels in 68% of patients while lower levels were observed in patients who had higher degress of liver dysfunction. [26] Similarly, decreased plasma VD levels were observed in 66% of HCV positive patients in a study by Melo-Villar et al. (2015). [24]

According to most studies, including this present study, plasma VD levels have a direct correlation with the grade of liver function in patients suffering from CLD. LFTs including serum albumin and platelet count were found to be directly while bilirubin levels and INR were found to be indirectly related to serum VD concentrations which is similar to the studies by Petta et al. (2010) and Bitetto et al. (2011). [28,29]

In this present study, normal serum VD levels were obtained in 91.3% of CLD patients after oral VD therapy. Similarly, normal VD levels post VD therapy were obtained in all 108 HCV patients studied by Ladero et al. (2013), but no change was seen in the biochemical laboratory values. [30] Our results, on the basis of Child-Pugh score, indicate a positive relation between normalization of plasma VD concentration and the function grade of liver. Nakano et al. (2011) observed similar results in an experimental animal study, in which rats receiving oral VD therapy showed dose dependant amelioration of Nonalcoholic steatohepatitis (NASH) progression. [31]

This present study had certain limitations. The exposure to sunlight of the patients varied greatly and was not precisely documented in the follow-up. Furthermore, because this experimental study design lacked a control group and randomization, the most appropriate dose of VD therapy could not be established. Although study was carried on more than 80 people, a larger sample size would yield better and more accurate results.

To conclude, based on the alarmingly high prevalence of inadequate plasma VD concentrations in patients suffering from CLD, it is advisable that periodic screening of VD levels should take place in CLD patients. And if VD levels are found inadequate, VD supplement therapy could not only be safe but also beneficial for CLD patients.

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