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Study of vitamin D levels and its correlation with child PUGH score in patients of chronic liver disease

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Abstract
Background: Vitamin D has anti fibrotic effect and anti-inflammatory effect other than the effects on calcium and skeletal metabolism. This anti-inflammatory and anti-fibrotic property of vitamin D is implicated in the causation, disease progression of chronic liver disease. Chronic Liver Disease (CLD) is defined as the process of long-term progressive destruction and regeneration of the liver, and with advancing disease, hepatic fibrosis (scarring) and cirrhosis. The Child-Pugh (CP) score is a widely used scoring system to predict the 1-year survival rate among cirrhotic patients.
Materials and Method: This prospective cross-sectional study entitled "was conducted after clearance from Board of Studies and Ethical committee in the Department of Medicine, Muzaffarnagar medical college, Muzaffarnagar (U.P.) during the period 2018-20.
The study population has been calculated by using G-power software with 80% of the power and 5% of the significance level. The total sample size was determined to be 100 patients, aged 18-60 years of age.
Results: The mean age of the study population was 41.83±10.36 (18-59) years. There were 67 (67.0%) males and 33 (33.0%) females among study population. Vitamin D level was found to be Deficient (≤ 20 ng/ml) among 32 (32.0%), Insufficient (20-30 ng/ml) among 26 (26.0%) and Optimum (> 30 ng/ml) among 42 (42.0%) subjects. The mean Vitamin D level was significantly more among Child Pugh Class A compared to class B which was significantly more than class C.
Conclusion: It also observed that the severity of cirrhosis as assessed by Child Pugh Score was inversely proportional with Vitamin D level. As the disease advances, the levels become more deficient. Vitamin D levels should be routinely checked in all patients suffering from advanced CLD, so that adequate replacement by vitamin D supplements can be initiated as a therapeutic adjunct in managing such patients. We found that in patients with liver cirrhosis, vitamin D deficiency was associated with poor survival.
Therefore, randomized controlled trials aiming to confirm this association and demonstrate the potential role of vitamin D supplementation in improving survival rates are needed.

Keywords: vitamin D, correlation with child PUGH, chronic liver disease, anti-inflammatory

Introduction

Vitamin D is a steroid hormone (secosteriod-where one of the bond in the rings is broken). It has multiple effects and uses in the human body. Vitamin D has anti fibrotic effect and anti-inflammatory effect other than the effects on calcium and skeletal metabolism. This anti-inflammatory and anti-fibrotic property of vitamin D is implicated in the causation, disease progression of chronic liver disease. There are many research studies stating that supplementing vitamin D will decrease the severity of chronic liver disease [1].

Vitamin D may be produced after exposure to sunlight. First, the skin absorbs ultraviolet B radiation which immediately converts 7-dehydrocholesterol to pre-vitamin D3, which is then converted to Vitamin D3 (cholecalciferol). It is then transported to the liver by vitamin D binding proteins [2]. Vitamin D may also be absorbed from dietary intake. Foods like milk, eggs, cereal and some fish naturally contain or are fortified with vitamin D3.Vitamin D3 absorbed from the diet is transported to the liver by chylomicrons [3].

Vitamin D3 is metabolized into 25-hydroxy vitamin D3. The liver produces 25-hydroxy (25-OH) vitamin D, also known as calcidiol, the immediate precursor to the metabolically active 1, 25-dihydroxy vitamin D which is known as calcitriol. 25-hydroxy vitamin D [25(OH)D3] is the most abundant circulating form of vitamin D, and its measurement is used to assess vitamin D deficiency. Calcidiol is then converted into its active form, Calcitriol by

1-α-hydroxylase enzyme in the kidney and other target tissues. This process is tightly regulated by parathyroid hormone (PTH), serum calcium, and phosphorous levels [3].
The regulation of both innate and acquired immune systems is modulated by Vitamin D. Though synthesized mainly in the liver, the extra skeletal benefits of vitamin D such as cellular proliferation, cell differentiation and immunomodulation is the one quoted in many studies for its pathogenesis altering effect of chronic liver disease. Vitamin D improves sustained viral response rate in chronic hepatitis C and decreases insulin resistance caused by its deficiency. Insulin resistance is related to the worsening of NAFLD [4, 5].
In patients with liver failure, the levels of 25-OH vitamin D can be low due to impaired synthesis. However, liver function needs to be severely compromised in order for this impairment to occur. Liver disease could also lead to impaired absorption of vitamin D, which is possibly connected to impaired bile acid production or gut oedema associated with portal hypertension. Low vitamin D levels and bone disease are well-recognized complications of "cholestatic" liver disease, which decreases the production or flow of bile. More recently, studies have confirmed low vitamin D levels in non-cholestatic liver disease [6].
Chronic Liver Disease (CLD) is defined as the process of long-term progressive destruction and regeneration of the liver, and with advancing disease, hepatic fibrosis (scarring) and cirrhosis [7]. The aetiology is unknown but profound immunological disturbances are found and PBC is often associated with other autoimmune disorders. Other causes of Chronic Liver disease can be alcoholic liver disease, chronic hepatitis (B, C), NAFLD/NASH (Non-alcoholic fatty liver disease/Non-alcoholic steatohepatits), Haemochromatosis, Wilson's disease, PBC/PSC (Primary biliary cirrhosis/Primary sclerosing cholangitis).
The Child-Pugh (CP) score is a widely used scoring system to predict the 1-year survival rate among cirrhotic patients. First described by Child and Turcotte and later modified by Pugh *et al.*, [8] this score uses five parameters (hepatic encephalopathy, prothrombin time (PT), ascites, serum bilirubin and serum albumin) to classify the patients in early, intermediate and advanced stages of liver cirrhosis. Esophageal varices, ascites, portal hypertension, hepatic encephalopathy and hepatocellular carcinoma are all well studied and well-known complications of liver cirrhosis [9].

Materials and Method

This prospective cross-sectional study entitled "To study vitamin D levels and its correlation with child Pugh's score in patients of chronic liver disease" was conducted after clearance from Board of Studies and Ethical committee in the Department of Medicine, Muzaffarnagar medical college, Muzaffarnagar (U.P.) during the period 2018-20.

Vitamin D levels

- Optimum >30 ng/ml
- Insufficiency 20-30 ng/ml
- Deficiency <20 ng/ml

Sample size

The study population has been calculated by using G-power software with 80% of the power and 5% of the significance level. The total sample size was determined to be 100 patients, aged 18-60 years of age.

The study subjects were chosen as per the inclusion and exclusion criteria:

Inclusion criteria

- Patients who are above 18 years and below 60 yrs of age and have given informed consent.
- Abnormal LFT detected in chronic liver disease.
- Chronic liver disease were established on the basis of history, clinical examination and ultrasound evidence of chronic liver disease which are taken as altered liver echogenicity, shrunken liver, portal hypertension with or without ascites.

Exclusion criteria

- Patients with Chronic Kidney Disease.
- Patients with Coronary Artery Disease.
- Pregnant patients.
- Patients with Orthopaedic bone diseases like trauma, fracture.
- Primary osteoporosis.
- Patients with Diabetes Mellitus

Study procedure

After approval from the Institutional Ethical committee all patients were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination and routine & amp; appropriate investigations were done for all patients.
A baseline history, including history of chronic alcohol intake, blood transfusion, trauma, intra-veinous injections, i.v drug abuse, clinical examination including per abdomen examination to rule out ascitis, hepatomegaly, splenomegaly, to look for specific signs for chronic liver disease and basic laboratory investigations including liver function test, prothrombin time/I.N.R and hepatitis b surface antigen and Hepatitis C virus test were done to establish the aetiology of chronic liver disease. The blood sample of the patients was also taken for the assessment of the serum vitamin D levels. Vitamin D levels were measured in the blood sample by ELISA KIT method.

Statistical analysis

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 21.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage.
The student t-test was used for comparing the mean values between the 2 groups whereas chi-square test was applied for comparing the frequency. The p-value was considered to be significant when less than 0.05.

Results

Table 1: Study population age group

	Minimum	Maximum	Mean	Std. deviation
Age	18	57	41.83	10.36

The mean age of the study population was 41.83±10.36 (18-59) years.

Table 2: Sex of study population

Gender	Frequency	Percent
Male	67	67.0%
Female	33	33.0%
Total	100	100.0%

There were 67 (67.0%) males and 33 (33.0%) females among study population.

Table 3: level of vit. D among study population

Vitamin D level	Frequency	Percent
Deficient (≤ 20 ng/ml)	32	32.0%
Insufficient (20-30 ng/ml)	26	26.0%
Optimum (> 30ng/ml)	42	42.0%
Total	100	100.0%

Vitamin D level was found to be Deficient (≤20 ng/ml) among 32 (32.0%), Insufficient (20-30 ng/ml) among 26 (26.0%) and Optimum (>30 ng/ml) among 42 (42.0%) subjects.

Table 4: Comparison of vit. D level using child pugh score

Child Pugh class	Vitamin D level				
	Mean	Std. deviation	F-value	p-value	Post-hoc comparisons
A	35.53	1.770	33.839	< 0.001*	
B	25.96	2.148			
C	14.15	0.471			

The comparison of mean Vitamin D level between the different Child Pugh Class using the one-way ANOVA test with post-hoc bonferroni test for inter-group comparisons. The mean Vitamin D level was significantly more among Child Pugh Class A compared to class B which was significantly more than class C.

Table 5: Correlation of vitamin D with child pugh score

		Vitamin D level
Child PUGH score	Pearson correlation	-0.577
	p-value	< 0.001*

There was a significant negative correlation of Vitamin D level with Child Pugh score.

Discussion

Buonomo *et al.* showed that the cohort of patients with liver cirrhosis, there was a high prevalence (64%) of vitamin D deficiency. This is probably due to the impairment of several mechanisms implicated in vitamin D absorption in advanced liver disease, such as activation and hydrolyzation of 25-OH-cholecalciferol or malabsorption due to portal hypertension. However, a significantly higher mortality was found in patients with liver cirrhosis and severe vitamin D deficiency compared with patients with serum 25-OH-vitamin D concentrations >10 ng/ml [15].

Age

Choubey and Ratlamwala [17] had majority of patients (52%) were in age group 41- 60 years followed by 21-40 years (30%). The mean age of patients in a study by Rech MA *et al*. [18] was 58.8±9.2 years. Gupta *et al.* [19] reported that mean age of the patients was 46.05±11.31years.

Gender

Choubey and Ratlamwala [101] had higher number of Male patients (72%) than females (28%). In the study by Rech MA *et al.*, [18] 53.3% patients were males [8]. Gupta *et al.* [19] reported that 91% were male and 9% were female. Jamil *et al.* [16] stated that 92% were females and 8% were males.

In the research by Karthikeyan and Rajaragupathy, [14] majority of subjects (88%) were males. This finding was consistent with other studies done by Putz-Banktietal, [10] (68%) and Barchetta *et al*. (52%) [11].

Etiology

Higher proportion of the study population had alcohol as the cause of CLD. This was similar with the findings of study by Putz-Bankti *et al*. [10] but a study by Arteh *et al.* [20] showed HCV as the cause of CLD. Higher population of males could be attributed to the primary etiology being alcohol-induced.

Distribution of vitamin D deficiency

Gupta *et al.* [19] found that the vitamin D deficiency (<20 ng/dl) among 43% patients, of which, 5% suffered from severe vitamin D deficiency (<10 ng/dl).Vitamin-D insufficiency (21-29.9 ng/dl) was found among 42%. Thus, vitamin D levels were sub-normal in 85 (85%) patients. Similar observations has been made by earlier workers [21-23].

Karthikeyan and Rajaragupathy, [14] found that the prevalence of vitamin-D deficiency was 82% while the study by Arteh *et al*. [20] showed a prevalence of 64-92%. According to this study results, CP score C contains more number of vitamin-D deficient cases than class A or class B. A similar result was seen in a study by Fisher *et al.* in which vitamin-D deficient cases were highly found in class C [12]. This study did not show significant correlation between vitamin-Dlevels but MELD score while the study by Putz-Bankti *et al*. [10] showed inverse correlation between MELD score and vitamin-D levels.

Comparison of vitamin D levels among subjects with different child Pugh class

Child-Pugh score (CPS) is an independent prognostic marker for complications of pulmonary arterial hypertension and also in predicting mortality in patients with cirrhosis. The Child-Pugh score is [24] still considered the prognostic marker of cirrhotic patients. In Choubey and Ratlamwala study, [17] majority of patients were in Child Pugh Class B (49%) followed by Child Pugh Class C (32%). In a study by Haq *MI et al.*, 17% patients were in Child Pugh class A and 35% were in Child Pugh class B and 48 (48%) were in Child Pugh class C [25].

Choubey and Ratlamwala [17] showed that the mean Vitamin D level was higher in the Child Pugh Class A in comparison to the Child Pugh Class B and C. Also the mean Vitamin D level was higher in the Child Pugh Class B in comparison to the Child Pugh Class C. Though the cause of vitamin D deficiency in cirrhotic patients is multifactorial, the main mechanism through which cirrhosis of the liver causes vitamin D deficiency is the inhibition of vitamin D hydroxylation [16].

Gupta *et al.* [19] found significant negative correlation with Child-Pugh score (r= –0.738) and MELD score (r = -0.667). So, low 25(OH)D levels were associated with increased severity of liver disease. Similar observations has been

made by Miroliaee A *et al*., [21] Putz-Bankuti C *et al*. [10] and Finkelmeier F *et al*. [13] We also found low vitamin D level was associated with poor outcome similar to Finkelmeier F *et al*. [13] Vitamin D might be both a biomarker of severity and a potential therapeutic target in CLD.

Finkelmeier *et al*. found that cirrhotic patients had a negative relation of liver function, namely MELD score and Child Pugh score, and serum vitamin D concentrations, which has also been observed in other cohorts of patients suffering from liver diseases [13].

Severe liver insufficiency is a reasonable cause for disturbance of the 25(OH)D3 generation. The hydroxylation of cholecalciferol to its bioactive form, namely 25(OH)D3, iscarried out by the liver, showing its key role in vitamin D metabolism [13]. This hypothesis is supported by the lack of difference between the 25(OH)D3 levels determined either in spring/summer or autumn/winter, indicating that an insufficient hydroxylation of cholecalciferol rather than a lack of sun exposure might be the main reason of vitamin D deficiency in cirrhotic patients. An uncoupling of vitamin D levels and sun exposure has recently been found in patients suffering from HCC [26]. So our study also proves that vitamin d is associated with prognosis of chronic liver disease implicating it as a biomarker of severity and an efficient therapeutic goal in chronic liver disease.

Conclusion

The mean age of the study population was 41.83±10.36 (18-59) years with 67.0% males and 33.0% females.

Vitamin D level was found to be Deficient (≤20 ng/ml) among 32.0%, Insufficient (20-30 ng/ml) among 26.0% and Optimum (> 30 ng/ml) among 42.0% subjects.

The mean Vitamin D level was significantly more among Child Pugh Class A compared to class B which was significantly more than class C. There was a significant negative correlation of Vitamin D level with Child Pugh score.

There was a significant negative correlation of Vitamin D level with Total serum bilirubin, Serum albumin, SGOT, SGPT, GGT, Alkaline Phosphatase and Serum creatinine.

This prospective cross-sectional study assessed the vitamin D levels and its correlation with child Pugh's score in patients of chronic liver disease among 100 patients, aged 18-60 years.

Vitamin D inadequacy is very common in non-cholestatic CLD patients and correlates with the severity of the disease. Therefore, we recommend that clinical guidelines for managing non-cholestatic CLD should include the assessment of vitamin D status in all patients.

It also observed that the severity of cirrhosis as assessed by Child Pugh Score was inversely proportional with Vitamin D level. As the disease advances, the levels become more deficient. Vitamin D levels should be routinely checked in all patients suffering from advanced CLD, so that adequate replacement by vitamin D supplements can be initiated.

We found that in patients with liver cirrhosis, vitamin D deficiency was associated with poor survival. Therefore, randomized controlled trials aiming to confirm this association and demonstrate the potential role of vitamin D supplementation in improving survival rates are needed.

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