Assessment of Vitamin-D level in patients with Compensated and Decompensated Cirrhosis of Liver

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Abstract

Introduction: The liver plays an important role in the activation of vitamin D. **Severity of liver disease or severity of cirrhosis** and recovery of cirrhosis disease might have some impact on serum calcitriol level. The Child-Pugh and MELD score are very objective scale for measuring clinical insight regarding chronic liver disease.

Objectives: The present study was conducted to observe association between serum calcitriol levels in compensated and decompensated cirrhosis of liver.

Methods: 3455 Eighty patients, 40 with compensated and 40 with decompensated cirrhosis,
were selected purposively according to predefined inclusion and exclusion criteria. Demographic, biochemical data were collected meticulously through clinical history, clinical examination by hepatologist and stringent medical laboratory services.

Results: The study had envisaged that middle-aged group people with hepatitis C infection were more prone to develop cirrhosis and the compensated patient had on average 17.34 mg/l more calcitriol than that of patient with decompensated cirrhosis of liver. The binary logistic regression showed that Child-Pugh and MELD scores had linear and positive correlation with serum calcitriol levels.

Conclusion: This study demonstrates a meaningful association between serum calcitriol level and clinical status in patients with liver cirrhosis

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Introduction

Liver cirrhosis is the fourth leading cause of death in many countries[1]. About one million deaths are due to liver cirrhosis each year. Among these, hepatitis C virus infection is a major cause of cirrhosis. Chronic hepatitis B infection, nonalcoholic steatotic hepatitis, alcohol, cholestatic disorders, chronic vascular obstructive diseases and autoimmune diseases, also result in liver cirrhosis.[1, 2]

Recent studies have shown that patients with chronic liver disease had higher prevalence of vitamin D insufficiency than in general population ranging between 64 and 92%.[3, 4]

Morbidities in cirrhosis of liver patients mainly include the complications of cirrhosis like, variceal bleeding, ascites, encephalopathy and hepatocellular carcinomas. Patients with chronic liver disease have an increased risk for the development of osteoporosis and fractures, reduced muscle strength, an impaired inflammatory response, and malignancy (5,6,7). Vitamin D deficiency, osteomalacia and osteoporosis have been well described in patients with cholestatic liver disease, particularly in primary biliary cholangitis (PBC).[8] But the extent of hypovitaminosis D in other chronic liver disease is not strongly established.Available data suggest an association between liver cirrhosis and vitamin D deficiency.[9]

Literature Review

Vitamin D is a fat-soluble secosteroid hormone. It plays an important role in maintaining serum calcium levels. The absorption of dietary calcium from gut, reabsorption of calcium from tubules in kidney is aided by this vitamin. Mineralization and mobilization of calcium in and from bones is integrated by vitamin D to maintain steady serum calcium level. However, vitamin D has pleiotropic effects including cellular proliferation, differentiation and immunomodulation.[10]

Solar energy plays a very important role in synthesis of endogenous vitamin D. The main source of vitamin D in human body is from the exposure of skin to sun light. After formation in the skin it is converted to 25-Hydroxy cholecalciferol (D2) in the liver and finally converted to the active form 1, 25-dihydroxy cholecalciferol (D3) in the kidney.[11]

The main source of vitamin D is biosynthesis from epidermal cells as a result of exposure to sunlight. Initially, 7-dehydrocholesterol, a metabolite of cholesterol, is converted into pre-vitamin D3 by ultraviolet-B radiation in the lower epidermis. Then, provitamin D3 is transformed into vitamin D3 (cholecalciferol) in a heat-dependent process. A significant percentage of vitamin D3 is generated by sunlight and so the equilibrium between pre-vitamin D3 and vitamin D3 is maintained. Both dietary and endogenously generated vitamin D can be stored in the adipocytes or it may undergo hepatic 25-hydroxylation.[12]

Vitamin D deficiency in cirrhosis is related to liver dysfunction rather than etiology and it is no longer considered.

In a recent meta-analysis by Garcıa - Alvarez et al,[13] a significant association between vitamin D status and liver fibrosis [cut-offs of 10 ng/mL (odds ratio, OR: 2.37, 95% CI: 1.20-4.72) and 30 ng/mL (OR: 2.22, 95% CI: 1.24-3.97)] was observed. However, two studies, similar to the study by Kitson et al,[14] challenged the results of the earlier studies regarding the relation of vitamin D with the stage of liver fibrosis.

Clinical Implication

Abnormal vitamin D metabolism in liver cirrhosis was first reported in the late 1970s.

Hepatic functional impairment of activation of 25(OH)-vitamin D of the precursor vitamin D by hydroxylation was considered as the main cause.[16, 17, 18]

Several clinical applications of 25(OH)D levels have been suggested, including its use as a non-invasive marker of liver fibrosis in chronic hepatitis C,[19] as a prognostic predictive factor for mortality and infections in patients with liver cirrhosis[20] and as a marker of unfavorable outcome and advanced disease stage in patients with hepatocellular carcinoma .[21]

Vitamin D has an important role in immunity, cancer, infectious diseases, fibrosis and chronic liver diseases. Vitamin D has pleiotropic effects on various cellular aciviteis. The pleiotropic effect of the hormone include the regulation of transcription of over 200 genes involved in cell proliferation and differentiation, immunomodulation, inflammation and fibrogenesis and their effects on liver disease. Study conducted by Han et al suggested two separate pools of 1,25 (OH)2D3 with distinct purposes.[22]

Methods

This Cross-sectional study was conducted at Hepatology department of BSMMU (Currently BMU) in 2020 the patients cirrhosis of liver patients irrespective of etiology those enrolled purposively with inclusion and exclusion criteria. Patient with age ranges between >18 and <65 years of both sexes with compensated and decompensated liver cirrhosis. The patients having vitamin D supplementation, CKD, uncontrolled DM, osteoporosis, PBC, other causes of secondary biliary cirrhosis, drugs like steroid, cirrhosis of liver patients with HCC, pregnant and lactating mother were excluded from the study. A total of 80 patients, 40 with compensated and 40 with decompensated cirrhosis, were included

Study Procedure

All the patients that were presented in the Hepatology Outpatient Department (OPD) or admitted in hepatology department were initially evaluated for diagnosis of cirrhosis of liver. Patients were diagnosed as cirrhosis of liver on the basis of history, clinical examination, and investigations like Ultrasonography (USG) of Hepatobilliary System (HBS), endoscopy of upper Gastro-intestinal Tract (GIT), fibro scan of liver. Patients with history or evidence of variceal bleeding, encephalopathy, ascites and jaundice were categorized as decompensated cirrhosis group. Those without those features were considered in compensated cirrhosis group. All data were collected in a preformed data collection sheet and was analyzed using the statistical package SPSS (Version 22.0 IBM Corp: Armonk NY, USA). Appropriate statistical tools such as the chi-square test, Student's t-test and binary logistic regression analysis were employed to achieve objective goal of the study with p-value <0.05 considered statistically significant.

Results

This observational study was carried out to assess serum vitamin D levels in chronic liver disease. A total of 80 subjects were selected purposefully in two groups in equal number - one as “Compensated cirrhosis” and another as “Decompensated cirrhosis” group as per selection criteria.

Table I: Demographic characteristics of the study populations (n=40)

Demographic pattern	Compensated	Decompensated	P
Mean±SD	44.7±14.0	49.9±14.3	0.108
Gender (M:F)	31:9	33:7	0.576
Socio-economic status (Lower/Middle/High)	13/26/1	7/33/0	0.166

Demographically (Table I) most of the participants in the study were male of middle age group included middle class economic status. In the study there were no significant difference in mean age (p= 0.108), in proportion of gender (p=0.576) and socio-economic status between two groups.

Table II: Distribution of the study patients according to clinical complaint

Clinical Variables	Compensated	Decompensated	P value
Jaundice (Yes /No)	1/39	15/25	0.001
Ascites (Yes /No)	2/38	34/6	0.001
Hepatic encephalopathy(Yes /No)	0/40	8/32	0.003
Variceal bleeding (Yes /No)	0/40	5/35	0.027

Regarding the clinical complaints (Table II) of the patient jaundice (p= 0.001), ascites (p= 0.001), hepatic encephalopathy (p= 0.003), variceal bleeding (p= 0.027), were markedly observed in patients in "Decompensated" group. Ascites (80%) was the most common complaint among patients with decompensated liver cirrhosis.

Table III: Distribution of patients according to examination findings

Clinical Examination	Compensated	Decompensated	P value
Anaemia	17	33	0.001
Jaundice	1	19	0.001
Oedema	2	25	0.001
Spleen palpable	5	19	0.001
Ascites	0	39	0.001

Clinical findings (Table III) observed in the subjects as anemia, jaundice, oedema, splenomegaly and ascites differed significantly between the two groups (all having p=0.001). Ascites, anemia and oedema were the frequent clinical findings in this study.

Table IV: Distribution of the study populations according to investigations

Investigations	Compensated (Mean±SD)		Decompensated (Mean±SD)		P value
Hb% (g/dl)	11.7	±2.2	10.2	±2.1	0.002
ESR in 1st hr	30.4	±22.9	42.4	±26.7	0.035
Platelet count (10^9/L)	192.4	±74.0	141.2	±57.3	0.001
TC (10^9/L)	8.0	±3.1	10.6	±14.1	0.253
Neutrophils (%)	66.4	±9.7	69.1	±8.6	0.211
Lymphocytes (%)	25.0	±8.0	21.9	±6.8	0.070
S. Bilirubin (mg/dl)	0.8	±0.4	3.4	±4.1	0.001
ALT (U/L)	54.7	±34.3	56.0	±77.3	0.919
AST (U/L)	52.9	±27.3	75.1	±44.5	0.009
ALK	103.4	±39.2	133.2	±86.3	0.053
Prothrombin time (s)	12.7	±1.6	16.6	±3.7	0.001
INR	1.10	±0.14	1.49	±0.38	0.001
S. Albumin (mg/dl)	36.7	±6.9	26.0	±7.8	0.001
AFP (ng/ml)	3.8	±2.4	6.2	±7.2	0.043
S. Creatinine (mg/dl)	0.9	±0.2	1.1	±0.2	0.003
Sodium (mmol/l)	138.5	±4.5	133.8	±5.8	0.001
Potassium (mmol/l)	3.9	±0.3	4.3	±0.6	0.005

All patients were tested for hematological and biochemical tests (Table IV). On average the patients with decompensated cirrhosis had 1. 5 g/dl lower hemoglobin concentration (p=0.001), 12 mm higher ESR in first hour (p=0.035) and around half a million less platelets counts (p=0.001) than those of compensated group. The serum bilirubin in compensated patient was within normal limit (0.8±0.4 mg/dl) whereas decompensated patient's level was raised by 2.6 mg/dl.

The secretory liver function was severely reduced in decompensated cirrhotic patient (p=0.009). Synthetic liver function assessed by serum albumin and prothrombin time was compromised in decompensated group with p value of 0.001 in each group. Liver enzyme aspartate transaminase but not alanine transaminase and alkaline phosphatase significantly rose in decompensated patient (p=0.009). Alfa feto-protein was slightly increased in decompensated patient (p=0.04). Serum creatinine was slightly increased in decompensated patient (p=0.043) but serum electrolytes sodium (p=0.001) and potassium (p=0.005) were significantly higher level in decompensated patient.

Table V: Distribution according to CP score, MELD and vitamin D level

Clinical Score		Compensated	Decompensated	P value
Group of CP score (%)	A	37(92.5)	3(7.5)	0.001
	B	3(7.5)	16(40)	
	C	0 (0)	21(52.5)	
MELD score (Mean±SD)		8.6±3.3	16.2±6.3	0.001
MELD range		6.0 - 24.0	6.0 - 30.0	
Vitamin D (Mean±SD) (ng/ml)		23.7±10.4	17.7±9.3	0.008
Vitamin D range (ng/ml)		8.7-63.0	7.6 – 61.1	

In regard of the proportion of CP score(Table V) about 90% of patient in decompensated group had CP score of grade C whereas in about 92% in compensated group had score of grade A. the proportion in between groups had significant difference (p=0.001). The MELD score (Mean±SD) in compensated and decompensated group were 8.6±(3.3) and 16.2±(6.3) respectively and differences in was statistically highly significant (p=0.001).

The patient in compensated group had mean (±SD) of 23.7 (±10.4) and decompensated group had mean (±SD) of 17.7(±9.3). On average patient of compensated group had 6 ng/dl more serum vitamin D concentration than that of decompensated group and the mean difference was highly statistically significant (p=0.008).

Table VI: Distribution of the study populations according to HBsAg and anti HCV

Parameters	Compensated	Decompensated	P value
HBsAg (Negative/Positive)	24/16	21/19	0.499
Anti HCV (Negative/Positive)	0/40	3/37	0.12
Varix (Present/Absent)	29/11	39/1	0.002

About 40% were previous hepatitis B infection and 4% had hepatitis C infection. The study sought no statistical significant association of clinical outcome with types of viral hepatitis. Esophageal

varices was found in 97.5% of patient with decompensated cirrhosis, whereas 72.5% compensated patient had this complication. So esophageal varices significantly differ in clinical group (p=0.002).

Table VII: Correlation and regression analysis on vitamin D and MELD score

Bivariate correlation: serum Vitamin D versus MELD score	
Pearson correlation coefficient	p value
− 0.329	0.003
Binary logistic regression	
-2 Log likelihood	Nagelkerke R Square
36.458	0.808

The bivariate correlation between vitamin D and MELD score showed mild reciprocal relationship Pearson correlation coefficient (r = − 0.3; p = 0.003).

Binary logistic regression was done to observe the clinical outcome as compensated versus decompensated patient taking serum vitamin D, CP score and MELD score as predictors. The regression analysis showed that those predictors fit well to clinical categorization (compensated versus decompensated) in about 80% of cases (Nagelkerke R square= 0.808; − 2 Log likelihood = 36.458).

Discussion

Vitamin D deficiency is a frequent finding in healthy populations worldwide. However, the proportion of patients with liver disease suffering from severe vitamin D deficiency is significantly higher compared to healthy controls.[23]

The study was carried out to explore clinical and biochemical outcomes across different severities of liver cirrhosis and observe any association with the active form of vitamin D3 (Calcitriol).

All together 80 patients were enrolled purposively in and were grouped dichotomously having compensated and decompensated cirrhotic liver disease.

Demographic data for the selected cohort that had been done by Bankuti et al found that most of the patient participants were white (76.7%), and male (53.3%) and the mean age was 58.8 ± 9.2 years (24). Kubesch et al found that mainly middle-aged individuals were more often affected by cirrhosis.

The author found that the patients who were hospitalized for decompensation had on average 61 years old while who were not admitted in hospital had a mean age of 59 years (25). Our study found that compensated and decompensated cirrhotic patient had 45 and 50 years of mean age respectively. So the patients of earlier age were affected by cirrhotic disorders in comparison to those of study conducted by Kubesch et al.

On average the patients with decompensated cirrhosis had 1. 5 g/dl lower hemoglobin concentration, 12 mm higher ESR in first hour and around 50 billion/L fewer platelets count than those of compensated group. All patients were tested biochemically for liver function, renal function and electrolytes profile. The serum bilirubin in compensated patient was within normal limit (0.8±0.4 mg/dl) whereas decompensated patient's level was raised by 2.6 mg/dl.

Rech, M. A et al observed median serum 25-hydroxyvitamin D levels were 28.0 (interquartile range 20–38) ng/mL, with 16 patients (8.9%) having levels.[26] The median 25(OH)D3 serum concentration of the entire cohort was 23 ng/mL[2]. Our study found that compensated and decompensated patient presented with mean of 27 and 18 ng/ml vitamin serum level. Bankuti et al[24] reported a significant association of 25(OH)D with the degree of liver dysfunction. They enrolled 75 patients with liver cirrhosis (various etiologies and severity; approximately 14% of the patients had Child-Pugh C cirrhosis). All patients were followed-up until hepatic decompensation or death. 25(OH)D levels were inversely correlated with MELD score and Child-Pugh score. Patients at the first (6.9±1.9 ng/mL) vs. the third/reference (27.1±6.3 ng/mL) 25(OH)D tertile had a relative risk for hepatic decompensation and mortality of 6.37 (95%CI: 1.75-23.2; P=0.005) and 4.31 (95%CI: 1.38-13.5; P=0.012), respectively, aft er adjustment for age and sex. In our study patient with compensated and decompensated cirrhosis had agreement with study of Banquit et al[24].

Savic Z et al reported a considerable incidence of vitamin D deficiency (86%). In the univariate analysis, low vitamin D levels were associated with mortality; levels ≤6 ng/mL were associated with an unfavorable outcome, whereas vitamin D level. In the multivariate Cox regression analysis including Child-Pugh score, infections and severe vitamin D deficiency, only the presence of infection was associated with mortality.[27] Lastly, Finkelmeier et al prospectively evaluated the role of serum vitamin D status as a prognostic marker in 200 patients with hepatocellular carcinoma. The authors reported that 25(OH)D3 levels negatively correlated with both the stage of cirrhosis and the stage of hepatocellular carcinoma. Patients with severe 25(OH)D3 deficiency had the highest mortality risk. In the multivariate analysis, very low 25(OH)D3 levels were independently associated with mortality together with MELD score and high α-fetoprotein levels (>400 ng/mL).[21]

Concerning etiology and causation of chronic liver disease viral hepatitis act as major causative agent. Zubia et al[29] found that, 93.6% were affected by chronic hepatitis C infection. The second cause of CLD was hepatitis B infection; affecting 4.8% patients and the rest of patient with CLD (1.6%) were seronegative for liver disease.

Three more studies, done by Anty R et al, two in cirrhotic cohorts[20] and another one in patients with hepatocellular carcinoma reached similar conclusions.

In present study, revealed hepatitis B infection as major cause implication in causation of cirrhosis rather than viral hepatitis infection. 44% of patient had previous hepatitis B encounter while only 4% had previous hepatitis C infection.

HCV was one of the important causation of cirrhosis in this study. The HCV monoinfected cohort of Kitson et al showed no association between the baseline 25(OH)D status and SVR [15].
The various studies have discovered the inverse relationship between Child-Pugh score and the serum calcium level. Bankuti et al[24] reported a significant association of 25(OH)D with the degree of liver dysfunction. They enrolled 75 patients with liver cirrhosis. The author found that approximately 14% of the patients had Child-Pugh C cirrhosis.

In our study we found that about half of patient with uncompensated cirrhosis had CP score of C grade. About 90% of patient in decompensated group had CP score of grade

C whereas in about 92% in compensated group had score of grade A which was statistically highly significant (p=0.001).

In the first study, the authors studied the association of vitamin D deficiency with survival in a cohort of 92 patients with advanced liver cirrhosis (82% Child-Pugh stages B and C).[29]

Patients were categorized according to CP class to assess the degree of liver dysfunction. Among the 125 patients, 38 (30.4%) had advanced liver disease and were in CP class C, 48 (38.4%) were CP class A, showing early liver cirrhosis, and 39 (31.2%) were CP class B, indicating the intermediate stage of liver cirrhosis. [24]

Vitamin D levels were notably related to Child-Pugh class (contingency coefficient = 0.5, $p<0.05$. On univariate and multinomial regression analyses, age, female sex, MELD and Child-Pugh class were predictors of low vitamin D levels. Age, model of end-stage liver disease score and Child-Pugh score were negatively correlated to vitamin D levels.[28]

MELD

All patients were followed-up until hepatic decompensation or death. 25(OH)D levels were inversely correlated with MELD score and Child-Pugh score.[23]

The MELD score (Mean±SD) in compensated and decompensated group were 8.6 ± 3.3 and 16.2± 6.3 respectively and differences in was statistically highly significant (p=0.001).

Our study had shown that vitamin severity of the cirrhosis focused by CP score and MELD had inverse relation of the serum level 0f vitamin D. The result from our study conforms to that of the study done by Putz-Bankuti et al.[24]

The prospective cohort study conducted by Kubesch A had shown that baseline vitamin D levels were inversely associated with liver-cirrhosis related systemic inflammation and the risk of hepatic decompensation.[25]

Conclusion

In conclusion, the association of vitamin D with liver cirrhosis showed great potential for clinical application. In the near future, we expect a variety of extra-skeletal indications to be explored. The relation between vitamin D deficiency and the degree of liver function, degree of fibrosis and infectious complications could support its use as a prognostic index and diagnostic tool. The role of vitamin D in liver cirrhosis needs to be further evaluated and validated in large prospective cohort studies and randomized trials.

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