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Hepatology

Association of Serum 25-Hydroxyvitamin D Level with the Grades of Hepatic Encephalopathy in Cirrhotic Patients

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Abstract **Original Research Article**

Background: Liver cirrhosis is the final phase of the hepatic fibrosis process, defined as a diffuse disruption of the normal architecture of the liver with fibrosis and nodule formation and it is one of the major cause of morbidity and mortality throughout the world. Hepatic encephalopathy (HE) is one of the complications of cirrhosis that identified in up to 55% of patients. The etiology of HE is complex and multifactorial. Vitamin D deficiency is more common in cirrhosis and associated with neuropsychiatric abnormalities and systemic inflammation as well as infection thereby giving rise to the development of HE. ***Objectives:*** This study aimed to evaluate the serum 25- Hydroxyvitamin D level in liver cirrhosis patient with or without hepatic encephalopathy and its relation with grades of hepatic encephalopathy. ***Materials and Methods:*** An observational cross-sectional study was carried out in the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka from December 2019 to August 2020. Patients who met the selection criteria were counselled and finally 54 were included in the study among them 27 had hepatic encephalopathy where 27 had not. Serum 25-Hydroxyvitamin D level was estimated by chemiluminescence immunoassay (CLIA) in our Biochemistry department. All data were presented as mean ± SD & analyzed by SPSS (version 20). Qualitative data were analyzed by Chi-square test & quantitative data were analyzed by student's t-test. Statistically significance of serum 25- Hydroxyvitamin D level among the grades of hepatic encephalopathy will be detected by ANOVA test. A statistically significant result was considered when p value less than 0.05. ***Result:*** Among 54 cirrhotic patients, age ranged from 20 to 72 years and the mean age was 50.2 ± 13.1 years. The Child-Pugh score and MELD score were negatively correlate with mean 25-Hydroxyvitamin D level. The mean level of 25-Hydroxyvitamin D was significantly lower in patients with HE compared to the control group (6.6±2.1ng/ml vs 13.6±4.2ng/ml, p< 0.05).The mean serum 25-Hydroxyvitamin D level was 8.6±0.7 in grade 1 HE, 6.5±1.5 in grade 2 HE, 3.9±0.8 in grade 3 HE and 3.5±0.00ng/ml in grade 4 HE with P<0.05.There was a significant negative correlation between serum 25- Hydroxyvitamin D level and worsening grades of hepatic encephalopathy (P<0.05). ***Conclusion:*** It is demonstrated serum 25-Hydroxyvitamin D level was inversely correlate with severity of cirrhosis and hepatic encephalopathy and level of serum 25-Hydroxyvitamin D proportionately reduced with severity of encephalopathy grades.

Keywords: Serum 25-Hydroxyvitamin D level, Hepatic encephalopathy, Cirrhotic patients.

INTRODUCTION

Hepatic encephalopathy (HE) describes a complex collection of neuropsychiatric symptoms ranging from sub-clinical neuropsychiatric changes to coma (Vilstrup *et al.*, 2014) and has been identified in up to 55% of patients with chronic liver disease (Kalaitzakis and Bjornsson 2008), reducing health-related quality of life and causing a reversible decline in cognitive function [1-3]. Symptoms include impaired cognition and motor function and reduced energy levels [4]. Hepatic

encephalopathy can be classified as either 'overt' or 'minimal'. Overt Hepatic Encephalopathy (OHE) is a syndrome of neurological and neuropsychiatric abnormalities that can be detected by bedside clinical tests. By contrast, patients with Minimal Hepatic Encephalopathy (MHE) present with normal mental and neurological status upon clinical examination but specific psychometric tests yield abnormal results.

A precise gradation of HE is essential to assess prognosis and plan an appropriate approach to treatment. According to the severity, HE has been traditionally divided into four stages based on alterations in the state of consciousness, intellectual function, behavior, and neuromuscular signs [4].

The aetiology of HE is complex and multifactorial, and includes abnormal ammonia metabolism, dysbiosis which promotes inflammation in the gut and liver (Rai *et al.*, 2015), [5] low levels of circulating branched chain amino acids, [6] electrolyte abnormalities and alterations in zinc and manganese levels [7].

Vitamin D is a multifunctional steroid hormone with diverse actions that are only partially understood. It is increasingly apparent that vitamin D is not just involved in calcium homeostasis and bone metabolism but has multiple biological targets mediated by vitamin D receptors (VDR) [8].

VDR protein is present in most neurons and the glia in the human brain [9]. The hypothalamus and the cortex of the human brain are key areas in cognition. The presence of both VDR protein and vitamin D metabolites in these areas of the brain are an indication that the vitamin D system is involved in the normal functioning of the human brain.

A linear relationship between 25-OHD deficiency and cognitive impairment has been identified in younger adults (30-60 years) as well as adults older than 60 years [10]. It is plausible that 25-OHD deficiency could not impact on cognitive function in CLD, a causative relationship nor a mechanism for this has been demonstrated. 25-OHD is associated with verbal fluency, a marker of executive function and therefore a marker of cognitive function.

Objective

The study is to assess the association of serum 25-Hydroxyvitamin D level with the grades of hepatic encephalopathy in cirrhotic patients.

METHODOLOGY

Study Design: This was a cross-sectional observational study.

Study Setting: The study was conducted in the Department of Hepatology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

Study Period: The study was carried out from December 2019 to August 2020.

Study Population: The study included hospitalized cirrhotic patients, with or without hepatic encephalopathy, who met the inclusion and exclusion criteria.

Sampling Method: Purposive sampling was employed to recruit participants.

Sample Size: The sample size was determined by the following formula-

$$N = \frac{\left\{ u\sqrt{[\pi(1-\pi)]} + v\sqrt{[\pi_0(1-\pi_0)]} \right\}^2}{(\pi - \pi_0)^2}$$

Where,

n was estimated sample size,

- u= 0.84, v= 1.96,
- π = 29 % or 0.29, π_0 = 10 % or 0.10 (Vidot *et al.*, 2017)
- So calculated sample size was 27 in case and 27 in control for statistically significant result.

Selection Criteria

Inclusion Criteria

- **Case Group**:
  1. Adult patients (>18 years) with liver cirrhosis and hepatic encephalopathy, diagnosed based on the West Haven criteria.
  2. Liver cirrhosis diagnosed through clinical features (e.g., vascular spiders, palmar erythema, gynecomastia, leukonychia, testicular atrophy) and laboratory findings (e.g., prolonged prothrombin time, reduced serum albumin).
  3. Additional supportive evidence such as esophageal varices on endoscopy and coarse liver texture on ultrasonography.
- **Control Group**:
  1. Adult patients (>18 years) with liver cirrhosis but no history or symptoms of hepatic encephalopathy.

Exclusion Criteria

1. Chronic renal failure.
2. Alcohol intoxication.
3. Malignancy.
4. Parathyroid disorders.
5. Rheumatological diseases.
6. History of taking vitamin D supplements.

7. History of hepatic encephalopathy.

Variables

- **Dependent Variable**:
  - Serum 25-hydroxyvitamin D levels.
- **Independent Variables**:
  - Age, sex, grades of hepatic encephalopathy, Child-Pugh (CTP) score, and MELD score.

Study Procedure

Patients admitted to the Department of Hepatology at BSMMU with liver cirrhosis were screened for eligibility. A total of 27 patients with hepatic encephalopathy (case group) were classified into four groups based on the West Haven criteria (WHC), while 27 patients without encephalopathy (control group) were selected.

Data collection involved a detailed history, clinical examination, and laboratory investigations. Demographic and clinical data such as age, sex, and cirrhosis-related complications (e.g., ascites, variceal bleeding, hepatorenal syndrome) were recorded.

Baseline investigations included:

- **Liver function tests**: Serum bilirubin (vanadate oxidation method), ALT and AST (spectrophotometric method), serum albumin (bromocresol green method), and prothrombin time (automated coagulation analyzer).
- **Renal function**: Serum creatinine (Jaffe method).
- **Ascitic fluid analysis**: Cytology, total protein, albumin, and SAAG.
- **Other tests**: Serum PTH (two-step immunochemical method), HBsAg and anti-HCV (ELISA), alpha-fetoprotein (quantitative immunochromatographic assay).
- **Imaging**: Abdominal ultrasonography.
- **Endoscopy**: Upper gastrointestinal tract endoscopy.

Serum 25-hydroxyvitamin D levels were measured using a chemiluminescence immunoassay (CLIA) on the Alinity ci machine. Grading of hepatic encephalopathy was performed according to WHC criteria, based on clinical and neuropsychological abnormalities.

Data Processing and Analysis

Data were collected using a structured questionnaire after obtaining informed consent from participants. The collected data were analyzed using SPSS (version 20.0).

- Quantitative variables were expressed as mean ± standard deviation (SD) or median (range), depending on distribution.
- Qualitative variables were analyzed using the chi-square test.
- Comparisons between case and control groups were performed using Student's t-test for continuous variables.
- The relationship between serum 25-hydroxyvitamin D levels and grades of hepatic encephalopathy was assessed using ANOVA.

A p-value < 0.05 was considered statistically significant.

RESULTS

It was observed that mean age was found 50.2±13.1 years. Male female ratio was 1.70:1.

Table I: Demographic characteristics of the study patients (n=54)

Demographic characteristics	Mean	±SD	min	-max
Age (Years)	50.	2±13.1	20	-72
Sex				
Male		34		
Female		20		

Table shows CTP score of the patients, it was observed that majority patients were in Child C in case, 23(85.2%) and Child B in control group, 20(74.1%). In case group mean of serum 25-Hydroxyvitamin D level in Child B was 7.7±1.8ng/ml, in Child C 6.4±2.1ng/ml. In control group mean of serum 25-Hydroxyvitamin D level in Child A was 16.5±6.1ng/ml, in Child B 13.5±4.5ng/ml and Child C was 12.6±1.5ng/ml. The difference was statistically significant (P<0.0001) between the groups.

Table II: Distribution of the study patients by CTP score and serum 25-Hydroxyvitamin D level (n=54)

CP score	Case (cirr with encep) (n=27)		Control (cirr without encep) (n=27)		P value
	n	25-OHD (Mean±SD)	n	25-OHD (Mean±SD)	
Child A	0	0.0	2	16.5±6.1	<0.0001[s]
Child B	4	7.7±1.8	20	13.5±4.5	
Child C	23	6.4±2.1	5	12.6±1.5	

Cirrh=cirrhosis, encep=encephalopathy,25-OHD=25-HydroxyvitaminD; s=significant P value reached from ANOVA test.

Table III shows MELD score of the patients, it was observed that majority of patient in case and control group were in MELD range 10-19. In case group mean 25- Hydroxyvitamin D level was 6.3±0, 7.3±1.8, 6.0±2.3 and 5.1±2.7 respectively. In control group mean 25-Hydroxyvitamin D level was 12.8±4.0, 14.2±4.5, 12.2±2.7 and 10.3±0 respectively. The difference was statistically significant (P=0.038) between the groups.

Table III: Distribution of the study patients by MELD score and serum 25- Hydroxyvitamin D (n=54)

MELD Score	Case (cirr with enc) (n=27)		Control (cirr without enc) (n=27)		P value
	n	25-OHD (Mean±SD	n	25-OHD (Mean±SD)	
<10	1	6.3±0	6	12.8±4.0	0.038[s]
10-19	15	7.3±1.8	18	14.2±4.5	
20-29	8	6.0±2.3	2	12.2±2.7	
≥30	3	5.1±2.1	1	10.3±0	

Cirr=cirrhosis, enc=encephalopathy;
s= significant
P value reached from ANOVA test

Figure shows correlation between the serum 25-Hydroxyvitamin D level and MELD score among the patients of cirrhosis without encephalopathy and different grades of encephalopathy. Mean 25-Hydroxyvitamin D level 11.9ng/ml in patients whose MELDs <10, 11.1ng/ml whose MELDs 11-20, 7.2ng/ml whose in 21-30 and 6.4 ng/ml whose MELD >30. Figure shows serum 25-Hydroxyvitamin D level decreasing when MELDs increasing which was statistically significant (p=0.032).

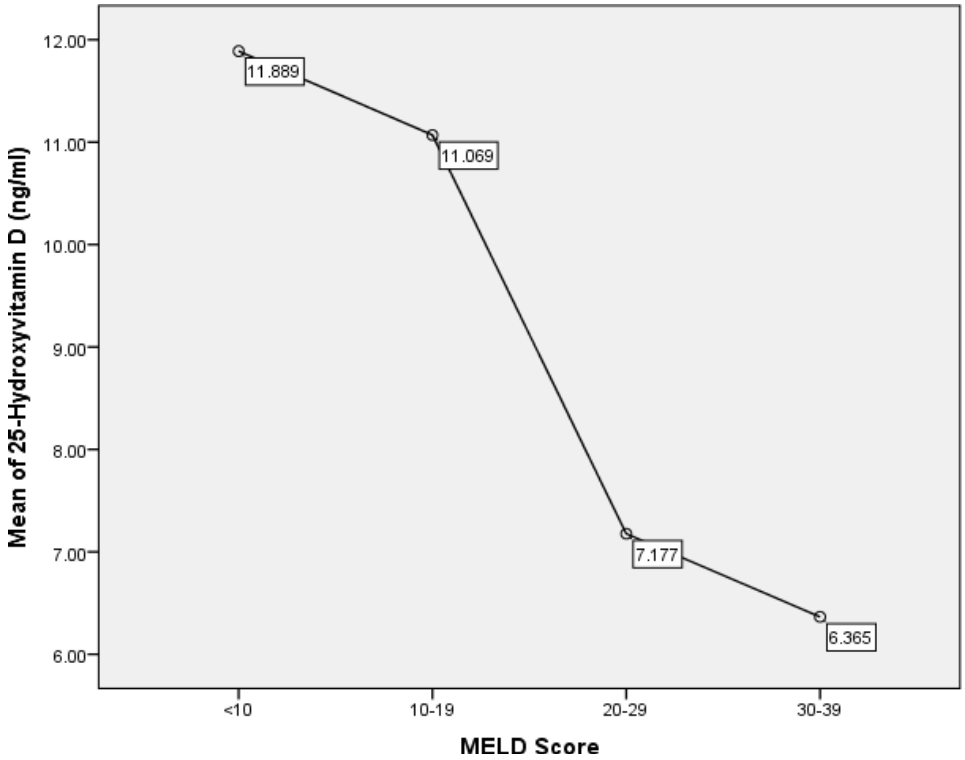

Figure 1: Correlation between the serum 25-Hydroyvitamin D level and MELDs among the patients.

Figure 2 shows correlation between the serum 25-Hydroxyvitamin D level and Child- Pugh class among the patients of cirrhosis without encephalopathy and different grades of encephalopathy. Mean 25-Hydroxyvitamin D level 16.5ng/ml whose Child-Pugh A, 12.6ng/ml whose in Child-Pugh B and 7.5ng/ml whose in Child-Pugh C. Figure shows serum 25-Hydroxyvitamin D level decreasing when Child-Pugh score increasing which was statistically significant (p<0.0001).

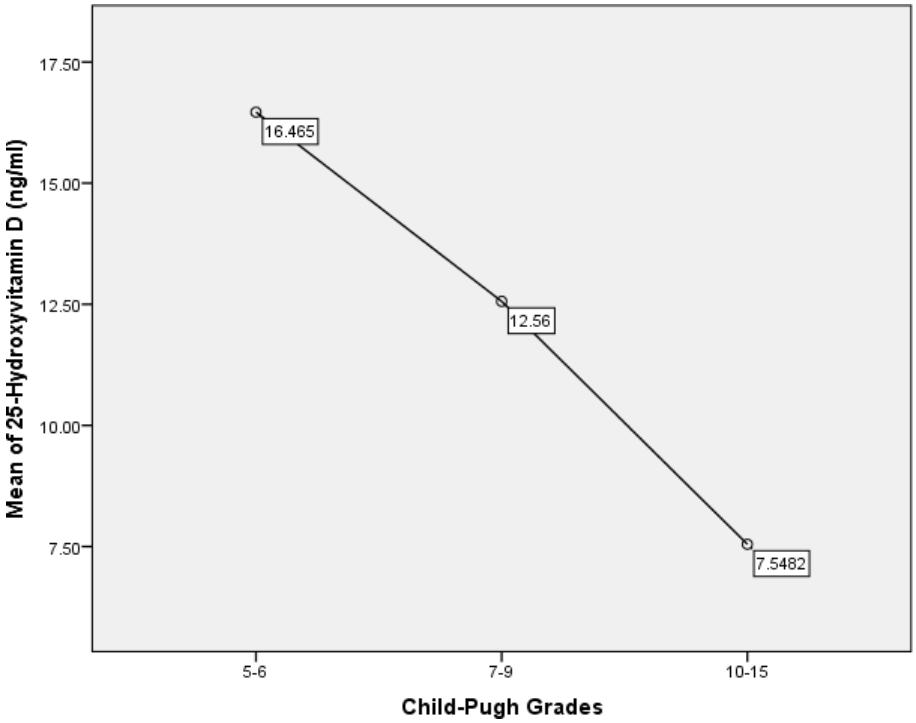

Figure 2: Correlation between the serum 25-Hydroxyvitamin D level and Child-Pugh class among the patients.

Figure 3 shows correlation between the serum 25-Hydroxyvitamin D level and among the patients of cirrhosis without encephalopathy and different grades of encephalopathy. Mean 25-Hydroxyvitamin D level 13.58ng/ml in patients whose encephalopathy, without 8.65ng/ml whose in grade 1 HE, 6.55ng/ml whose in grade 2 HE, 3.92ng/ml in grade 3 HE and 3.50ng/ml in grade 4 HE. This Figure shows serum 25-Hydroxyvitamin D level inversely proportional to the severity of encephalopathy which was statistically significant (p<0.0001).

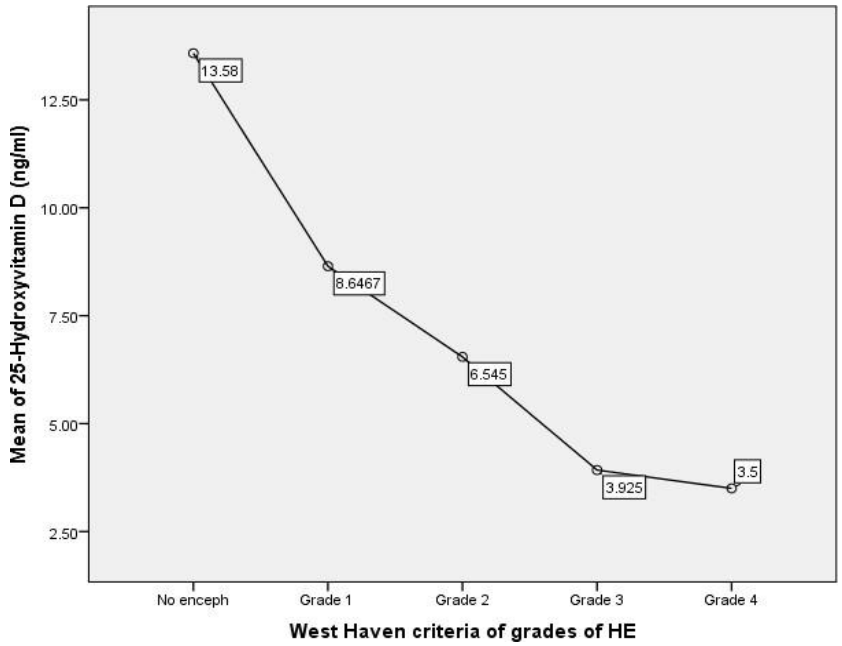

Figure 3: Correlation between the serum 25-Hydroxyvitamin D level and severity of encephalopathy among the patients

DISCUSSION

In our study, it was observed that mean serum level of 25-Hydroxyvitamin D level is reducing when MELD score was increasing. Mean serum level of 25-Hydroxyvitamin D was 11.9±4.4ng/ml, 11.1±4.9ng/ml, 7.2±3.5ng/ml and 6.4±3.4ng/ml in MELD score <10,10-19,20-29 and 30-39 respectively. The differences were

statistically significant (p=0.032) between the groups. Jamil *et al.*, (2018) showed in one study that mean MELD score 14.94, 18.43 and 23.19 group patients has sufficient, insufficient, deficient level of vitamin D respectively and the differences were statistically significant (p=0.003) between the groups [11].

In our study, it showed that mean serum 25-Hydroxyvitamin D level in control group was 13.6±4.2ng/ml and in case group mean serum 25-Hydroxyvitamin D level was 8.6±0.7 in grade 1 HE, 6.5±1.5 in grade 2 HE, 3.9±0.8 in grade 3 HE and 3.5±0.00ng/ml in grade 4 HE were statistically significant (p<0.0001) between the groups.

Similar finding was elicited by Kumar *et al.*, (2020) showed that mean serum 25- Hydroxyvitamin D level in control group was 37.44±18.61nmol/L and in case group mean serum 25-Hydroxyvitamin D level was 30.64±21.64 in grade 1 HE, 12.03±11.05 in grade 3 HE with $P < 0.0001$and 18.8±16.88nmol/L in grade 4 HE with $P < 0.0001$ when compared to grade 1 HE [12]. In another study, Vidot *et al.*, (2017) where mean serum 25-Hydroxyvitamin D level was 30±13nmol/L in case group and 42±16nmol/L in control group was statistically significant (p<0.05) between two groups [13]. In another study, Yousif *et al.*, (2019) showed that where mean serum 25-Hydroxyvitamin D level was 6.81±2.75ng/ml in patient group and 16.28±6.60ng/ml in healthy group was statistically significant (p<0.05) between two groups [14].

CONCLUSION

Our study demonstrated a strong association in serum 25-Hydroxyvitamin D level and cirrhosis which is inversely correlate with serum 25-Hydroxyvitamin D level and severity of liver cirrhosis. It is observed that, level of serum 25-Hydroxyvitamin D proportionately reduced with severity of encephalopathy grades.

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