Relationship between 25-Hydroxyvitamin D Deficiency and Hepatic Encephalopathy in Patients with Cirrhotic Liver Disease

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Abstract

Background & aim; Patients who experience repeated episodes of hepatic encephalopathy (HE can have persistent and cumulative deficits in working memory, response inhibition and learning. There is rising evidence of clinical connections between vitamin D status and global and particular areas of cognitive function and that vitamin D insufficiency may be connected with both depression and schizophrenia. This research was aiming to examine the connection between 25 hydroxy vit D insufficiency and hepatic encephalopathy in patient with cirrhotic liver disease. Methods: We included a total of 50 patients with liver cirrhosis, who were separated into two equal groups; the Non-HE group contained 25 instances without HE, and the HE group which included the remaining 25 cases with HE. Results: Vitamin D exhibited a substantial decline in the HE group, as it had a mean value of 31.22 nmol/l compared to 42.89 nmol/l in the other group. Vitamin D insufficiency was observed in 68 and 96 percent of patients in the Non-HE and HE groups respectively. Vitamin D levels revealed no significant link with any of the measured variables other from CTP score, that exhibited a significant negative relationship with the tested vitamin. Using a cut-off value of 37.61, blood vitamin D level exhibited sensitivity and specificity of 68 and 60 percent respectively for identifying hepatic encephalopathy in cirrhotic individuals. Conclusion; A substantial connection was discovered between vitamin D deficiency and the development of HE. The degree of vitamin D insufficiency is highly connected with the severity of liver functioning state.

Keywords: 25-Hydroxyvitamin, viamin D Deficiency, Hepatic, Encephalopathy, cirrhosis.

1. Introduction

Throughout 2 million people die each year from liver disease around the globe, with 1 million of those deaths resulting from liver cirrhosis-related complications, according to the Global Burden of Disease research (Mokdad et al., 2014). This condition is responsible for 1.6 per cent of all deaths in the globe and ranks 11th in mortality rates worldwide [1].

cirrhosis is the last stage of all chronic liver disease, and it is caused by fibrosis. Portal hypertension and/or hepatic dysfunction are also possible outcomes of cirrhosis. Ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome, and coagulation abnormalities may result from one of these conditions alone or in combination. As cirrhosis progresses, the quality of life suffers as well as the chance of survival [2].

As many as 55% of patients with chronic liver illness are diagnosed with hepatic encephalopathy (HE), which encompasses a range of neuropsychiatric symptoms, from sub-clinical neuropsychological abnormalities to coma [3].

Dysbiosis, which causes inflammation in the gut and liver, low levels of circulating branched-chain amino acids, electrolyte abnormalities, and changes in zinc and manganese levels are all thought to have a role in the HE aetiology [4].

The varied activities of vitamin D, a multifunctional steroid hormone, are still poorly known. Vitamin D isn't just important for calcium homeostasis and bone metabolism, but it also has multiple biological targets mediated by vitamin D receptors (VDRs) that are found in more than 30 tissues, including the brain, kidneys, intestine, parathyroid gland, pituitary, prostate, mammary glands, cardiac and skeletal muscle, non-parenchymal liver cells, endothelial cells, and the immune system [5].

Vitamin D may be found in food and through sunlight exposure. The hydroxylation of cholecalciferol to 25-hydroxyvitamin D (25-OHD) in the liver is the initial step in the activation of vitamin D [6].

Hepatitis C virus, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) have all been linked to a lack in vitamin D, which has been linked to an increased risk of developing liver disease [7].

The decline in liver function that occurs as a result of 25-OHD insufficiency is quite substantial. As more and more people learn about the connection between cirrhosis patients' disease severity and 25-OHD level declines, this finding makes sense [8].

HE is characterised primarily by neurobehavioral problems, which have been linked to elevated levels of inflammatory cytokines [9].

We wanted to find out whether there was a link between 25-hydroxyvitamin D insufficiency and cirrhosis-induced hepatic encephalopathy. disease.

2. Patients and methods

This The Internal Medicine Department at Benha University Hospitals performed a prospective comparison research between January 2020 and January 2021. Two equal groups were formed from the total of 50 patients diagnosed with liver cirrhosis; the non-HE group contained 25 patients with no present or past history of HE. In addition, there were 25 instances in the HE group, which comprised those who had or had reported past encounters with HE.

2.1 Requirements for inclusion

A diagnosis of liver cirrhosis is made on the basis of the patient's medical record and examination

findings as well as laboratory testing (liver function test, coagulation profile and Radiology).

From 18 to 70 years of age.

Criteria for exclusion

There is a condition known as chronic renal disease.

 Malnutrition.

Deficiency in nutrients (coeliac sprue, short bowel syndrome, cystic fibrosis).

Moderate exposure to the sun.

Steroid usage history.

A history of drugs, such as phenobarbital, rifampicin, and Dilantin, that stimulate the hepatic p450 enzymes that catalyse vitamin D degradation.

An ethics committee and Institutional Review Board (IRB) of Benha University's college of medicine approved the research. At any point, patients were allowed to withdraw from the research. The acquired data were solely utilised for scientific reasons, and the privacy of the patients was protected at all times. After a thorough discussion of each intervention's benefits and risks, all participants signed an informed consent form.

All patients received a thorough medical history, clinical examination, and diagnostic testing as part of their treatment. Liver function tests, including serum albumin, hepatic transaminases, bilirubin, prothrombin time, and international normalised ratio (INR), serum creatine, random blood sugar, and serum vitamin D level, are included in the blood count.

Each patient's blood was drawn and allowed for 30 minutes to clot naturally. Finally, the samples were centrifuged at 3000 rpm for 5 minutes and kept at 20 °C for further analysis. ELFA (Enzyme Linked Fluorescent Assay) was used to detect 25-OH levels (VIDAS® 25 OH Vitamin D Total). Severe deficiency (12.5 nmol/L) was defined as 25-OH vitamin D status less than or equal to 12.5 nmol/L, while mild deficiency was classified as 25-50 nmol/L. [10].

After a thorough clinical and laboratory evaluation, all patients in the two groups were assigned to the same CTP class [11].

Hepatobiliary ultrasonography was carried out by an expert radiologist to check for abnormalities such as splenomegaly and other intraabdominal pathologies such as liver texture and localised lesions.

2.3. Analysis of data

SPSS (Statistical Package for Social Sciences) version 26 for Windows® was used to code, process, and analyse the obtained data (IBM SPSS Inc, Chicago, IL, USA). The Shapiro Walk test was used to determine whether the data were normal. Frequencies and relative percentages were used to depict qualitative data. For the comparison of qualitative variables, chi square tests and Fisher exacts were employed as stated. The mean standard deviation (SD) was used to convey quantitative data (Standard deviation). This method was used to compare two independent groups of regularly distributed variables (parametric data), whereas the Mann Whitney U test was used for non-normally distributed data (non-parametric data). For non-parametric quantitative data, Spearman's correlation was applied. Analysis of the receiver operating characteristic (ROC) For various cutoffs, this graph shows the sensitivity as a function of cutoff value minus specificity (the false positive rate). Using the Youden index J, the furthest point on the ROC curve from the diagonal line of equality [maximum (sensitivity + specificity)-1] was used to establish the appropriate cutoff value. A test's overall accuracy may be gauged by looking at its area under the receiver operating characteristic (AUC) curve. The greater the AUC, the better a test's ability to distinguish between sick and healthy individuals. Null hypothesis (the hypothesis that there is no difference) was rejected at a significance level of 0.05 in all applicable tests, and the P-values associated with test statistics showed the significance level at which the null hypothesis (the hypothesis that there is no difference) was rejected.are highly significant.

4. Results

The mean age of the included cases was 61.3 and 64.2 years in the Non-HE and HE groups respectively. Male patients represented 72% and 56% of cases in the same groups respectively, while the remaining cases were females. No significant difference was detected between the two groups regarding age or sex (p > 0.05), table (1).

Table (1) Demographic criteria in the two studied groups.

Variables	No HE (N=25)		HE (N=45)		Significance Test	P value
Age (mean± SD)	61.3 ± 9.83		64.2 ± **8.22**		t= -1.008	0.274
			Sex			
Males	18	72%	14	56%	χ^2=1.389	0.239
Females	7	28%	11	44%		

T: Independent samples t-test (Students t-test), $\chi^{2:}$ Chi-square test.

CTP score showed significantly higher values in the HE group, as it had a mean value of 10.96 compared to 9.84 in the Non-HE group (p = 0.011). Child C patients were more encountered in the HE group (68% vs. 28% in the other group – p 0.013), table (2)

Table (2) The severity of liver cirrhosis assessed by Child-Pugh classification in the two groups.

|		No HE (N=25)		HE (N=45)		Significance Test	P value
Child-Pugh Score (mean± SD)		9.84 ± 2.44		10.96 ± 1.51		t= -2.559	0.011*
Child-pugh classification							
Child A		10	40%	3	12%		
Child B		8	32%	5	20%	χ^2= 8.862	0.013*
Child C		7	28%	17	68%		

*Significant difference (p value <0.05). T: Independent samples t-test (Students t-test).

Vitamin D showed a significant decrease in the HE group, as it had a mean value of 31.22 nmol/l compared to 42.89 nmol/l in the other group (p = 0.013). Vitamin D deficiency was detected in 68 and 96% of cases in the Non-HE and HE groups respectively (p = 0.032). table 3 & figure (1).

Table (3) Vitamin D level and status in the two studied groups.

Variables	No HE (N=25)		HE (N=45)		Significance Test	P value
Vitamin D (nmol/l)	42.89 ± 16.91		31.22 ± 14.83		z = 2.595	0.013*
Vitamin D status						
Deficient	17	68 %	24	96 %		
Insufficient	5	20 %	1	4 %	FET = 6.868	0.032*
Sufficient	3	12 %	0	0 %		

*Significant difference (p value <0.05). $\chi^{2:}$ Chi-square test
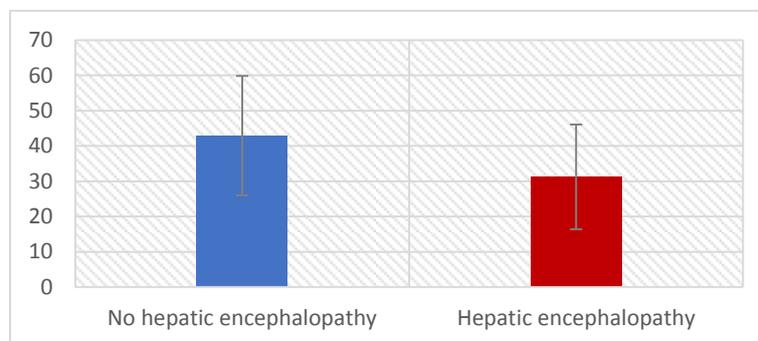
Fig. (1) Serum vitamin D in the two studied groups.

Vitamin D levels showed no significant correlation with any of the tested variables apart from CTP score, that had a significant negative relationship with the tested vitamin (p = 0.016). table (4)

Table (4) Correlation between serum vitamin D level and other laboratory markers.

Variables	Correlation Coefficient (r)	P value
Age	-0.026	0.901
HGB	-0.073	0.730
WBCs	0.123	0.558
Platelets	-0.026	0.901
RBS	-0.255	0.219
Creatinine	0.040	0.849
ALT	-0.027	0.898
AST	-0.105	0.619
Albumin	-0.011	0.959
Total bilirubin	-0.384	0.058
Direct bilirubin	-0.321	0.118
INR	-0.327	0.110
PT	-0.370	0.069
Child Pugh score	-0.478	0.016*

Using a cut-off value of 37.61, serum vitamin D level had sensitivity and specificity of 68 and 60% respectively for detecting hepatic encephalopathy in cirrhotic patients. Figure 2
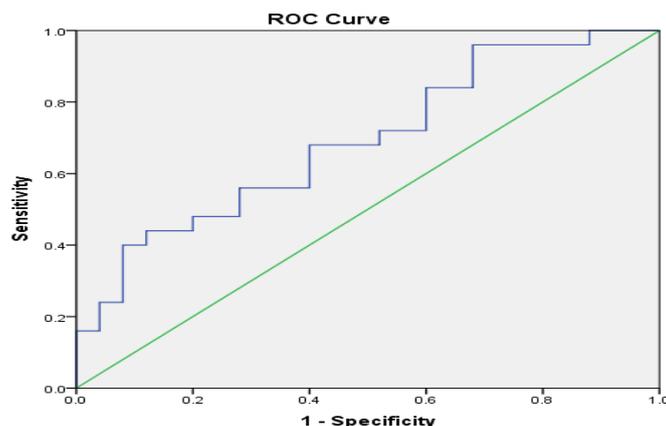
Fig. (2) ROC curve analysis for serum 25-OHD as a marker for HE.

5. Discussion

This Patients with cirrhotic liver disease were studied at Benha University Hospitals to see whether a lack of 25 hydroxy vitamin D was linked to hepatic encephalopathy. The non-HE group contained 25 instances without HE, while the HE group included the remaining 25 cases with HE. This gave us a total of 50 patients with liver cirrhosis.

Vitamin D levels in the HE group were significantly lower than in the control group, at 31.22 nmol/l as opposed to 42.89 nmol/l (p = 0.013). Non-HE and HE patients were found to have vitamin D insufficiency at a rate of 68% and 96%, respectively, (p = 0.032).

Another study conducted by Afifi et al. [12] found that patients with HE had significantly lower blood levels of the same vitamin. There were mean values of 27.2 nmol/l in the HE group and 41 nmol/l in the Non-HE group (p 0.001). The frequency of vitamin D insufficiency in the HE group (p 0.001) was substantially higher.

The vitamin D concentrations in the HE and non-HE groups were 30 and 42 nmol/l, respectively, with a significant difference (p 0.05) between the two groups.

In addition, Yousif et al. [14] did an Egyptian investigation at Zagazig University that supported the prior results. The HE and Non-HE groups exhibited mean serum vitamin D levels of 6.81 and 16.28 ng/ml, with a significant difference between them (p = 001). Vitamin D insufficiency was found in all of the HE patients, whereas only 77.78 percent of the Non-HE patients had the same finding.

This connection may be explained by 25-OHD's insufficient anti-inflammatory effects. Precursors to HE include inflammation throughout the body and alterations in hepatic metabolism, such as higher ammonia levels [13,15].

25-OHD insufficiency has been linked to the development of all-cause dementia and a decline in cognitive function that is not restricted to the elderly (16). In both young individuals (30-60 years old) and those over 60, a link has been shown between a lack of 25-OHD and cognitive decline [17]. An extensive assessment of vitamin D and cognitive impairment

determined that "25-OHD deficiency undoubtedly adversely impacts particular cognitive processes, such as explicit episodic memory," although more clinical work is needed in this area [18].

CLD sufferers may be affected by a lack of 25-OHD, although no proof of a causal link or mechanism for this has been shown. Uncertainty surrounds the extent to which 25-OHD insufficiency impacts the brain's function. As an indicator of executive function and, by extension, of cognitive ability, 25-OHD is linked to verbal fluency. Those with 25-OHD levels of more than 100 nmol/L performed much better on verbal fluency tests than those with lower levels, supporting the theory that vitamin D plays a role in cognitive decline [19].

We found a significant negative correlation between vitamin D level and CTP score in the present research (r = -0.478 – p = 0.016)

According to Afifi and his colleagues [12], 25-OHD levels in children A and B were greater than those in children C, showing a negative association between these two parameters. A research by Fisher et al. [20] revealed similar findings, with more vitamin D-deficient patients observed in class C. [20].

In addition, our findings were in line with those of several previous research showing a negative relationship between vitamin D levels and both the CTP and MELD scores [21]. Fernández et al. [22] and Zhao et al. [23] carried out two experiments in which they discovered that vitamin D levels fall more as liver cirrhosis progresses. In comparison to individuals with lower CTP and MELD scores, those with greater CTP and MELD scores had vitamin D levels that were lower by a significant margin.

There seems to be a strong correlation between declining liver function and a shortage in 25-OHD. As more and more people learn about the connection between cirrhosis patients' disease severity and 25-OHD level declines, this finding makes sense [8].

We found no significant link between our study parameters and vitamin D, save than CTP, in our research.

Other researchers have shown a strong link between serum levels of vitamin D, albumin, GGT, salt,

zinc, and retinol binding protein, all of which are found in the blood. BMI and BMI were shown to have a substantial negative connection with vitamin D. [13].

Others found a link between albumin levels and serum 25(OH)D (r = -0.29, P = 0.03), but only in the HE group (r = -0.29, P = 0.03) [14].

It is normal to discover some discrepancies in these correlations across various research, and this might be due to the fact that different populations, samples, and statistical tests were used in each study.

As a single site study with a limited sample, our research has certain limitations. To further understand the effects of vitamin D on this illness, these patients should have been given vitamin D and followed up. In the forthcoming investigations, these limitations should be thoroughly examined.

6. Conclusion

Patients with liver cirrhosis are more likely to suffer from vitamin D insufficiency. Vitamin D insufficiency has been linked to an increased risk of developing HE. The severity of liver dysfunction is closely linked to one's level of vitamin D insufficiency.

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