Research Article

Correlation Between Vitamin D Deficiency and Severity of Liver Disease among Cirrhotic Patients

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Abstract

Background: Data from many studies suggest that deficiency of vitamin D has got role in pathophysiology of cirrhosis. Though the vitamin D deficiency has strong assossiation with chronic liver diseases and cirrhosis, yet its relation with development of advanced liver fibrosis is still controversial. The objective of our research was to determine the correlation between deficiency of vitamin D (< 30 ng/ml) and severity of liver disease among cirrhotic patients.

Methods: Levels of Vitamin D were evaluated in 125 patients suffering from Chronic Liver Disease. The participants were categorized in three groups on the basis of Child-Pugh scoring system: A, B and C. The association of vitamin D levels with Child-Pugh grade and additional variables in the research was calculated by the contingency coefficient and chi-square by means of p-values.

Results: Amongst the patients, 65.6% had scarce or deficient levels of vitamin D, 23.2% had inadequate values of Vitamin D and remaining 11.2% had adequate stores of vitamin D ($p > 0.05$). Levels of vitamin D were remarkably associated with Child-Pugh class ($p < 0.05$).

Conclusion: A decreased level of Vitamin D is markedly associated with severity of liver disease. Vitamin D levels must be regularly monitored in patients with advanced liver cirrhosis (Child-Pugh class B and C) and this deficiency should be corrected well in time for improvement of prognosis in patients having hepatic cirrhosis.

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Key Words: Vitamin D deficiency; Liver Cirrhosis; Liver Disease Vitamin D levels should be routinely checked in patients with advanced liver cirrhosis (Child-Pugh class B and C) and this deficiency must be addressed in a timely manner to improve general well-being of cirrhotic patients.

Introduction:

Liver cirrhosis has become a chief community health problem across the whole world, data from a number of countries report it as 4th leading cause of mortality[1]. According to an estimate liver cirrhosis is responsible for a million deaths in a single year.[2] A number of researches provide evidence that hepatitis C virus is the most common reason of liver malignancy across different geographic regions of the world. Some other sources that are related to onset of liver cirrhosis include hepatitis B virus, nonalcoholic fatty liver disease, alcohol, cholestatic disorders, and autoimmune disorders.[1,3] One of the commonly used scoring system for estimation of one-year life expectancy in patients of liver cirrhosis is Child-Pugh (CP) score. It was at first developed by

Child and Turcotte and afterwards changed by Pugh et al.,[4] CP score comprises of 5 components (hepatic encephalopathy, prothrombin time (PT), ascites, serum bilirubin and serum albumin) on the basis of which patient is put into one of three stages i.e. initial, middle and progressive stages of liver cirrhosis. Liver cirrhosis is associated with development of a number of complications some of which are varices of esophagus, collection of fluid in abdominal cavity, portal hypertension, altered state of consciousness and hepatocellular carcinoma.[5] One of less commonly known complication of cirrhosis is scarcity of Vitamin D. Among patients of cirrhosis the association concerning serum calcium, phosphate, parathyroid hormone and quantity of vitamin D is affected in a way that it results in vitamin D deficiency. These bony expressions in patients affected by disease of liver are labeled as hepatic osteodystrophy. Hepatic osteodystrophy is associated with increased susceptibility to fractures in patients with liver disease, increasing their morbidity.[6,7]

Vitamin D is essential for normal functioning and good health of both muscles and bones in our body. Moreover, vitamin D has got many roles outside skeleton. A number of long-standing diseases e.g. diabetes mellitus, persistent infections and cancers (breast, prostate and colon), has less chances of development when body has sufficient levels of vitamin as these cells (hepatocytes, macrophages, immune B and T cells) manifest vitamin D receptors on their surface.[8,9,10,11]

It is observed that patients having long-standing liver diseases have low levels of vitamin D. Approximately 30% of patients suffering from cirrhosis are having inadequate stores of vitamin D. Studies are being done to unrevealed role of vitamin D outside skeletal system.[12,13,14,15] Reduced levels of vitamin D in prolonged liver disease is known to be related to increased chance of bacterial infections, problems due to portal hypertension, severe liver cirrhosis and poor prognosis. As it is evident that vitamin D deficiency is associated with liver disease, it is important to find its relation with severe CLD.[16,17] The chief aim of the research was to find prevalence of decreased levels of Vitamin D in CLD patients, and determination of its association with Child-Pugh grading of liver cirrhosis.

Methods:

A cross-sectional study was conducted in Mayo Hospital Lahore, Pakistan during period of 1st July 2019 to 31st August 2019. Patients were diagnosed to have CLD if having anyone, or more, of the following characteristics: abnormal liver function tests in patients already diagnosed with CLD (for more than one year); ultra-sonographic features suggesting CLD (nodule formation in liver, coarse liver texture, heterogeneous appearance of liver and increased growth or loss of some segment of liver)[14]; liver biopsy showing parenchymal changes; medical record giving clue of CLD (patient giving history or having written record of one or more hospital admissions due to altered state of consciousness, ascites (abdominal fluid collection), blood in vomiting or black tarry stools.

125 patients who satisfied above mentioned features were recruited in the study. Patients were excluded from the research if they were taking drugs that can interfere with vitamin D levels e.g. vitamin A, calcium and vitamin D supplements, steroids, antiepileptic drugs and bisphosphonates, etc. or if they were having an ailment that can result in deranged calcium and vitamin D metabolism, like renal failure, disorders causing mal-absorption and tuberculosis.

Ethical permission was obtained by the ethical committee of hospital before carrying out the research. Detailed characteristics of participants were recorded. A complete history was taken and detailed physical examination was done. Venous blood samples were drawn and complete blood analysis was conducted, for evaluation of serum bilirubin level, serum albumin, the international normalization ratio (INR) and 25-hydroxyvitamin D. Vitamin D of less than 10ng/ml were labeled as severe deficiency and 10-20 ng/ml were regarded as insufficient levels of vitamin D. Detection of hepatitis C and B was also conducted to determine reason of CLD.

Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences) version 25. Qualitative variables were expressed as absolute number and percentage. Quantitative variables were expressed in terms of mean and standard deviation. Chi-square is applied to evaluate association between Vitamin D deficiency and grade or severity of liver

disease. A p value < 0.05 was considered statistically significant.

Results:

Of these 125 patients, 62 patients were male and remaining 38 were females. The lowest age recorded was 22 years, highest was 78 years, and the mean age of participants was recorded as 52.66 years. The subsequent source of cirrhosis was reported as hepatitis B and 09 (7.2%) patients were affected by it; the remaining 5 (4.0%) patients had no identifiable reason of CLD.

Patients were characterized on the basis of CP grade for evaluation of the level of abnormality of liver. Amongst the 125 patients, 108(88.6%) were known cases of hepatitis C virus infection. Among the 125 patients, 45(36.0%) were having highly progressed liver disease and according to CP class scoring were falling in category C, 20 (16.3%) were present in CP class A, representing initial stage of liver disease, and 60 (47.7%) were graded as CP class B, demonstrating the middle level of cirrhosis. The distribution of certain reference variables of the research population is represented in Table 1.

Table 1: *Distribution of variables among the 125 patients with chronic liver disease*

Variables	n	Maximum	Minimum	Mean	S.D
Hemoglobin mg/dl	125	14.6	6.4	8.44	2.55
WCCx10^9	125	18.80	2.2	7.24	3.54
Platelets x10^9 /L	125	355	18.34	86.67	67.94
Bilirubin mg/dl	125	32.03	0.34	2.44	2.67
ALT, U/L	125	329	18.90	53.22	39.32
ALP,U/L	125	554	98.65	227.6	84.76
INR	125	2.84	1.00	1.54	0.54
Albumin	125	4.32	2.12	3.67	0.56
CP score	125	13.00	4.00	7.29	3.01

The outcomes of the research concluded that majority of patients affected by cirrhosis of liver had low or near to low levels of vitamin D. Most of the patients with cirrhosis of liver (n = 82) were found to have deficient levels of vitamin D. 29(23.2) patients were having inadequate quantity of Vitamin D. Normal or adequate vitamin D levels were reported in no more than 14 (11.2%) patients affected by liver malignancy.

The study concluded that levels of vitamin D were having strong association with CP scale of liver cirrhosis. Majority of patients having CP class C were found to be scarce in levels of vitamin D. On contrary the participants with A class of CP scale had normal or adequate quantity of Vitamin D. The results of the research showed that level of vitamin D in cirrhotic patients have high correlation with CP categorization. p-value is assessed both by contingency coefficient and Chi-square and is 0.001 which indicates that high or C-class of CP score is significantly associated with deficiency of Vitamin D Table 2.

Table 2: *Relationship of vitamin D levels with CP class of cirrhosis of the liver*

Vitamin-D Level	CP Class			
	A	B	C	p-value
Deficient	0(0)	38(30.4%)	45(36.0%)	0.001
Inadequate	6(4.8%)	22(17.6%)	0(0%)	
Sufficient	14(11.2%)	0(0%)	0(0%)	

Discussion:

The objective of this study was to report or provide clue of decreased quantity of vitamin D in patients of CLD. Though the reason of scarcity of vitamin D in cirrhotic patients is due to a combination of various factors, the chief process involved in production of vitamin D scarcity in cirrhotic patients is the stoppage of hydroxylation of vitamin D. Mean quantity of vitamin D was reported to be 21.96 ng/mL ng/mL in patients of CLD, showing that most patients suffering from CLD had inadequate reserves of vitamin D. Sufficient or normal vitamin D stocks (30 ng/mL) were present only in 12% of cirrhotic patients.

This is because of the reason that reduced levels of vitamin D are reported in normal non -diseased community of a number of geographic regions of the world. A research done by Kiani et al.[22] reported that 83% of patients reporting in the OPD of various ailments had reduced values of vitamin D, having average value of 13 ng/dL. Another research done by Mehboobali et al.[18] including 858 participants reported that 55% of normal non-diseased adult population in developing world is suffering from deficiency of vitamin D. The reasons of vitamin D scarcity among these communities is due to a number of factors, such as nutritional, ecological and hereditary reasons[22,23]. The point to be pondered is that if vitamin D is deficient in such a high proportion (55%) of population then how the importance of liver cirrhosis in causing further deficiency of Vitamin D can be evaluated. This question needs to be addressed. The main objective of the research was to evaluate the relationship of quantity of vitamin D with CP grading of liver cirrhosis.

The results of the study concluded that as the liver disease progresses the levels of Vitamin D become more. This is almost same to the conclusion of a number of researches which show that CP grading and Vitamin D levels have got an inverse relationship in CLD. Two other researches done by Fernandez et al. and Zhao et al.[19,20] also gave the same conclusion i.e. the levels of Vitamin D continue to decrease as the CLD progresses. Hence the patients falling in upper category of CP grading have remarkably lower levels of vitamin D levels. Further forecasters of low vitamin D levels were also considered as the lesser objective of our research. Female gender and advancing age of participants were reported to have relation to low levels of vitamin D, along with high grading of CP class.

Junaid et al.[24] done a study to determine major causes of scarcity of vitamin D in a normal adult healthy population and reported that lower level of knowledge about diet supplements regarding, reduced sun exposure (< 30m) and inadequate usage of calcium and vitamin D supplements in routine life are the major causes of vitamin D deficiency. Being female, low socioeconomic position, living in a city, smoking and polymorphisms in the sequences programming vitamin D mandatory proteins are other threats, which play a role in reduced levels of vitamin D in normal healthy adult populations.

Our study showed inverse relation between vitamin D levels and age CP scores. This means that with advancement in age and CP grading, the values of Vitamin D continues to decrease. The above mentioned results are almost same to the conclusions of research done by Kumar et al.,[21]. He also reported inverse relationship between low levels of vitamin d and age and CP grading. However he was not successful in finding cause of association of liver disease with deficiency of Vitamin D. Similarly we were also unable to determine cause of liver cirrhosis contributing in development of reduced levels of Vitamin D. Some of the causes playing role in causing deficiency of Vitamin D can be uncompensated liver disease at early stage and increased death rates[25].

Conclusion:

A number of studies have reported that sufficient substitution of vitamin D by using vitamin D supplements can lead to enhance disease status of patient, outcome, CP grading, and general illness of patients with CLD. Hence, it is suggested that this insufficiency should be focused in a prompt manner so that patients with CLD can get benefit and prognosis can be improved and morbidity can be lessened.

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