

Variation Of Hepatic Enzymes With Vitamin B12 And D3 Levels In Cirrhotic Patients

ORIGINAL

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Abstract

Objective: To determine variation of hepatic enzymes Vitamin B12 and D3 levels in cirrhotic patients.

Design: Cross sectional study.

Setting: Cirrhotic patients in Abbasi Shaheed Hospital..

Participants: 250 patients in Abbasi Shaheed Hospital with diagnosis of cirrhosis including 141 males and 109 females.

Variable parameters: They include mean ALT, GGT, Alkaline phosphatase levels along with Vitamin B12 and D3 levels in blood.

Results: Vitamin B12 levels were 1249.59 ± 487.01 pg/ml and 1422.28 ± 627.75 pg/ml in males and females respectively while Vitamin D3 levels were found to be 17.15 ± 10.45 nmol/L in males and 14.80 ± 14.24 nmol/L in females. Vitamin B12 levels were found to be positively correlated with the elevation of ALT and were negatively correlated with elevation of ALT, GGT and Alkaline Phosphatase. The ALT levels were 50.0 ± 21.88 in males and 14.80 ± 14.24 in females, Alkaline phosphatase to be 311.46 ± 107.98 in males while female Alkaline phosphatase were 346.47 ± 101.60 . GGT levels to be 41.70 ± 10.62 in males and 45.01 ± 13.74 in females.

Conclusion: Cirrhotic patients suffering from severe hepatocellular damage have their elevated levels of Vitamin B12 and depressed Vitamin D3 levels in plasma accompanied by a positive association with elevated ALT and GGT plasma levels

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Keywords

Cirrhosis, Vitamin B12, Vitamin D3, ALT, GGT, Alkaline phosphatase

Introduction

Vitamin D maintains calcium homeostasis by interacting with the VDR in osteoblasts. It induces the expression of plasma membrane protein receptor activator of NF- κ B ligand (RANKL). The RANK on the plasma membrane of pre-osteoclasts binds RANKL, which induces the pre-osteoclasts to convert into the mature osteoclast [1, 2, 3]. The mature osteoclasts are responsible for the release of hydrochloric acid and collagenases that dissolve bones and results into the releases of calcium and phosphorus into the blood circulation. Deficiency of Vitamin D is associated with the increased risk of colon, breast and prostate cancer [4], cardiovascular infections [5, 6] and autoimmune diseases. 25(OH)₂D is used to measure the level of Vitamin D in the circulation. It has a half-life of 2 weeks, and it correlates with secondary hyperparathyroidism, rickets, and osteomalacia [7]. Vitamin D deficient individuals develop abnormalities in glucose metabolism such as type 2 diabetes and hypertension, abdominal obesity, hyperlipidemia, and insulin intolerance. [8, 9] There is a strong association of vitamin D3 levels and the presence of liver disease. Vitamin D3 increases the expression of vitamin D receptor (VDR) and inhibits the viral replication in cell culture [10]. It is also thought to increase the immunity by showing antimicrobial effects in both acute and chronic illness [11, 12]. In chronic liver disease, vitamin D is not converted into its active form, resulting in hypovitaminosis. Research showed that almost 2/3rd of the patients with chronic viral hepatitis had abnormal levels of vitamin D while 1/3rd had some deficiency.

Vitamin B12 is a water soluble vitamin necessary for normal neurological function and formation of Red Blood Cells. A deficiency can cause neuronal demyelination and axonal degeneration, and if left untreated will eventually result in neuronal death. Therefore, early diagnosis and timely treatment are imperative. [13]

Cirrhosis is defined as the histological development of regenerative nodules surrounded by

fibrous bands in response to chronic liver injury, leading to portal hypertension and End Stage Liver Disease (ESLD). [14] Two of the main causes of hepatic fibrosis are viral hepatitis and alcohol abuse. [15] Globally, Hepatitis B virus is the major risk factor for the development of hepatocellular Carcinoma (HCC), Cirrhosis, and decompensated liver disease. [16] Also, Chronic HCV infection is accompanied by variable degrees of hepatic inflammation, damage to the liver and progressive fibrosis with an increased risk of progression towards Cirrhosis and HCC. [17] It is also seen that Alcohol accounts for 80% of all liver cirrhosis cases in district general hospitals in the UK. [18] Most of the cirrhotic patients die of liver-related causes, which may include acute bleeding and infections. [19] A study conducted at Alençon Hospital showed that 22% of deaths in Cirrhotic patients resulted from HCC, 12% from gastric bleeding and Liver Failure in 21% of cases. In 31% of patients, the cause was unrelated to cirrhosis, and in 13% the cause was unknown. [20] Cirrhosis is the leading cause of death in Asia and it ranks as the tenth most common cause of death in US, [21] whereas worldwide, it is the 12th most common cause. [22] According to W.H.O, the disease accounts for 1.8% of all deaths in Europe, causing around 170,000 deaths per year. [23] Medical treatments that may slow down the progression of compensated cirrhosis to decompensated cirrhosis are currently being developed. [24] Liver Transplantation, however, is the only option in a selected subgroup of patients with ESLD and HCC. [24]

Materials and methods

This is a cross sectional study conducted in Abbasi Shaheed Hospital from November 2013 to May 2014. The sample size of the study is 250. 141 patients were male while 109 were female patients. Those who were diagnosed of Cirrhosis and previously infected with Hepatitis B and C virus were

included while patients taking vitamin supplements especially Vitamin B and Vitamin D complex were excluded. Diagnosis of the disease was based on clinical signs, laboratory abnormalities and ultrasound findings. The analytical parameters determined were Vitamin B12, D3, ALT and GGT levels in blood. SPSS 19 was used for statistical analysis.

Figure 1: Number of patients with hepatitis B & C.

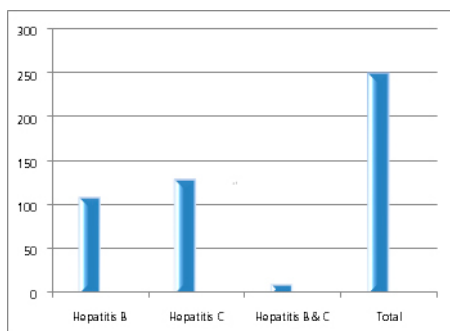


Figure 2: Number of male patients with hepatitis.

Male Patients

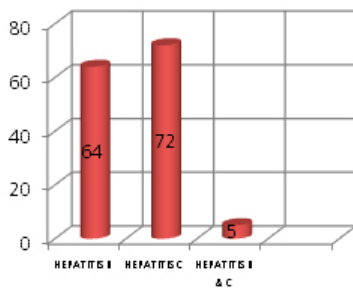
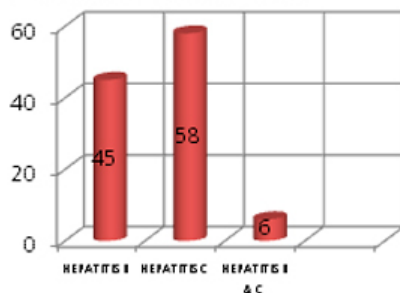


Figure 3: Number of female patients with hepatitis.

Female Patients



Results

The value of R^2 is 0.334 which means that the model explains 33.4% variation of the dependent variable. The P Value of F statistic is <0.001 which means that the regression model is a good fit of the data. 1 unit increase in ALT leads to 10.83 units increase in Vitamin B12 level, while 1 unit increase in GGT leads to 18.80 units increase in Vitamin B12 level, and 1 unit increase in Alkaline phosphatase leads to 15.02 units increase in Vitamin B12 level. The p value of ALT, GGT and Alkaline Phosphatase is less than alpha which means that their coefficients are statistically significantly different from 0.

The value of R^2 is 0.37 which means that the model explains 37% variation of the dependent variable. The P Value of F statistic is <0.001 which means that the regression model is a good fit of the data. 1 unit increase in GGT leads to 0.043 unit decrease in Vitamin D3 level while 1 unit increase in ALKALINE PHOSPHATASE leads to 0.043 unit decrease in Vitamin D3 level and 1 unit increase in ALT leads to 0.42 unit decrease in Vitamin D3 level.

The p value of both Alkaline Phosphatase and ALT is less than alpha which means that their coefficients are statistically significantly different from 0.

Table 1. Mean values of variables.

	Males (mean value±s.d)	Females (mean value±s.d)
Vitamin b12	1249.59±487.01	1422.28±627.75
Vitamin d3	17.15±10.45	14.80±14.24
Alt	50.0±21.88	50.96±11.20
Gamma gt	41.70±10.62	45.01±13.74
Alkaline phosphatase	311.46±107.98	346.47±101.60

Table 2. Regression analysis of vitamin b12 with other variables.

Model	R	R Square	Adjusted R Square
1	0.578	0.334	0.313
ANOVA			
Model	df	F	Sig.
1	3	16.02	0.0001
Coefficients			
Model	Unstandardized Coefficients	Standardized Coefficients	Sig.
	b	Beta	
SGPT ALT	10.83	0.236	0.007
Gamma GT	18.802	0.48	0.0001
Alkaline Phosphatase	15.02	0.43	0.003

Table 3. Regression analysis of vitamin d3 with other variables.

Model	R	R Square try to explain more	Adjusted R Square try to explain more
1	0.60	0.37	0.35
ANOVA			
Model	Df	F	Sig.
1	3	28.58	0.0001
Coefficients			
Model	Unstandardized Coefficients	Standardized Coefficients	Sig.
	B	Beta	
GGT	-0.043	0.053	0.471
Alkaline Phosphatase	-0.043	0.334	0.0001
ALT	-0.42	0.35	0.0001

Discussion

Around 170 million people worldwide have chronic hepatitis C (CHC) infection [25] causing a substantial burden of chronic liver disease globally [26]. The majority of subjects with CHC are vitamin D deficient (<50 nmol/L) [27] with 25% having severe deficiency (<25 nmol/L) [28]. In those with chronic liver disease the prevalence of vitamin D insufficiency (<75 nmol/L) is almost universal, with vitamin D deficiency (<50 nmol/L) present in around two-thirds of subjects [29]. Various studies suggest that vitamin D effects may play a significant role in the pathogene-

sis of chronic liver diseases. [30] Even in the absence of cirrhosis, vitamin D deficiency is present in the majority of subjects. In those with cirrhosis, the prevalence of severe vitamin D deficiency (<25 nmol/L) increases with increasing severity of synthetic liver dysfunction [31, 32]. Another study also showed that vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C. [33] Research showed that vitamin D supplementation during antiviral treatment of recurrent HCV patients result in frequent sustained viral response compared to those who were not supplemented.[34]. Harald

[35] in his study demonstrates the inverse relationship between serum 25 OH vitamin D level and HBV viral load rendering increased viral replication to be responsible for decreased 25 OH vitamin D levels. [36] A study by Davide that included only patients with chronic hepatitis C, the occurrence of vitamin D deficiency (≤ 20 ng/mL) was observed in Alkaline Phosphatase approximately one-half of the patients and severe vitamin D deficiency (≤ 10 ng/mL) in Alkaline Phosphatase approximately 16% of them. [36] There were limitations to our study, including the cross-sectional design which does not possess any control group which limits the conclusions about directionality; viral load couldn't be performed due to the lack of funds.

Our findings suggest that cirrhotic patients admitted for complications presented with elevated plasma levels of vitamin B12 which were 1249.59 ± 487.01 pg/ml in males and 1422.28 ± 627.75 pg/ml in females. The results also demonstrate a positive association between vitamin B12 and the hepatic enzymes where ALT is 50.0 ± 21.88 pg/ml and 50.96 ± 11.20 pg/ml, and GGT is 41.70 ± 10.62 and 45.01 ± 13.74 pg/ml in males and females respectively. It means that with increasing hepatocellular damage as indicated by elevated hepatic enzymes, serum vitamin B12 also tends to increase. [37] Very frequently it has been reported that cirrhosis leads to elevated vitamin B12 levels in serum. Our findings are in accordance with Hubertus et al, who studied male alcohol dependent patients with hepatocellular damage and found that the serum concentration of vitamin B12 was positively correlated with plasma ALT, AST and GGT. An explanation may lie in the fact that vitamin B12 bound with hepatocytes and storage of transcobalamin is disrupted in liver damage causing vitamin B12 to leak out of the liver into the circulation to produce severe tissue B12 deficits leading to metabolic dysfunction regardless of an elevated plasma total vitamin B12. [37]. Certain other studies also relate plasma vitamin B12 levels to the development of tumors or increased rate of deaths for this

reason. Goel A et al, in one of their study have also regarded vitamin B12 levels as a useful non invasive marker to differentiate non-cirrhotic portal hypertension from cryptogenic cirrhosis. [38] Johan F.B. Arendt et al, in their study have considered elevated vitamin B12 level as a proposal of diagnostic strategy. They unexpectedly got into consideration 8% of patients with high plasma vitamin B12 levels among patients with its deficiency. After summarizing the association between elevated levels and diseases, finally they concluded that after ruling out the risk of cancer, diseases of liver and kidney can be considered responsible for the elevation. [39] Areekul S et al; also found out that serum vitamin B12 levels in patients with infectious hepatitis and cirrhosis were higher than that of the normal subjects. [40] Furthermore, Lambert et al; in 1997, found a positive association of vitamin B12 with ALT only. [41] Our results demonstrate a substantial positive relationship with ALT as well as GGT.

Conclusion

Our results found elevated vitamin B12 levels in patients with liver cirrhosis and their positive affiliation with increased hepatic enzymes while decrease in Vitamin D3 levels associated with cirrhosis.

Abbreviations

ALT: Alanine transaminase.

GGT: Gamma-glutamyl transferase.

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