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POTENTIAL ROLE OF VITAMIN D DEFICIENCY IN NONALCOHOLIC STEATOSIS

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ABSTRACT

Hypovitaminosis D is a wide spread and largely under recognizedpresent day epidemic. Since vitamin D undergoes activation in the liver, hepatic steatosis thought to be caused primarily due to insulin resistance can play a role in vitamin D deficiency. Hence the present study was conducted in 75 adult non diabetic patients in the age group of 25-55(45 males, 30 females) with hepatic steatosis. Liver function tests were estimated in the plasmaspectrophotometrically. Vitamin D was determined by ECLIA. Study groups included vitamin D deficient (group I), insufficient (group II) and sufficient groups (group III). Plasma ALT , ALP and total bilirubin levels were significantly higher in group I and II compared to group III patients. However, AST/ALT ratio was significantly higher groupIII compared to others. Plasma bilirubin and ALT showed significant negative correlation with vitamin D (r=-0.553,p=0.01) and AST/ALT ratio showed a positive correlation. The inverse association of vitamin D and hepatic markers attributes a possible hepatoprotective role of vitamin D. Patients with risk of impaired liver function need to be screened for vitamin D deficiency and its supplementation may prove beneficial.

KEYWORDS: **VitaminD,Steatosis, Liver function tests**

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INTRODUCTION

Non alcoholic steatohepatitis is a common chronic liver disease characterized by predominantly macrovesicular hepatic steatosis occurring in individuals who do not consume alcohol[1].Hypovitaminosis D is a wide spread and largely under recognized present day epidemic[2]. Vitamin D undergoes hepatic 25 hydroxylation rendering liver critical to the metabolic action of this vitamin . In patients with liver failure, the levels of vitamin D can be low due to impaired activation. However, liver function needs to be severely compromised in order for this impairment to occur as in case of parenchymal liver disease [3]. Liver disease could also lead to impaired absorption of vitamin D, possibly due to impaired bile acid production. Vitamin D inadequacy has been reported in diseases like diabetes mellitus and thyroid disorders[4,5]. The primary cause of steatosis is thought to be insulin resistance which causes increased lipolysis and delivery of free fatty acid to liver[6]. On the contrary, since vitamin D is reported to play a role in free fatty acid flux regulation from the periphery to the liver, its deficiency may promote fat deposition into the hepatocytes. Vitamin D receptor has been widely detected in the liver, its expression increases in inflammatory hepatocytes[7]. Therefore, vitamin D may possibly play a role in the progression of metabolic liver damage. Whether serum vitamin D status can affect liver function is poorly understood, hence the aim of the study is to explore the association between hypovitaminosis D and steatohepatitis.

MATERIALS AND METHODS

75 adult non diabetic patients in the age group 25-55 years (45 males, 30 females) with hepatic steatosis diagnosed by upper abdomen ultrasonography were enrolled for the study. Patients with serum ALT and AST >40 IU/L and who were nonalcoholics were considered for the study. Exclusion criteria included patients with diabetes mellitus or presence of secondary causes of fatty liver such as gastro intestinal bypass surgery or those on medications that induce steatosis. The study was approved by the institutional ethics committee and informed consent was collected from all the subjects.Fasting blood sample was collected in heparinized vacutainer, centrifuged at4500g for 5 minutes to obtain plasma. Total cholesterol, total bilirubin, direct bilirubin,total protein, albumin, AST,ALT, ALP were estimated in plasma spectrophotometrically[8]. 1,25 dihydroxycholecalciferol (1,25 DHCC) was determined based on the competitive principle by ECLIA [9]. Vitamin D deficiency was defined as plasma 1,25 DHCC concentration less than 20ng/mL, insufficiency between 21-29ng/mL and sufficiency ≥30ng/ mL. The study population was thus divided into three groups based on vitamin D concentration. Statistical analysis was performed using SPSS software version 20. Intergroup comparison was done by ANOVA and correlations between vitamin D and other variables were tested by Spearman coefficient and p value less than0.05was considered significant.

RESULTS

Mean plasma 1,25 DHCC concentration of all patients was 23.9 ng/mL. There was no significant difference in prevalence of either vitamin D deficiency or insufficiency between the sexes.To explore the probable interaction between vitamin D and other liver function parameters, analysis were performed based on vitamin D tertiles .Mean plasma ALT, ALP significantly increased with decreasing vitamin D levels. AST/ALT ratio increased with increasing vitamin D levels. However, AST did not vary statistically with vitamin D between the groups. Further, direct bilirubin decreased with higher plasma vitamin D . However, intergroup comparison showed no statistically significant changes in other parameters (TableI).Plasma bilirubin and ALT showed significant negative correlation with vitamin D (r=-0.553,p=0.01) and AST/ALT ratio showed positive correlation(r=0.558,p=0.009)(TableII).However, correlations between other liver function markers and the vitamin remained statistically insignificant.

Table I
Comparison of liver function tests between vitamin D tertiles

	Group I (n=25)	Group II (n=25)	Group III (n=25)	P (ANOVA)
Vitamin D (ng / dL)	13.64± 4.03	25.73 ± 2.4	36.58± 9.3	0.001
TotalCholesterol(mg/dL)	174± 96.06	189 ±32.39	260± 30	0.578
Total Bilirubin (mg/dL)	0.87± 0.49**	0.49± 0.15**	0.55± 0.49	0.154
Direct bilirubin (mg/dL)	0.26± 0.11	0.17 ± 0.05	0.12± 0.12	0.023
Total protein (mg/dL)	7.81 ± 1.8	7.46± 0.33	7.45 ± 0.49	0.850
Albumin (mg/dL)	4.82 ± 0.58	4.46± 0.21	4.5 ± 0.1	0.264
Globulin (mg/dL)	2.99 ± 1.84	3 ± 0.37	2.95± 0.49	0.999
AST (IU/L)	42.83± 10.85	41.14 ± 30.41	48 ± 9.89	0.491
ALT (IU/L)	74.71± 22.25	48.25± 23.07*	28.5 ± 21.9*	0.05
AST/ ALT Ratio	0.43± 0.36	0.74 ± 0.36***	2.2 ± 1.34***	0.003
ALP (IU/L)	106 ± 58	68 ± 15*	68 ± 14*	0.05

******p<0.003 , *p<0.05 Statistically significant between Group II & III (Post Hoc test)***
*****p<0.02 statisticallysignificant between group I&II(Post Hoc test)***

Table II
Correlation of liver function test parameters with vitamin D values

	r	p
Total Cholesterol (mg/dL)	0.2	0.476
Total Bilirubin (mg/dL)	-0.411	0.034*
Direct bilirubin (mg/dL)	-0.590	0.006*
Total protein (mg/dL)	-0.085	0.714
Albumin (mg/dL)	-0.182	0.430
Globulin (mg/dL)	-0.019	0.934
AST (IU/L)	0.142	0.539
ALT (IU/L)	-0.553	0.010*
AST/ ALT Ratio	0.558	0.009*
ALP (IU/L)	-0.237	0.300

****statistically significant***

DISCUSSION

The rapid economic development accompanied by a change in life style behaviours like less exposure to sunlight has increased the incidence and prevalence of vitamin D deficiency in India, a country with ample sunshine throughout the year. However, data from epidemiologic studies in India are still limited. Our study shows that more than 65% of the adults with steatohepatitis are in suboptimal vitamin D status. This finding supports the earlier report of prevalence of hypovitaminosis D in NAFLD by Catena et al [10].Vitamin D deficiency has been linked with a predisposition to insulin resistance and diabetes due to its potent immunoregulatory effect . The primary cause of steatosis is thought to be insulin resistance, which increases lipolysis and the delivery of free fatty acids to the liver[6]. Our study showed that having high levels of ALT and AST increased the risk of hypovitaminosis D in steatohepatitis patients. Similar observations were made by Skaby et al[11] who found an inverse relation between vitamin D status and incident of liver disease as well as the severity of the disease[12].On the contrary, vitamin D supplementation did not alter plasma transaminases significantly in one of the earlier studies[13].An inverse correlation between vitamin D and the enzymes ALT, ALP suggest that vitamin D may exert a dose dependent effect on fat accumulation into the hepatocytes[14].The results of the present study also emphasizes on the fact that ratio of AST/ALT correlated better with vitamin D status in steatohepatitis than individual enzymes. Vitamin D mediates its intracellular signals via its receptor(VDR) which is constitutively

expressed in the hepatocytes. VDR expression on hepatocytes of NAFLD subjects decreased[15].but expression of enzymes for hydroxylation of vitamin D was preserved[16], which questions the hypothesis of a decreased hydroxylation capacity of hepatocyte as a cause of NAFLD .Vitamin D receptor (VDR) deletion in cholestasis model of rat showed higher expression of genes involved in bilirubin metabolism. VDR null mice had elevated plasma conjugated bilirubinandurine bilirubin level decreased suggesting impaired excretion of conjugated bilirubin[17].The result of the present study also showed that serum conjugated bilirubin was significantly higher in steatohepatitis patients This fact was supported by elevated levels of ALP. The inverse association of 1,25 DHCC status and steatohepatitis observed in our study is in agreement with the earlier report showing the inverse association of 25hydroxy vitamin $D_3$with hepatic inflammation[16] which attributes a possible hepatoprotective role to vitamin D.

CONCLUSION

Outcome of the study suggests a significant contribution of hypovitaminosis D in the pathogenesis of steatohepatitis. Further studies are needed to determine whether patients in risk of impaired liver function should be screened for vitamin D deficiency . Under such circumstances, supplementation of vitamin D may prove to be beneficial in the prevention of the progression of steatohepatitis to hepatic fibrosis and cirrhosis.

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