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Research Article

A STUDY ON SERUM 1,25 DIHYDROXY VITAMIN D3 LEVELS AND ITS CORRELATION WITH THE SEVERITY IN PATIENTS WITH CIRRHOSIS OF LIVER

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A B S T R A C T

Background: Vitamin D is an important secosteroid hormone with pleiotropic effects. While its role in the regulation of calcium and bone homeostasis is well established, recently there is increasing recognition that Vitamin D has immune modulatory, anti-inflammatory and anti-fibrotic properties and plays an important role in the regulation of cell proliferation and differentiation. Liver is a major organ participating in activation of Vitamin D to 25 (OH) Vitamin D. In cirrhosis synthesis of 25 hydroxy Vitamin D is reduced as consequence the circulating active form 1-25(OH)2 vitamin D3 is reduced. This in turn affects the prognosis of liver disease of any etiology. ***Aim of The Study:*** To study the correlation of severity with serum 1-25(OH)2 Vitamin D3 levels in patients with cirrhosis of liver. ***Methodology:*** To study the correlation of severity with serum 1-25 (OH)2 vitamin D3 levels in patients with cirrhosis of liver. The levels of Serum vitamin D3 levels was assessed by chemiluminescence method. The relations of vitamin D3 deficiency to the severity of liver impairment were determined by Child Turcott Pugh score (CTP) and model for end stage liver disease (MELD) score. ***Results:*** In this study the mean serum Vitamin D levels was 13.46mg/dl. Thirty one (62%) patients had insufficiency (20-30ng/ml) and 19 (38%) had deficiency (<20ng/ml). Thirty eight (76%) patients belonged to child C category, Ten (20%) to child B and 2 (4%) to child A. The mean MELD score was 17.84. ***Conclusion:*** The severity of Vitamin D deficiency correlated with the severity of liver disease as evidenced by the correlation between the child status and MELD scores. The association of vitamin D with liver cirrhosis shows great potential for clinical application. The relation between vitamin D deficiency and the degree of liver function, degree of fibrosis and infectious complications could support its use as a prognostic index and diagnostic tool.

INTRODUCTION

Vitamin D is a fat soluble vitamin that plays an important role in bone metabolism. Vitamin D is an important secosteroid hormone with pleiotropic effects. While its role in the regulation of calcium and bone homeostasis is well established, recently there is increasing recognition that vitamin D has immune-modulating properties, anti-inflammatory and anti-fibrotic properties and plays an important role in the regulation of cell proliferation and differentiation.

Vitamin D is hormone precursor that is present in two forms, ergocalciferol or vitamin D2 is present in plants and some fish, Cholecalciferol or vitamin D3 is synthesized in skin by sunlight[(1)]. Vitamin D insufficiency and deficiency are considered to be common in the general population and more frequent among elderly people and individuals with chronic diseases.

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It has been reported that 1 billion people have inadequate serum levels of 25(OH)D levels [2] .

Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 70%-100% in the general population. In India, widely consumed food items such as dairy products are rarely fortified with vitamin D. Indian socio- religious and cultural practices do not facilitate adequate sun exposure, thereby negating potential benefits of plentiful sunshine. Consequently, subclinical vitamin D deficiency is highly prevalent in both urban and rural settings, and across all socioeconomic and geographic strata **[3].**

Cirrhosis is defined anatomically as a diffuse process characterized by fibrosis and nodule formation in the liver. It is the end result of fibrogenesis that occurs with chronic liver injury **[4]**

Patients with liver diseases are at a particularly high risk of

vitamin D deficiency and it has been documented that low 25 (OH) D concentrations are associated with liver dysfunction and mortality. Decreased 25 (OH) D levels have also been observed in patients with non-alcoholic fatty liver disease (NAFLD), and several epidemiological and experimental studies suggest that vitamin D might be useful for the treatment of liver fibrosis[5].

Vitamin D deficiency has been also associated with advanced stages of hepatocellular carcinoma and poor prognosis. Finally, there are studies suggesting that patients with chronic hepatitis C and normal vitamin D levels have higher virological response to treatment.

In a study by Fisher *et al*, vitamin D deficiency was higher in cirrhotic patients in Child-Pugh class C than in patients in Child-Pugh class A [6].

However, there are not enough studies conducted in cirrhotic only populations. The association between vitamin D and cirrhosis demonstrates a great potential for clinical application. The relation between vitamin D deficiency and the degree of liver function, degree of fibrosis and infectious complications could support its use as a prognostic index and a diagnostic tool.

Aim of the Study

1. To estimate the levels of serum 1-25(OH)2 vitamin D3 in patients with cirrhosis of liver.
2. To assess the relations of vitamin D3 deficiency to the severity of liver impairment as evidenced by Child Turcott Pugh score(CTP) and model for end stage liver disease (MELD) score.

MATERIAL & METHODS

This is a cross sectional study done at Tertiary Care Hospital and includes 50 subjects presenting to medicine OP with cirrhosis of liver and the study was conducted between December 2019 to November 2021.

Collection of data

Method of collection of data is by evaluation, which is be done by taking detailed history, clinical examination and laboratory investigations through proforma specially designed for this study.

Inclusion criteria

1. All cirrhotic patients admitted to Gandhi hospital of age group 17-70 years.

Exclusion criteria

1. Patients with calcium replacement or on diuretics
2. Other systemic diseases interfering with serum vitamin D level human immune deficiency virus (HIV) infection, Sarcoidosis pancreatitis and autoimmune disorders
3. Cirrhosis with hepatocellular carcinoma
4. Chronic hemodialysis

Investigations

Hemoglobin (g/dl); TLC, DLC.(cell/mm^3); Platelets(cell/$mm^{3)}$; hematocrit; Blood urea(mg/dl) and Serum creatinine(mg/dl); Random blood sugar(mg%); Total serum protein(g/l); Serum albumin (g/l); Serum globulin(g/l); 10.Serum bilirubin(mg/dl); SGOT (IU/L); SGPT(IU/L); ALP (IU/L); Calcium (mg/dl); Phosphate (mg/dl); Spo2 (%); Serum vitamin D3 levels(ng/ml); Chest Radiography and Ultrasound abdomen.

Assessment of serum vitamin D3

Three milliliter of blood was drawn in a plain vacutainer and serum was allowed to separate.

Serum vitamin D3 levels was assessed by chemiluminescence method (CIA)[72]. All the samples were sent to the same laboratory for uniformity of the estimation of the vitamin. The laboratory reference values were used to define normal (>30ng/ml), insufficiency (20- 30ng/ml) and deficiency (<20ng/ml).

Vitamin D3 Assessing Machine (Advia Siemens)

Severity of liver failure was estimated by the child-pugh and the MELD scores.

Child Pugh Score

It is used to assess the prognosis of chronic liver disease, mainly cirrhosis.

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Meld Score

MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to the following formula:

- MELD = 3.78*ln[serum bilirubin (mg/dL)] + 11.2*ln[INR] + 9.57*ln[serum creatinine (mg/dL)] + 6.43
- MELD scores are reported as whole numbers, so the result of the equation above is rounded.
- UNOS has made the following modifications to the score:
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0 mg/dL
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8 a value of 1.0 is used) to prevent subtraction from any of the three factors, since the natural logarithm of a positive number below 1 (greater than 0 and less than 1) yields a negative value.

Statistical Analysis

In the present study the data collected is analysised, the

difference between different parameters based on quantitative variables are compared and difference is considered statically significance when p value < 0.05.

Ethical considerations

Institutional ethical clearance will be obtained before the start of the study.

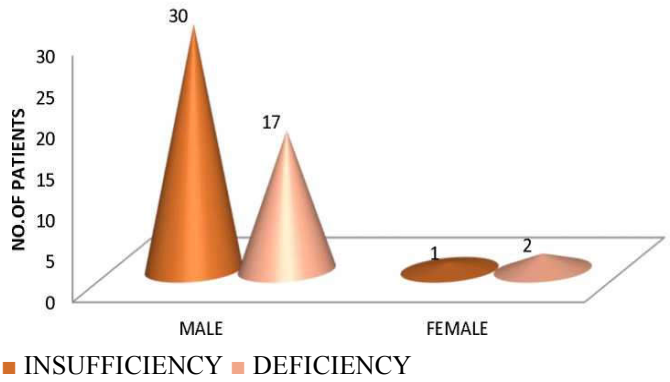
RESULTS

Table 1 Distribution of Various Parameters Among Subjects

Parameter	All Patients (N=50)
Mean age (years)	41.2
Gender (M/F)	47/3 (94%/06%)
Aetiology of cirrhosis	
Alcohol (%)	45 (90%)
Hepatitis (B %)	5 (10%)
CTP score	
A	2 (4%)
B	10 (20%)
C	38 (76%)
Mean albumin (g/L)	2.93g/dl
Mean haemoglobin	10.2g/dl
Ascites (%)	41 (82%)
HRS (%)	10 (20%)
GI bleed (%)	12 (24%)
H. Encephalopathy (%)	32 (64%)

Table 2 Distribution of Various Parameters Based on Serum Vitamin D3 Degree of Deficiency

Parameter	Insufficiency (20-30ng/ml)	Deficiency (<20ng/ml)
Age (mean)	40.77	41.88
Males	30	17
Females	1	2
Hepatitis B	3	2
Alcohol	29	16
Jaundice	1	5
Pedal edema	17	12
Decreased urine output	12	11
GI bleed	7	2
Hepatomegaly	3	5
Ascites	22	19
Hepatic encephalopathy	14	18



Graph 1 Distribution of Serum Vitamin D3 Levels According To Gender

Table 3 Distribution of Degree of Vitamin D Deficiency Based on Various Parameters

Variable / laboratory Parameters	Vitamin D	Mean	Std. Deviation	PValue
Age	insufficiency	40.774	9.3013	0.584
	deficiency	42.421	11.6824	
Duration	insufficiency	13.032	6.2795	0.272
	deficiency	11.211	4.3151	
Haemoglobin	insufficiency	10.455	0.9818	0.743
	deficiency	10.368	0.7402	
total leucocyte count	insufficiency	6687.097	2114.6555	0.294
	deficiency	7289.474	1634.7425	
total serum bilirubin	insufficiency	1.358	0.5233	0.007
	deficiency	2.474	2.1118	
AST	insufficiency	34.065	29.4459	0.806
	deficiency	36.526	40.9422	
ALT	insufficiency	42.097	14.6864	0.216
	deficiency	60.105	78.2126	
AST/ALT	insufficiency	3.832	1.0371	0.602
	deficiency	3.668	1.123	
Alkaline Phosphate	insufficiency	99.484	67.4225	0.707
	deficiency	106.895	67.0836	
Albumin	insufficiency	3.042	0.6505	0.132
	Deficiency	2.758	0.6122	
Serum Creatine	Insufficiency	1.116	0.3725	0.087
	deficiency	1.379	0.6917	
Prothrombin Time	Insufficiency	9.052	4.9779	0.001
	deficiency	18.121	8.6926	
International Normalizedratio	Insufficiency	1.7429	0.40936	0.001
	deficiency	2.4858	0.70889	
Serum Calcium	Insufficiency	7.719	0.4415	0.92
	Deficiency	7.705	0.5338	
Meld	Insufficiency	15.065	4.4865	0.001
	deficiency	22.368	5.4895	

Table 4 Distribution of Degree of Vitamin D Deficiency Based on CTP Score

	CTP score			Total	p-Value
	A	B	C		
Deficiency	0	0	19	19	
Insufficiency	2	10	19	31	0.008
Total	2	10	38	50	

Analysis of the different laboratory parameters in the insufficiency group and deficiency group was done using two tailed student t test.

The P value was highly significant for INR, PT, Serum bilrubin and not significant for Hb, TLC, Serum Albumin, Serum Creatinine and Serum Calcium

DISCUSSION

We studied total number of 50 patients. Forty seven (94%) were males and (6%) were females. The predominant etiology was alcohol in 45 (90%) patients and the rest 5 (10%) were suffering from hepatitis B. Hepatitis C was not present in any of our patients.

The presenting symptoms included abdominal distension in 38 (76%) patients. Pedal edema was present in 29 (58%), pain abdomen in 28 (56%), fever in 25 (50%). Twenty three (46%) complained of decreased urine output.

The predominant finding was ascites in 41 (82%) patients followed by hepatic encephalopathy in 32 (64%) patients. Hepatomegaly was found in 8 (16%) patients.

Most of our patients had anemia and the mean Hb value was 10.2g/dl. Platelets were reduced in 35 (70%) patients. The mean serum bilirubin was 2.21mg/dl, mean albumin was 2.93g/l. Coagulopathy was present in many patients with a mean INR of 2. Thirty eight (76%) patients belonged to child

C category. Ten (20%) to child B and 2 (4%) to child A. This indicates that most of our patients are decompensated.

The mean MELD score was 17.84 in our study population.
The mean serum vitamin D levels was 19.58 mg/dl. Thirty one (62%) patients had insufficiency (20-30ng/ml) and 19 (38%) had deficiency (<20ng/ml).

As all our patients fell in the category of insufficiency we have compared the insufficiency group with the deficiency group.

Significant difference was for only serum bilirubin, INR value, MELD score and CTP score in these sub groups. There was no significant difference with respect to haemoglobin, total count, serum albumin and serum calcium.

Bankuti *et al*[7] reported a significant association of serum vitamin D3 with the degree of liver dysfunction, found that serum vitamin D3 levels were inversely correlated with MELD score and Child-Pugh score.

Anty R *et al* [8] conducted in a cohort of hospitalized cirrhotics of various etiologies. Almost 60% of the patients had severe vitamin D deficiency (<10nmol/l) The authors found an inverse correlation of 25(OH)D levels with the Child-Pugh score.

A similar study conducted by Buonomo *et al*[9] evaluated the prevalence of vitamin D deficiency in liver cirrhosis. Vitamin D deficiency rates were higher in patients with decompensated cirrhosis (Child-Pugh B vs A, p = 0.008, and Child-Pugh C vs A, p = 0.024).

Fisher *et al* [10] conducted a similar study to determine the prevalence and type of vitamin D-parathyroid hormone (PTH) disturbance in non cholestatic chronic liver disease (CLD) patients and its relationship with disease severity and liver function. The study included 100 patients. The prevalence of vitamin D deficiency was significantly higher in cirrhotic vs non cirrhotic patients (86.3% vs 49.0%;*P* = .0001).

Joe George *et al* [11] conducted similar study on 72 Indian patients with cirrhosis (63 male, 9 female; aged < 50 years). Etiology of cirrhosis was alcoholism (n = 37), hepatitis B (n = 25) and hepatitis C (n = 10). Twenty-three patients belonged to Child class A, while 39 were in class B and 10 in class C.

Table-5 Comparision of Our Study with Other Studies Based on Mean Age of Subjects

Studies	Total cases (n)	Age in years Mean ± SD
Our study	50	41.2±10.11
Fisher L *et al* (2007)	100	49.0±12.11
Putz - Bankuti C *et al*[12] (2012)	75	58±11
Crawford *et al* [13]	113	50.3±0.9
Miroliaee A *et al* [14]	90	40.98±9.29
Rhode *et al*[15]	158	54±15.6
Petta *et al*[16]	197	52±12
Arteh J *et al*[17]	118	53±9

Table 6 Comparision of Our Study with Other Studies Based on Sex Distribution

Studies	Total cases (n)	Males
Our study	50	47 (96%)
Fisher L *et al* (2007)	100	63 (63%)
Putz-Bankuti C *et al* (2012)	75	51 (68%)
Crawford *et al*	113	72%
Miroliaee A *et al*	90	60%
Rhode *et al*	158	52%
Arteh J *et al*	118	50%

Table 7 Comparision of Our Study with Other Studies Based on Alcohol as Etiology of Cirrhosis

Studies	Alcohol etiology	Percentage
Our study	45	90%
Fisher L *et al* (2007)	40	40%
Putz-Bankuti C *et al* (2012)	46	61%
Jeo George *et al*	37	51%
Rode *et al*	34	22%

Comparison of Viral Other Etiologies among Patients

In our study the etiology of cirrhosis of liver in vitamin D deficiency patients is 10% viral etiology compared to the study of Fisher L *et al*, where viral etiology in 50% and other etiologies in 10%. In Putz-Bankuti C *et al* study other etiologies in 39%

Table 8 Comparision of Our Study with Other Studies Based On Other Etiologies among Patients

Studies	Viral etiology	Other etiology
Our study	10%	NA
Fisher L *et al* (2007)	50%	10%
Putz-Bankuti C *et al* (2012)	NA	39%
Jeo George *et al* (2010)	35%	50%
Rode *et al*	37%	41%

Various Studies

In our study we used the laboratory reference values to define insufficiency (20- 30mg/dl) and deficiency (<20mg/dl). All our patients had low level of vitamin D levels.

In a similar study conducted by Fisher L *et al* they found the prevalence to be 83%. An Indian study conducted by Joe George *et al* from Mumbai was similar to our patient population with respect to age gender and etiology. The prevalence of low vitamin D in their study was 92%.

In our study we had patients predominately of child C status (76%) followed by child B (10%) and child A (2%). The vitamin D levels correlated with the child status with more severe deficiency found in child C patients.

This was in concordant with the other studies conducted by Fisher L *et al* In Child Pugh class C patients, serum vitamin D3 levels were significantly lower than in class A patients (22.7 ± 10.0 nmol/L vs 45.8 ± 16.8 nmol/L; *P* < .001). He finally concluded that Vitamin D inadequacy is common in non-cholestatic CLD and correlates with disease severity.

The study done by Putz-Bankuti C *et al* also found an inverse correlation of the serum vitamin D levels with the severity of cirrhosis.

Miroliaea, A *et al* also reported an inverse correlation of serum vitamin D levels with the child status of the patient.

Venu M *et al*[18] did not find any correlation between the child status and the serum vitamin D levels in a multivariate analysis.

Chen C *et al*[19] also observed an inverse correlation between the severity of cirrhosis with the serum vitamin D levels.

Comparison of Vitamin D Defeciency with the Meld Score

In our study there was an inverse correlation between the MELD score and the serum vitamin D levels.

Putz-Bankuti C *et al* also found an inverse correlation of MELD score with the serum vitamin D levels

Levels

In our study we found no significant association between the serum calcium levels and the serum vitamin D levels.

Miroliaea A *et al* (2010) also reported a non significant association between serum calcium and vitamin D levels.

Comparison of Vitamin D Defeciency with Other Laboratory Parameters

In our subgroups analysis there was a significant association between the serum bilirubin, INR and serum vitamin D levels. The other laboratory parameters like HB TLC, Serum Albumin, Serum creatinine did not show any significance.

In a study conducted by Miroliaea A *et al* they found a significant association between coagulopathy, hyperbilirubinemia, hypoalbuminemia, anemia and thrombocytopenia

CONCLUSION

- Our study suggests that there is a high prevalence of vitamin D deficiency in patients with cirrhosis which is in concordance with the published literature.
- Vitamin D insufficiency was seen in 62% patients where as severe deficiency was seen in 38% of our patients.
- The severity of vitamin D deficiency correlated with the severity of liver disease as evidenced by the correlation between the child status and MELD scores.
- The association of vitamin D with liver cirrhosis shows great potential for clinical application. The relation between vitamin D deficiency and the degree of liver function, degree of fibrosis and infectious complications could support its use as a prognostic index and diagnostic tool.

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