Original Article

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Estimation of Vitamin D Level in Patients of Chronic Liver Disease and its Association with Child Turcotte Pugh's Score

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Abstract

Background: Chronic liver disease (CLD) has a fairly high occurrence in the Indian subcontinent due to variety of etiological factors including alcohol abuse, viral hepatitis, etc. As liver plays a crucial role in digestive as well as metabolic functions, its significant dysfunction is related to severe imbalance of vitamin D. Though for long the role of vitamin D in bone mineral metabolism is known yet recent literature has suggested its significant role in immune modulation, inflammatory response and in fibrosis. Since insufficient data on vitamin D levels in CLD patients exists in Indian population, hence we planned this study. **Subjects and Methods:** Hundred patients of CLD were included in our study following approval from institutional ethics committee, obtaining informed written consent and excluding bone disease, chronic renal disease, known cardiac disease & known malignancy. All patients underwent estimation of vitamin D levels and appropriate tests to diagnose CLD with further categorization into A, B, C as per Child-Turcot-Pugh (CP) Criteria. Appropriate statistical tests were then applied to find out the association between CLD and vitamin D levels. **Results:** Majority of the CLD patients were males and in 3^{rd}-5^{th} decade with most of them i.e. 89% in our study, had insufficiency or deficiency of vitamin D in their serum with majority having moderate to severe grades of CLD as per CP score. This association was statistically significant with p value of less than <0.01. Also, a negative Pearson correlation was observed meaning thereby that as the CP score increases, the vitamin D levels decrease. **Conclusion:** Since vitamin D plays a key role in immune based responses, its serum level is crucial in patients suffering with chronic liver diseases, where the serum vitamin D levels decrease as the Child-Turcot-Pugh score of liver disease increases. Early recognition of insufficient or deficient levels of serum vitamin D by their simple & inexpensive serum estimation may go a long way in not only instituting early therapy but also in preventing related morbidities.

Keywords: Vitamin D, Chronic Liver Disease, Child Turcotte Pugh's Score.

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Introduction

Chronic Liver Disease(CLD) is described as a process involving prolonged destruction which is progressive and regeneration of liver, developing eventually to cirrhosis.[1] CLD accounts as a greatest contributor to mortality and morbidity across the globe, accounting for about 2% of all casualities in European nations (1,70,000 anuually) with the rates further escalating in various countries.[2] Literature of recent origin done on a cohort which was multiethnic at USA has demonstrated Non – alcoholic fatty liver disease (NAFLD) constitutes predominant usual etiology of CLD among cultural categories cumulatively (fifty two percent), subsequently due to alcoholic hepatic disease.[3]

Additional etiological reasons for CLD include Hepatitis C of chronic origin, chronic Hepatitis B and various liver disease due to autoimmunity.[4,5] A literature finding of a study done in Rajasthan's western region, CLD due to alcohol remained as predominant usual cause.[6]

Hepatic diseases are among the top ten killer diseases in India.[7] According to the WHO data published in May 2017, death due to liver diseases in our country has attained the range of 259,749 people or 2.95% of the overall deaths.[8] Alcohol abuse, viral hepatitis, obesity and sedentary lifestyle constitute as the major common susceptibility factors in the emergence of liver dysfunction.[9]

Cases affected with CLD exhibit a protein-calorie malnutrition(PCM).[10] In CLD, range of vit. D is not clear, but as per considered description, both deficient and insufficient levels are observed in a greater section of cases, from a lower limit of 64 % reaching a higher limit of 92 %.[11]

Vitamin D is better described as a hormone than a truer vitamin as sunlight exposure itself accounts to adequate requirement.[12] It is accountable to physiological operations of mineralization of bone and homeostasis of calcium[13] Along with this it is accountable to further processes such as proliferation of cell, cell death, differentiation and inflammatory processes.[14,15] Off late, increased occurrence of 25(OH)D 25-hydroxyvtamin D dearth is reported in cases affected with hepatic disorder and the intensity of 25 (OH) D dearth in cases linked to hepatic dysfunction's severity.[15–18]

Liver disorder coexists along with innate immunity activation and vitamin D range negatively correlates with tolllike receptors (TLRs) expressing in monocytic cells, hinting an negative association of vitamin D range with inflammation of systemic origin.[16]

Recent statistics recommends that vitamin D as a significant modulator of inflammation response and healing of wound. It might regulate the inflammatory response and consequent fibrosis through TNF-a inhibition, playing a key role in regulating immune response and by inhibition of fibrosis development as direct suppression of TGF-b, a multiple functional cytokine which might affect progression of fibrosis.[19–21]

Vitamin D, as in case of kidneys is thought to play anti – fibrotic and anti – inflammatory roles in hepatic system through target gene promoter binding, resulting in negative regulation in production of TNF-a and TGF-b.[22]

Descriptive survey statistics put forth that deficiency of Vitamin D is usually found in cases with severe liver disease.[23] Fisher et al,[24] assessed vitamin D ranges in hundred hepatic pathology cases of which, 51 having cirrhotic exhibits and the rest without it. It also included 38 cases having severe liver disease due to HCV. Occurrence of vitamin D insufficiency is significantly more in cases affected with cirrhosis than without (86.3% vs 49%). Additionally, vitamin D ranges reduced with increment of Child grades; vitamin D ranges found to be predominantly lesser among individuals having Child class C as compared to Class A. But the cross sectional study design limits such study validity. Hence, though a correlation exists vitamin D insufficiency and progressing liver disorder is appreciated, vitamin D insufficiency potentiality poses as a predicting factor for progressive hepatic disorder is not yet extrapolated.

Child-Pugh(CP) grading is employed globally for prediction of 1-year survival rate in cirrhotic affected patients. Described for the first time by Child & Turcotte and then changed by Pugh,[25] the grading utilizes 5 variables (hepatic encephalopathy, prothrombin time(PT),degree of ascites,S.bilirubin and S.albumin) to categorize cases in mild, moderate and severely progressive liver cirrhotic disorders. Esophageal Varices, ascitic conditions, portal htn, hepatic and liver associated malignancy are very widely documented along with clear delineation of liver cirrhosis.[26] Lesser understood and explored liver cirrhotic complication is skeletal manifestation.

AIM

- To evaluate level of Vitamin D among CLD subjects & its association with Child-Turcotte-Pugh's score.

Objectives

- Evaluation of vitamin D level in CLD cases.
- To assess CP score in all CLD patients.
- To determine the level of Vitamin D correlation with CP score.

Subjects and Methods

This observational study was conducted in Teerthanker Mahaveer Medical College and Research Centrefollowing approval of Institutional Ethics Committee on 100 cases of Chronic Liver Disease over a period of one year after obtaining written Informed consent.

Inclusion Criteria

All patient >18 years with clinical/biochemical/ radiological evidence of Chronic Liver Disease were included in this study. Subjectswere categorized as CLD case, with either 1 or >1 of the characteristic features:

- Laboratory analysis suggesting CLD, such as impaired hepatic function test along with risk variables(>3 months);
- USG findings suggestive of CLD
- Clinical records indicating CLD (interventions or previous admissions because of encephalopathy, ascites or variceal bleeding)

Exclusion Criteria

- Patients on Vitamin D supplementation therapy for known underlying bone disease.
- Patients suffering from terminal stage of medical disease like Chronic Kidney Disease, Cardiac Failure.
- All patients with known underlying malignancy.
- Acute Hepatic Failure patients.

The data was collected by a preformed pre-structured interviewer led questionnaire which was pre- tested with alterations made before its usage in the study. The patients were assessed

for demographic information, socio - economic standing, medical history and previous history of consuming medicines and supplements.

Patient blood samples were gathered and submitted for blood investigations including 25(hydroxyl)vitamin D. Hepatitis C serology and hepatitis B serology have both been conducted to assess the etiology of CLD.

Child-Turcotte-Pugh Score

Patient scoring was as per Child-Pugh (CP) classification and categorized into 3 kinds: Grade-A, B and C. 5 parameters were utilized to allot the grades to cases. The parameterswere ascites, hepatic encephalopathy, S.bilirubin (mg/dL), INR and S.albumin (g/dL). Every variable was scored as 1,2 or 3. Lowest score of CP grades was 5 and the highest was 15. The Ascites were graded as mild, moderate or severe by doing a trans abdominal ultrasound (Famio 5 Ultrasound Machine; Abex Medical System, Toshiba, Japan).[25]

Encephalopathic grades were established during assessment. 3 mL of bood was taken in serum bottles, and findings were obtained by utilizing a chemistry analyzer. 3 mL of blood taken in a tube containing 3.2% Na-citrate was employed to establish P T, and findings assessed by usingthe Sysmex CA-500 Coag Analyzer. INR was assessed manually byusing the cases and controls.[25]

Vitamin D.[27]

Blood(2mL) was drawn to assess vitamin D levels. Levels were verified in serum using the Elecsays Analyser (Analyser Cobas_e_411). Vitamin D deficiency was termed as:

- <20 ng/mL as deficient vitamin D
- 21ng/mL to 30ng/mL- insufficient vitamin D and
- >30ng/mL was regarded sufficient vitamin D.

The record of 100 cases with CLD was compiled in structured data collection forms. All the findings and observations were coded at the time of recording.

Data collected was analyzed by using appropriate statistical tests and the significance amount was set at p-value < 0.05. To compare the vitamin D level and CP Score, the Pearson correlation test was used.

Results

Out of 100 subjects in our study, 66 were male and 34 were female

Maximum subjects in our study belonged to the 31-40 years age group (32%) followed by 41-50 years (29%).

In our study, albumin level (2.78) was low among the study subjects. Mean SGOT, SGPT and Alkaline Phosphate was also in higher range i.e. 73.72±67.074, 55.01±52.142 and 151.45±87.688 respectively [Table 1].

HIV was not found in any of the subject. HCV and HBsAg was reactive among 39% and 22% of the subjects respectively [Figure 1].

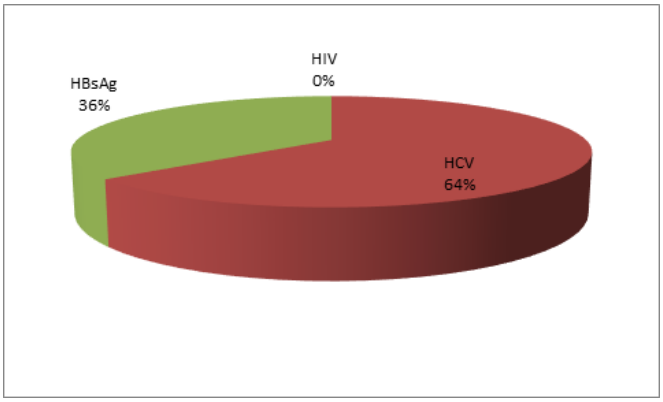

Figure 1: Viral Markers (reactive) among the study subjects

Deficiency of vitamin D (<20 ng/mL), insufficiency of vitamin D (21-30 ng/mL) and sufficiency of vitamin D (>30 ng/mL) Vitamin D was found among 59%, 30% and 11% of the subjects. The average (Mean) vitamin D level was 17.07±8.02 ng/mL [Figure 2].

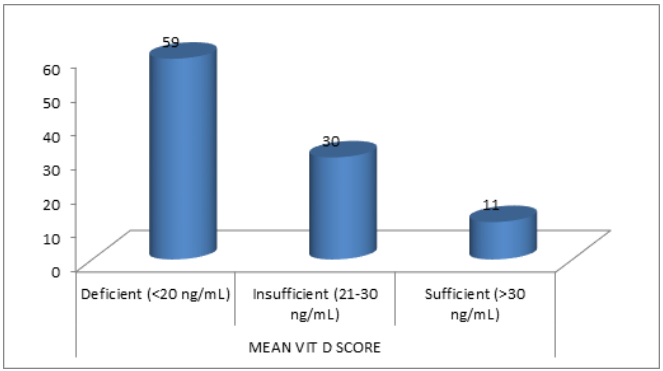

Figure 2: Mean vitamin D score among the study subjects

In our study, according to Child Turcotte Pugh Score, mild, moderate and severe liver disease was found among 8%, 52% and 40% of the subjects respectively. Mean Child Turcotte Pugh Score was 9.51±2.54 [Figure 3].

In our study, among 59 vitamin D deficient subjects, 33 and 26 were having severe and moderate liver disease respectively.

Table 1: LFT profile among the study subjects

LFT Parameters	Maximum	Mean	Std. Deviation
Total Bilirubin	22	2.21	3.118
Direct Bilirubin	16	1.27	2.465
Indirect Bilirubin	6	.84	.961
Total Protein	9	6.32	1.004
Albumin	5	2.78	.746
Globulin	6	3.55	.821
SGOT	506	73.72	67.074
SGPT	364	55.01	52.142
Alkaline Phosphate	560	151.45	87.688

Table 2: Association of Vitamin D and CP score

		Child Pugh Grade			Total
		Mild Liver Disease	Moderate Liver Disease	Severe Liver Disease	
Vitamin D	Deficient	0	26	33	59
	Insufficient	2	21	7	30
	Sufficient	6	5	0	11
	Total	8	52	40	100
Chi Square		47.81			
p-value		<0.01*			

*: statistically significant

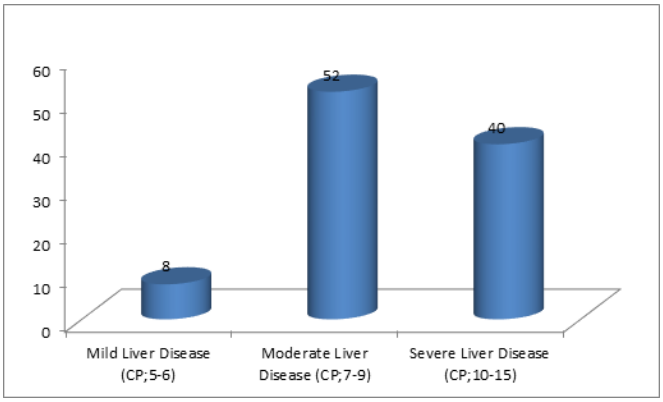

Figure 3: Mean Child Turcotte Pugh Score among the study subjects

Moderate liver disease was found among 21 subjects, out of 30 vitamin D insufficient subjects. Severe liver disease was not reported among any of the subject with sufficient vitamin D. When vitamin D level was associated with severity of liver disease, it was determined to be significant statistically as p-value<0.05 [Table 2].

In our study, significant inverse correlation (r=-0.847, p=<0.01) was revealed among Vitamin D and CP Score i.e. as the CP score increases, vitamin D level decreases.

Discussion

Several studies are available on vitamin D level in CLD patients in western countries but very few studies have been done in India. Further less studies have been done on Vitamin D levels in Chronic Liver Disease in Western region of Uttar Pradesh despite having significant number of CLD patients.

Dominance of male as seen in our study, was also reported by Ravikant Kumar et al in their study.[28] However in a study by Zubia Jamil et al,[29] majority of their individuals were females. This difference might be due to the reason that their study was done in a health care benefitting retired servicemen.

In our study, the average age was 47.62 years. It was similar to a study by Ravikant Kumar et al,[28] where mean agewas 47.98±12.13 years.Mushtaq A. Khan et al,[30] in their study had average age of 48.85±13.6 years while Zubia Jamil et al,[29] had a mean age of 56.86 years.

In our study, deficient(<20 ng/mL), insufficient(21-30 ng/mL) and sufficient(>30 ng/mL) levels of vitamin D was found in

59%, 30% and 11% patients respectively. Average vitamin D level(mean value) was 17.07±8.02 ng/ml in our study.

Arteh et al,[17] recorded same type of Vitamin D deficiency in 92 percent of patients.Mushtaq A. Khan et al,[30] similarly revealed that out of seventy-five CLD patients, Vitamin D deficiency (<20 ng/dl) was found in thirty one (41.4 percent) cases.Zhao et al,[31] in their study on 345 advanced liver disease cases revealed that vitamin D was remarkably reduced in their cases. Yet another literature reported by Fernandez et al,[32] demonstrated that amongst ninety four cirrhotic cases, 87 percent showed deficient numbers of Vitamin D. Kumar et al reported reduced levels of Vitamin D in 80 percent of their patients.[29] All these study results are in concordance with our study findings, wherein vitamin- D is scarce in cases affected with CLD.

When Vitamin D level was associated with liver disease, it was observed to be highly significant as p-value<0.05. In our study, significant inverse correlation (r = -0.847, p = <0.01) was found between Vitamin D and CP Score i.e. as the Child Turcotte Pugh Score increase, vitamin D level decreases. The study findings are in concordance to various miscellaneous literature showing vitamin D levels have negative correlation to the CP gradings and MELD levels. The analysis done by Fernandez et al,[32] and Zhao et al,[31] reported that vitamin D reduces much more with advancing cirrhosis of liver. Hence, cases having greater scores in the categorization of CP score and MELD score shows remarkably lesser Vitamin D levels in contrast to cases with lesser CP and MELD grades.

In a study by Mushtaq A. Khan et al,[30]showed inverse association with CP score (r = -0.7376, P < 0.0001).Zubia Jamil et al,[29] in their study found that levels of vitamin D were highly associated to CP categorization of severity of liver disease. These findings suggested that vitamin D levels in advanced liver disease cases are related with CP categorization (p-value< 0.05). Hence, as CP class progresses, vitamin D levels reduces. These findings were similar to our study.

In a study by Ravikant Kumar et al,[28] the average level of vitamin D reduced with rise in the intensity of hepatic pathology as evaluated by CP score.

Summary

- Chronic liver disease is more common in males with maximum patients in 3^{rd}-5^{th} decade.
- HBV & HCV are the common causes of chronic liver disease.
- Significant no. of cases with vitamin D deficiency have moderate and severe liver disease.
- A significant degree of inverse correlation exists between Vitamin D & CP score i.e. as the CP score increases, Vitamin D level decreases.

Conclusion

Vitamin D deficiency is well recorded in the most of the cases associated with CLD, especially the one with severely progressed pathology. With the disease progression, the levels go towards deficiency. VitaminD levels must be regularly monitored in every case who suffers from CLD, so that required supplementation by vitamin D supplements could be started early as interventional therapy in treating these cases.

Limitation of Study

- Cross-sectional architecture of study
- Lack of control group.
- Small study population.
- A single center study.

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