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Clinical Relevance of Serum Retinol in Patients with Cirrhosis of Liver

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Abstract

Background: Vitamin A has multitude of function and liver plays pivotal role in its metabolism. Diseases of liver of various etiology and severity may affect vitamin A status.

Aims: To determine vitamin A level and clinical manifestation of vitamin A deficiency in patients with cirrhosis of liver and the relationship between severity of cirrhosis of liver with vitamin A status.

Methods: Patients of cirrhosis of liver due to various etiology were evaluated clinically and biochemical test including LFT and serum Retinol level were estimated.

Results: Sixty three percent (95/150) of patients with cirrhosis of liver had vitamin A deficiency while Night blindness was present in only 13/150 (8.67%) patients. Most common etiology of cirrhosis of liver was alcohol (45/150, 30%) and most common presentation was ascites (109/150, 73%). Vitamin A status had no relation to etiology of cirrhosis of liver. Of the patients of CTP-A, 18(41%) had low vitamin A level and none of them had severe deficiency. In CTP-B and CTP-C, 36(62%) and 41 (83%) had vitamin A deficiency respectively. Xerophthalmia in the form of night blindness, conjunctival/corneal xerosis or Bitot's spot was present in 1, 4 and 8 patients in CTP –A, CTP-B and CTP-C respectively.

Conclusion: Vitamin A deficiency is highly prevalent in patients with cirrhosis of liver irrespective of etiology of cirrhosis. The functional indicator in the form of night blindness/ xerophthalmia is not a good indicator of serum retinol status. In view of multitude of function of vitamin A, its estimation and replacement may be considered in case of deficient cirrhotic patients inspite of absence of night blindness.

Keywords: Deficiency; CTP; MELD; Night Blindness; Severity

List of abbreviations: AIH: Autoimmune Hepatitis; CTP: Child Turcotte - Pugh; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; MELD: Model for End Stage Liver Disease; VAD: Vitamin A Deficiency; WHO: World Health Organization

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Vitamin A is fat soluble retinoids that include retinol, retinal and retinyl esters which is essential for vision, growth, reproduction and immunity. Liver plays pivotal role in absorption of vitamin A as its absorption is mediated by bile salt induced micelles formation. In a normal liver, hepatic stellate cells are major storage sites for vitamin A. Hepatic stellate cells following activation lose vitamin A and transformed into myofibroblasts resulting in fibrosis and cirrhosis development through multiple pathways [1]. Intake, diseases of gastrointestinal tract, pancreas and liver can lead to deranged serum vitamin A level and consequently clinical manifestation of vitamin A deficiency. Vitamin A deficiency leads to night blindness and xerophthalmia in the form of Bitot's spots, xerosis, keratomalacia, and even retinopathy [2,3]. Literature is full of data pertaining to vitamin D status in cirrhosis of liver but data related to vitamin A status in non-cholestatic chronic liver diseases and relation between low serum retinol level and clinical manifestation in the form of xerophthalmia are limited and inconclusive. Out of 63 patients of cirrhosis of liver being evaluated for liver transplant, Venu M *et al.* reported vitamin A deficiency in 69.8 percent but none had clinical manifestation of night blindness [4].

Aims

- To determine vitamin A level and clinical manifestation of vitamin A deficiency in patients with cirrhosis of liver and
- To determine the relationship between severity of cirrhosis of liver with serum retinol level

Material and methods

After approval of Institutional Ethics Committee, this observational study was conducted in the department of Gastroenterology and Hepatology, M.L.N. Medical College and Swaroop Rani Nehru Hospital, Allahabad. Patients of cirrhosis of liver diagnosed on

the basis of combination of history, clinical, biochemical, ultrasonographic and upper GI endoscopic finding were include. Base line investigation including liver function test and etiological workup for cirrhosis of liver were done. Patients were also classified according to the Child-Pugh (CTP) classification. This classification is based on scoring system that incorporates ascites, hepatic encephalopathy, serum albumin, serum bilirubin and prothrombin time, which are well-known indicators of prognosis. MELD score was calculated using serum creatinine, bilirubin and International normalized ratio (INR). Informed consent was taken.

Patients with age less than 18 years, celiac disease, pancreatic insufficiency, malabsorbation syndrome, cholestatic liver disease, gastric bypass, vitamin A supplementation in last 6 months were excluded.

Vitamin A status was assessed by clinical and biochemical method. Assessment of night blindness was done by WHO questionnaire [5] i.e. (1) Do you have difficulty in seeing during the day? (2) Do you have difficulty in seeing in decreased light or at night? (3) Do you have night blindness? Night blindness was present if answer is 'no' to question 1 and 'yes' to questions 2 and/or 3.

Serum vitamin A level (retinol level) was measured on venous sample taken after 12 hour of fast. Separation and quantification of the serum retinol was carried out by a validated method for online solid phase Extraction coupled with HPLC-MS (Sigma chemical Company, St Louis, MO, USA). Vitamin A level was classified by WHO as adequate level ≥ 1.05 μmol/l, vitamin A deficiency (VAD) < 1.05 μmol/l [Mild deficiency ≥ 0.70 μmol/l and <1.05 μmol/l, Moderate deficiency ≥ 0.35μmol/l and <0.70μmol/l) and Severe deficiency < 0.35 μmol/l.] [6,7].

Statistical Methods

Univariate analysis to identify whether age, gender, race, body mass index (BMI), severity of liver disease or etiology is associated with vitamin A deficiency. Associations between the categorical variables were performed by chi-square test and continuous variables were analyzed by student's t-test. P value of < 0.05 considered statistically significant.

Results

One hundred fifty patients of cirrhosis of liver with mean age of 47.98 ± 12.13 years were enrolled in study. Table 1 showed clinical and biochemical characteristic of patients with cirrhosis of liver. The most common presentation was abdominal distension

	N=150 (Mean±SD)
Age (years)	47.98 ±12.13
M:F	94:56
Weight (in kg)	54.8±11.78
Height (meter)	1.58±0.08
Hb (gm/dl)	8.7±0.08
TLC (per cc)	6816±2618
Sugar (mg/dl)	91.6±22.5
Urea (mg/dl)	34.2±14.5
Creatinine (mg/dl)	0.95±0.23
Bil (mg/dl)	2.1±1.1
SGPT/ALT (IU/L)	55.4±23.8
SGOT/ AST (IU/L)	79.9±80.4
ALP (IU/l)	226.14±104.6
Protein (gm/dl)	5.13±0.94
Albumin (gm/dl)	2.98±0.5
S. Retinol (μmol/l)	0.57±0.28
MELD	14.42±4.32

Table 1: Baseline Characteristic and Serum Retinol in Cirrhosis of Liver

Symptoms / Signs	Number of patients (%)
Abdominal distension	109(72.67%)
Jaundice	28(18.67%)
Hemetemesis / melena	24(16.0%)
Generalized weakness	21(14.0%)
Hepatic encephalopathy	16 (10.67%)
Night blindness	13(8.67%)
HCC	11(7.33%)

Table 2: Presentation of Cirrhosis of Liver

(ascites) which was present in 109 of 150 (72.67%) patients. Jaundice was the second most common presentation [28(18.67%)]. Gastrointestinal bleed [24(16.0%)], generalized weakness [21(14.0%)] and encephalopathy [16(10.67%)] were other presentation (Table 2). Alcohol was the most common etiology (45, 30%) of cirrhosis of liver in this study. Viral hepatitis [hepatitis B virus (41 pts), HCV (18 pts)], Nonalcoholic fatty liver disease (20), Wilson's disease (7), Autoimmune hepatitis (4) were other etiology of cirrhosis. Fifteen patients had cryptogenic cirrhosis.

The mean serum retinol level in cirrhosis of liver was 0.57 ± 0.28 µmol/l. Vitamin A deficiency defined by vitamin A level less than <1.05µmol/l was found in 95 (63.3%) of patients with cirrhosis of liver. Fifty five (26.7%) cirrhotic had optimal vitamin A level.

Out of 150 patients of cirrhosis of liver, night blindness as diagnosed on the basis of WHO criteria was present in only 13(8.67%) patients. Conjunctival xerosis and Bitot`s spot was present in two patients only. None of the patients had corneal xerosis or scar.

Relation between Severity of Cirrhosis and Vitamin A Status

Out of 150 patients with cirrhosis of liver 43, 58 and 49 patients belonged to CTP-A, CTP-B and CTP-C respectively. Of the patients of CTP-A, 18(41%) had low vitamin A level and none of them had severe deficiency. In CTP-B and CTP-C, 36(62%) and 41(83%) had vitamin A deficiency respectively. There was statistically significant difference in serum retinol level between CTP-A TO CTP-B, CTP-A TO CTP-C and CTP-B TO CTP-C (Table 3). Mean CTP and MELD scores in patient with severe vitamin A deficiency were 11.48 ±1.53 and 18.3 ± 3.68 respectively. There was significant difference in CTP and MELD scores in different categories of vitamin A deficiency. CTP and MELD scores progressively increased as serum vitamin A level decreases (Table 4).

Sr Retinol (µmol/l)	>0.35 and <1.05	<0.35	P-value
CTP-A (43)	18(41%)	0	A-B=0.002
CTP-B (58)	23(40%)	13(22%)	B-C=0.012
CTP-C (49)	14(28%)	27(55%)	A-C =0.0001

Table 3: Relation between Vitamin A Status and Severity of Chronic Liver Disease

S. Retinol (µmol/l)	CTP	MELD
<0.35	11.48±1.53	18.3±3.68
>0.35, <0.70	10.09±1.65	15.12±4.35
>0.70, <1.05	8.88±2.0	13.64±3.57
>1.05	6.82±1.69	10.74±2.33
P value	**<0.05**	**<0.05**

Note: CTP- Child Turcotte- Pugh, MELD- Model For End Stage Liver Disease
Table 4: Relation of Serum Retinol Level with Severity of Cirrhosis of Liver

Discussion

Vitamin A is now widely recognized to have multiple health related functions. Vitamin A and its retinoid derivatives are essential for physiological functions, including vision, cellular proliferation and differentiation and immune system activity. The liver is one of the major organs involved in its metabolism. In present study, 150 patients with liver cirrhosis of various etiologies were evaluated for vitamin A status. Alcohol is the most common etiology of cirrhosis (45,30%) followed by HBV infection in our study. In a study from North India, Kumar R *et al.,* [8] concluded alcohol as the most common etiology for cirrhosis of liver followed by hepatitis B & C. Out of 150 patients, 95 (63%) were deficient in vitamin A and 40 (26%) had severe vitamin A deficiency. Prevalence of vitamin A deficiency was reported to be 54.3% in 140 patients of hepatitis C patients by Peres *et al*., [9]. Paula *et al*., [10] found vitamin A deficiency in 60% of 58 patients of cirrhosis of liver. There were multiple mechanisms for vitamin A deficiency in chronic liver disease. One of them was because of poor nutrition. Low intake of animal sources also contributes to the reduced serum retinol levels observed in CLD patients. Dietary beliefs, taboos and constraints associated with liver disease lead to reduced intake of protein and fat and, consequently, compromise the intake and absorption of preformed vitamin A, as well as other micronutrients [11]. There was also malabsorption of vitamin A and other fat soluble vitamins. There was a reduction in hepatic synthesis of the retinol carrier protein due to dysfunction of the organ or protein–energy malnutrition [12,13]. The conversion of β-carotene to retinol occurring in the liver might be deficient in these patients, contributing to the lowered levels of serum retinol in this group [14].

Mean vitamin A level decreased as the severity of liver disease assessed by CTP and MELD score increased. In CTP-A class, none had severe vitamin A deficiency. According to biochemical indicators, the present results confirm the progressive decrease in serum retinol with the increase severity of liver disease and this finding corroborates prior studies involving CLD patients [15,16].

This progressive drop in serum vitamin A levels as cirrhosis advances found in the present study could be a consequence of reduced amounts of vitamin A in the hepatic stellate cells. Hepatic stellate cells are the major site of vitamin A storage in liver. There was activation of stellate cells with loss of intracellular vitamin A. But it was still unclear whether vitamin A loss causes their activation, stimulation or whether it was simply an event that occurs during their activation. Biochemical variables for assessing liver function,

such as total bilirubin and prothrombin time, were significantly higher in individuals with inadequate serum retinol levels [17]. There was statistically significant difference in albumin levels and a tendency towards reduced albumin levels in patients with inadequate serum retinol levels. Rocchi *et al*., [10] and Chaves *et al*., [18] found a significant negative correlation between serum retinol and total bilirubin in individuals with cirrhosis and non-alcoholic fatty liver disease, respectively. In the present study, in individuals with inadequate serum retinol levels, liver function tests such as AST and ALT presented a significantly higher median values. Night blindness was found in only thirteen (9%) patients corneal and Bitot's spots in two patients only. Night blindness was the first functional parameter to become deranged in vitamin A deficiency before corneal xerosis and Bitot's spots became evident. These functional parameters were present in very less number of patients of chronic liver disease with vitamin A deficiency. So there was need to evaluate vitamin A level in all chronic liver disease patients. Previous studies by Ukleja *et al.,* [19], through the application of a pre-validated questionnaire, and dark adaptometer found a prevalence of vitamin A deficiency in 22%. Mahmood *et al.*, [20] have reported night blindness in 64 out of 137 (47%) patients with cirrhosis, also describing cases of conjunctival xerosis and Bitot's spots in some of these individuals. Drawback of this study are that no control group were taken for comparison as prevalence of vitamin A deficiency and its clinical manifestations are well established and effect of vitamin A supplementation was not assessed as present study design was observational.

Conclusion

In conclusion, vitamin A deficiency determined by serum retinol level is highly prevalent in patients with cirrhosis of liver irrespective of etiology of cirrhosis. The functional indicator (night blindness) is not a good indicator of vitamin A nutritional status in cirrhosis of liver. So, evaluation and replacement of serum retinol in liver cirrhosis patients of any stage may be considered as optimal strategy as it would result in greater oxidative protection and lower risk of development of complications from liver cirrhosis and the development of HCC, but further studies need to be conducted on fat-soluble vitamin supplementation in deficient patients with cirrhosis to assess clinical outcomes.

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