ORIGINAL RESEARCH PAPER

Medical Science

VITAMIN A STATUS IN PATIENTS WITH CIRRHOSIS OF LIVER – A CASE CONTROL STUDY

KEY WORDS: Deficiency, CTP, MELD, Severity

Kandarp Nath Saxena Assistant Professor, Department of Gastroenterology, National Institute of Medical Sciences, Jaipur-302002

Ravikant Kumar* Assistant Professor, Department of Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna-800014 *Corresponding Author

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 and compare vitamin A level in patients with cirrhosis of liver with normal population and the relationship between etiology 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 vitamin A level were estimated. Apparently normal relatives of patients were taken as control. Results- Sixty three percent (95/150) of patients with cirrhosis of liver had vitamin A deficiency while only about six percent of controls had low vitamin A level ($p < 0.05$). 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. **Conclusion-** Vitamin A deficiency is highly prevalent in patients with cirrhosis of liver irrespective of etiology of cirrhosis. The functional indicator (night blindness) is not a good parameter for assessing the vitamin A nutritional status. In view of multitude of function of vitamin A , its estimation and replacement may be considered in case of deficient cirrhotic patients.

Vitamin A is fat soluble retinoids that include retinol, retinal and retinyl esters which is essential for vision, growth, reproduction and immunity. In a normal liver, hepatic stellate cells are major storage sites for vitamin A. Following the activation of hepatic stellate cells, a loss of the characteristic stored intracellular Vitamin A occurs. Hepatic stellate cells following activation transformed into myofibroblasts and results 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 consequenctely clinical manifestation of vitamin A deficiency. Being a fat soluble vitamin, its deficiency in cholestatic liver diseases is well established but studies on noncholestatic chronic liver diseases are limited and inconclusive.

Aims-

1 To determine and compare vitamin A level in patients with cirrhosis of liver with normal population

2 To determine the relationship between etiology of cirrhosis of liver with vitamin A deficiency

Material and methods

After approval of Institutional Ethics Committee, this observational case control study was conducted in the department of Gastroenterology and Hepatology, M.L.N. Medical college and Swaroop Rani Nnehru 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. Apparently healthy relatives of patients were taken as control group. Informed consent was taken.

Patients with age less than 18 years, 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 questionnarie2 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 nightblindness ? 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 were carried out by a validated method for online solidphase 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.] 3,4

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. Statistical comparisons for significance were made using the Kruskal–Wallis non-parametric test as appropriate. The Mann–Whitney test was used to compare the numeric variables between the two groups. Associations between the categorical variables were performed by chi-square test and continuous variables was 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 and 140 healthy control control with mean age of 48.26 ±13.47 years were enrolled in study. Mean haemoglobulin, albumin, bilirubin and transaminases were significantly lower in patients with cirrhosis of liver. The mean vitamin A level in cirrhosis of liver was 0.57 ± 0.28 µmol/l which was significantly lower than the controls in which it was 1.93 ± 0.67 µmol/l ($p < 0.001$). (Table 1). The most common presentation was abdominal distension (ascites) which was present in 109 of 150 (72.67%) of patients. Ascites was followed by jaundice 28(18.67%)], hemetemesis /melena [24(16.0%)], generalized weakness [21(14.0%)] and altered sensorium [16(10.67%)]. Night blindness was present in only 13(8.67%). Thus functional indicator (night blindness) was not a good parameter for assessing the vitamin A nutritional status. HCC present in 11(7.3%) Alcohol was the most common etiology (45, 30%) followed by hepatitis B virus (41 pts) , HCV (18 pts), NASH (20), 7 Wilson's disease (7), AIH (4) and cryptogenic cirrhosis in 5 patients .

Table 1- Baseline characteristic and Serum retinol in cirrhosis of liver and control

	Patients(N=150) (Mean±SD)	Normal (N=140) (Mean±SD)	P value
Age (years)	47.98 ±12.13	48.26 ±13.47	NS
M:F	94:56	86:54	NS

Weight (in kg)	54.8±11.78	61.8±5.27	NS
Height (meter)	1.58±0.08	1.59±0.05	NS
Hb (gm/dl)	8.7±0.08	12.98±0.75	<0.001
TLC (per cc)	6816±2618	7414±1732	NS
Sugar (mg/dl)	91.6±22.5	81.56±9.8	NS
Urea (mg/dl)	34.2±14.5	24.22±5.6	NS
Creatinine (mg/dl)	0.95±0.23	1.03±0.14	NS
Bil (mg/dl)	2.1±1.1	0.45±0.17	<0.001
SGPT (IU/L)	55.4±23.8	30.1±6.6	<0.001
SGOT (IU/L)	79.9±80.4	27.96 ±8.2	<0.001
ALP (IU/l)	226.14±104.6	154.25±22.5	NS
Protein (gm/dl)	5.13±0.94	7.03±0.31	NS
Albumin (gm/dl)	2.98±0.5	3.9±0.25	<0.001
S. Retinol (µmol/l)	0.57 ± 0.28	1.93 ± 0.67	<0.001
MELD	14.42±4.32		

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 and 8 (5.7%) of normal control with p-value <0.001. Optimal vitamin A level was found in 55 (26.7%) of cirrhotics and 142 (94.3%) of normal control.(Table 2)

Table 2. Vitamin A status in cirrhosis and normal population

Vit. A (µmol/l)	Mean Vit. A	Normal >1.05	Deficiency <1.05	P value
Control	1.93±0.67	132 (94.3%)	8 (5.7%)	0.0001
Patients	0.57±0.28	55 (26.7%)	95 (63.3%)	

Vitamin A deficiency was seen irrespective of etiology of cirrhosis of liver. Mann-whitney U test showed no significant association between etiology of disease and VAD. (Table 3)

Table 3. Relation between etiology of cirrhosis and vitamin A deficiency

Vit.A	>1.05 N	<1.05 N	P –value
Alcoholic cirrhosis (45)	13	32	0.267
Non-alcoholic cirrhosis (105)	42	63	
Hep.B cirrhosis (41)	13	28	0.568
Non-hep.B cirrhosis (109)	42	67	

Relation between severity of cirrhosis and vitamin A deficiency:

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 vitamin A deficiency between CTP-A TO CTP-B, CTP-A TO CTP-C and CTP-B TO CTP-C. 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)

Table-4 Relation of serum retinol level with CTP and MELD scores

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

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. Of them 96 (64%) 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.5 Paula et al 6 found vitamin A deficiency in 60 % of 58 patients of cirrhosis of liver. There were multiple mechanism 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.7 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 malnutrition8,9. The conversion of -carotene to retinol, for it occurring in the liver, might be deficient in these patients, contributing to the lowered levels of serum retinol in this group.[10]

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.[11,12]

This progressive drop in serum vitamin A levels 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 cause their activation, stimulation or whether it was simply an event that occur 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.13 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.6 and Chaves et al.14 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%) in patient group, corneal xerosis in three patients and Bitot's spots in two patients and none in control group. Night blindness was the first functional parameter to became 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.15, through the application of a pre-validated questionnaire, and dark adaptometer found a prevalence of 22 %. Mahmood et al.16 have reported night blindness in 47% of individuals with cirrhosis, also describing cases of conjunctival xerosis and Bitot's spots in some of the individuals

CONCLUSIONS

In conclusion, vitamin A deficiency is highly prevalent in patients with cirrhosis of liver irrespective of etiology of cirrhosis. The functional indicator (night blindness) was not a good parameter for assessing the vitamin A nutritional status. This above observations suggest that there is need for evaluation and

replacement of vitamin A in liver cirrhosis patients of any stage, which would result in greater oxidative protection and lower risk of development of complications from liver cirrhosis and the development of HCC, but further studies are necessary to confirm it or dismiss it.

REFERENCES

1 Bataller R & Brenner DA (2005) Liver fibrosis. J Clin Invest 115, 209–218.
2 Pinzani M & Rombouts K (2004) Liver fibrosis from bench to Clinical targets. Dig Liver Dis 36, 231–242.
3 Leo MA, Sato M, Lieber CS. Effect of hepatic vitamin A depletion on the liver in humans and rats. Gastroenterology. 1983; 84(3):562-72.
4 Abbott-Johnson WJ,Kerlin P,Abiad G,Clague AE,Cuneo RC. Dark adaptation in vitamin A-deficient adults awaiting liver transplantation: improvement with intramuscular vitamin A treatment. Br J Ophthalmol 2011;95:544-548.
5 Peres WA, Chaves GV, Gonçalves JC, Ramalho A, Coelho HS.Vitamin A deficiency in patients with hepatitis C virus-related chronic liver disease. Br J Nutr.2011 Dec;106(11):1724-31
6 Rocchi E, Borghi A, Paolillo F, et al. (1991) Carotenoids and Lipossoluble vitamins in liver cirrhosis. J Lab Clin Med 118, 176–185.
7 Cincinatus R, Chaves GV, Aquino LA, et al. (2007) Consumo Diete´tico de macronutrientes e micronutrientes e a sua Relac¸a˜o com a gravidade da doenc¸a hepa´tica. Rev Soc Bras Alim Nutr 32, 61–77.
8 Russell RM, Iber FL, Krasinski SD, et al. (1983) Proteinenergy Malnutrition and liver dysfunction limit the usefulness Of the relative dose response (RDR) test for predicting Vitamin A deficiency. Hum Nutr Clin Nutr 37, 361–371.
9 Calamita Z, Dichi I, Papini-Berto SJ, et al. (1997) Plasma Levels of transthyretin and retinol-binding protein in child-A cirrhotic patients in relation to protein-calorie status And plasma amino acids, zinc, vitamin A and plasma thyroid Hormones. Arq Gastroenterol 34, 139–147.
10. World Health Organization (1996) Global prevalence of vitamin A. Indicators for assessing vitamin A deficiency and Their application in monitoring and evaluating intervention Programmes. Micronutrient Series, WHO/NUT10. Geneva: WHO.
11 Newsome PN, Beldon I, Moussa Y, et al. (2000) Low serum Retinol levels are associated with hepatocellular carcinoma in patients with chronic liver disease. Aliment Pharmacol Ther 14, 1295–1301
12 Clemente C, Elba S, Buongiorno G, et al. (2002) Serum retinol And risk of hepatocellular carcinoma in patients with Child–Pugh class A cirrhosis. Cancer Lett Mecocci P, Polidori MC, Troiano L, et al. (2000) Plasma antioxidants And longevity: a study on healthy centenarians. Free Radic Biol Med 28, 1243–1248
14 Chaves GV, Pereira SE, Saboya CJ, et al. (2008) Nonalcoholic Fatty liver disease and its relationship with the Nutritional status of vitamin A in individuals with class III Obesity. Obes Surg 18, 378–385.
15 Ukleja A, Scolapio JS, Mcconnell JP, et al. (2002) Nutritional Assessment of serum and hepatic vitamin A levels in patients With cirrhosis. JPEN 26, 184–188.
16 Mahmood K, Samo AH, Jairamani KL, et al. (2008) Serum Retinol binding protein as an indicator of vitamin A status In cirrhotic patients with night blindness. Saudi J Gastroenterol 14, 7–11.