Original Article

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Internal Medicine Section

Thyroid Profile in Patients of Cirrhosis of Liver: A Cross-sectional Study

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ABSTRACT

Introduction: Liver plays an important role in the metabolism of thyroid hormones. It also has a dominant role in the production and secretion of thyroid binding globulin. So, patients of cirrhosis of liver may be clinically euthyroid but thyroid hormones and thyroid binding globulin are altered. Low free T3 and free T4 along with increased reverse T3 (rT3) and decreased T3:T4 ratio are the common alterations observed in thyroid profile of such patients.

Aim: To evaluate thyroid profile in patients with cirrhosis of liver and correlation of thyroid profile with clinical and biochemical parameters of severity in patients with cirrhosis of liver.

Materials and Methods: A observational, cross-sectional study was conducted at a tertiary care hospital evaluating thyroid profile in 102 patients with cirrhosis of liver.

Results: Low free T3 and T4 was found in 72.5% and 26.47% of patients with cirrhosis of liver respectively. TSH towards the upper limit of normal range was observed in 52.3% of patients. Low free T3 and free T4 was found to be inversely related to the severity of liver disease. A significant correlation was also found between low free T3 levels, hyponatremia (p=0.004) and raised INR (p=0.038). Similarly, a significant correlation was also observed between low free T4 levels, serum bilirubin (p=0.049) and SGPT (p=0.008) levels.

Conclusion: Derangement in thyroid profile is common in patients with cirrhosis of liver. Low free T3 and T4 levels are associated with more severe liver injury and may be used for prognostication in patients with cirrhosis of liver.

Keywords: Cirrhosis of liver, Liver function tests, Subclinical hypothyroidism, Thyroid function test

INTRODUCTION

Cirrhosis of liver is a leading cause of morbidity and mortality worldwide. Liver plays a vital role in thyroid hormone metabolism and circulation of thyroid hormone by producing thyroid binding globulin [1]. Liver also plays a role in the production of triiodothyronine (T3) by the action of selenium dependent 5' deiodinase. Moreover, another selenium independent deiodinase acts on the phenolic ring of thyroxine (T4) to produce the hormonally inactive reverse T3 (rT3) [2].

The levels of thyroid hormone and thyroid binding proteins are altered in patients of chronic liver disease. Low free T3 syndrome is frequently described in patients with cirrhosis of liver and is characterized by increased rT3, low T3 and decreased T3:T4 ratio [3]. Low T3 may be an adaptive thyroid response to reduce the basal metabolic rate of hepatocytes and preserve liver function [4].

Hence, we conducted a study to evaluate thyroid profile in patients with cirrhosis of liver and to find correlation of thyroid profile with clinical and biochemical parameters of severity in patients with cirrhosis of liver, as well as to find out its prognostic implications.

MATERIALS AND METHODS

A observational, cross-sectional study was conducted in the Department of Medicine, King George Medical University (KGMU), Lucknow, India over a period of one year (August 2014-July 2015).

The sample size was calculated based on the systematic review by Eshraghian A and Taghavi SA [5]. According to this review, the prevalence of thyroid abnormalities in cirrhosis of liver ranges from 13% to 61%. The total sample size was calculated according to the formula;

$$N = z^2pq/L^2$$

(where z=1.96, p stands for prevalence (61%), q = 100- p, L = relative error = 15% of p), the corrected sample size was 113. However, we managed to enroll 102 patients in our study.

Patients with cirrhosis of liver aged more than 12 years, who were admitted with evidence of hepatocellular dysfunction and portal hypertension evident clinically and by portal vein diameter >13mm on Ultrasonography (USG) and presence of oesophageal varices as visualised using upper gastrointestinal endoscopy were included in the study.

Patient with sepsis, cardiac failure, renal failure, nephrotic syndrome, pregnancy, personal or family history of thyroid disorders and patient on drugs known to alter thyroid functions were excluded from the study.

All enrolled patients were thoroughly evaluated by detailed history and clinical examination. All relevant investigations including complete blood count, random blood sugar, kidney function test, liver function tests (serum bilirubin, transaminase, transglutamase, Serum Alkaline Phosphatase (SALP), serum protein and albumin), prothrombin time, International Normalized Ratio (INR), and antibodies against HIV, hepatitis C hepatitis B were carried out. Ultrasound of whole abdomen was done by expert radiologist giving special attention to portal vein diameter, liver echotexture, splenomegaly and ascites. Upper gastrointestinal endoscopy, ascitic fluid examination and fasting thyroid profile including free T3, free T4 and TSH was also carried out in all enrolled patients.

Thyroid function test were evaluated by cobas e411 thyroid immune analyser by Roche diagnostics. Normal reference range for free T3=3.10-6.80 pmol/L, free T4=12.0-22.0 pmol/L and TSH=0.27-4.20 mIU/mL was considered. Based on results of thyroid function, Patients were divided into three groups; lower than normal, normal and higher than normal levels of thyroid hormones separately for each thyroid hormone test. Ascites was semi-quantified using

the following system: Stage 1+ is detectable only after careful examination, Stage 2+ is easily detectable and not tensed, Stage 3+ is massive, but not tense ascites, Stage 4+ is tense ascites [6]. Patients were divided into two groups: mild ascites=stage 1/2 and severe ascites = stage 3/4. Severity of liver disease was assessed in patients by Child-Pugh (CP) score [7] and Model of End Stage Liver disease (MELD) score [8].

STATISTICAL ANALYSIS

All the statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, USA). Data were presented as mean±SD or number (%) unless specified. All parametric data were analysed using student's t-test. All non-parametric data were analysed by Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

Based on inclusion criteria, 102 patients were enrolled in our study in which 73 were males and 29 were females with a mean age of 41±13.7 years.

[Table/Fig-1] depicts mean value of free T3; free T4 & TSH in enrolled patients. Low free T3 and free T4 was found in 72.5% and 26.47% in patients of cirrhosis of liver respectively. TSH towards the upper limit of normal range was observed in 52.3% of patients.

Based on CP score, four patients (3.92%) were classified as Child-Pugh class A, 40 patients (39.22%) as Child-Pugh class B and rest of the 58 patients (56.86%) as Child-Pugh class C [Table/Fig-2].

Thyroid function test	Mean value in patients of cirrhosis of liver	Normal reference value
Free T3 (pmol/L)	2.32±0.17	3.10-6.80
Free T4 (pmol/L)	12.5±0.38	12.0-22.0
TSH (mIU/mL)	4.12±0.32	0.27-4.20

[Table/Fig-1]: Mean value of thyroid function test in patients of cirrhosis of liver.

Free T3 levels	Child-Pugh class							
	Child-Pugh class A (n=4)		Child-Pugh class B (n=40)		Child-Pugh class C (n=58)		Total (n=102)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Low	2	50.00	24	60.00	48	82.76	74	72.55
Normal	2	50.00	16	40.00	10	17.24	28	27.45
	χ^2=7.220 (df=2); p=0.027							

[Table/Fig-2]: Comparison of Free T3 levels of patients with Child Pugh Class.

Free T3 levels	MELD Score ≤20 (n=64)		MELD Score >20 (n=38)		Total (n=102)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Low	41	64.06	33	86.84	74	72.55
Normal	23	35.94	5	13.16	28	27.45
	χ^2=6.212 (df=1); p=0.013					

[Table/Fig-3]: Comparison of Free T3 levels of patients with MELD score.

Based on MELD score, 64 (62.75%) and 38 (37.25%) patients were found to be less than and more than 20 MELD score respectively [Table/Fig-3].

[Table/Fig-2] depicts correlation of free T3 with severity of liver disease as assessed by Child-Pugh classification. It shows that patient with low free T3 levels were highest in Child-Pugh class C (82.76%) followed by Child-Pugh class B (60 %) and Child-Pugh class A (50%) and this difference was found to be statistically significant (p=0.027).

[Table/Fig-3] depicts correlation of free T3 with severity of liver disease as assessed by MELD score. It shows that patients with low free T3 having MELD score of more than 20 were significantly higher as compared to the patients with MELD score less than 20.

[Table/Fig-4] depicts correlation of free T4 with severity of liver disease as assessed by MELD score. Only one patient of high free T4 with MELD score <20 was found. Patients with low free T4 having MELD score of more than 20 were significantly higher as compared to the patients having MELD score less than 20.

Free T4 levels	MELD Score ≤20 (n=64)		MELD Score >20 (n=38)		Total (n=102)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
High	1	1.56	0	0	1	1
Low	11	17.19	16	42.11	27	26.47
Normal	52	81.25	22	57.89	74	72.55
	χ^2=7.979 (df=2); p=0.019					

[Table/Fig-4]: Comparison of Free T4 levels of patients with MELD score

Statistically no significant difference was found between TSH levels and either Child-Pugh class or MELD score and free T4 with Child Pugh class.

The most common cause of liver cirrhosis in our study was alcoholic cirrhosis comprising of 34(33.3%) patients followed by 29(28.43%) of cryptogenic cirrhosis, 28 (27.45%) of hepatitis B related cirrhosis and 11 (10.78%) of hepatitis C related cirrhosis. Low free T3 levels were found in 67.8% (n=19/28) of patients with hepatitis B related cirrhosis, 54.5% (n=6/11) of patients with hepatitis C related cirrhosis, 67.6% (n=23/34) of patients with alcoholic cirrhosis and 83.8% (n=26/29) patients with cryptogenic cirrhosis. Though low free T3 was found in higher proportion of patients with cryptogenic cirrhosis, this difference was not found to be statistically significant. No statistical significant difference was found between free T4 levels & TSH levels with etiology of cirrhosis of liver.

[Table/Fig-5] depicts that, patients with low fT3 levels were found to have a higher incidence of complications like ascites, hepatic encephalopathy and bleeding varices. This correlation between low fT3 with severe ascites (p=0.022) and hepatic encephalopathy (p=0.011) was found to be statistically significant. No significant correlation was found between complications of cirrhosis of liver and free T4 & TSH levels.

Complications of cirrhosis of liver	Low Free T3 levels (n=74)		Normal Free T3 levels (n=28)		Total (n=102)		Statistical significance	
	No. of patients	%	No. of patients	%	No. of patients	%	χ^2	'p'
Mild Ascites	41	55.41	13	46.43	54	52.94	0.657	0.418
Severe Ascites	17	22.97	1	3.57	18	17.65	5.262	0.022
Hepatic Encephalopathy	27	36.49	3	10.71	30	29.41	6.499	0.011
Bleeding Varices	13	17.57	8	28.57	21	20.59	1.504	0.220

[Table/Fig-5]: Comparison of Free T3 levels with complications of cirrhosis of liver.

Among various biochemical parameters compared with thyroid function test, student's t-test revealed statistically significant correlation between low fT3 levels with raised INR (p=0.038) and hyponatremia (p=0.004). Similarly, statistically significant correlation was also found between low free T4 with hyperbilirubinemia (p=0.049) and SGPT (p=0.008). No significant correlation was seen between TSH and various biochemical parameters.

DISCUSSION

The low T3 syndrome has frequently been reported in patients with chronic liver disease [3]. We also observed low fT3, fT4 and slightly raised TSH in most of our enrolled patients.

Out of the 102 patients, 56.8% (n=58) were adjudged as Child-Pugh class C, 39.8% (n=40) as Child-Pugh class B and remaining 3.9%(n=4) as Child-Pugh class A. This shows that most of the patients presented to us in advanced stage with decompensated liver cirrhosis.

We found that free T3 levels were inversely correlated with the Child-Pugh class and previous studies also suggested similar results [9,10,11]. Several mechanisms have been postulated for this occurrence of lower free T3 levels in patients with cirrhosis of liver and its inverse correlation with the severity of liver injury. Most common hypothesis states that loss of peripheral deiodination as the primary cause of decreased free T3 levels, the so called sick euthyroid syndrome[1,8,10,11,12,13,14]. Poor nutrition in cases of liver cirrhosis has been linked to decrease in free T3[13]. Release of cytokines such as Interleukin-6 (IL-6) might also be responsible for the syndrome of sick euthyroid syndrome. Further, alcohol intake has been associated directly with impaired hepatic deiodinase activity [15]. Free T4 levels and TSH levels were not found to be significantly related to Child-Pugh class.

There was significant inverse correlation between MELD score and free T3 levels in our study, when 20 was used as a cut off for separating more severe disease from less severe (p=0.013) and this was also supported by Tas A et al., [11]. Based on MELD scoring, 2 groups were identified in our study, 62.7% (n=64) of patients belong to group 1 with MELD score <20 and 37.2%(n=38) into group 2 with MELD score>20. Significant inverse correlation was also found by us between free T4 levels and MELD score (p=0.019), which was in accordance with Dehghani SM et al., [10]. The basis of this probably lies in increased conversion of free T4 to rT3 by type 3 deiodinase. We found no significant correlation between TSH and MELD score and this is similar to the observations made by previous studies [1,10,11].

No statistically significant correlation was found between gender of population and thyroid profile. This was in accordance with U.M. Al-Jarhi U et al., who observed that thyroid hormone profile in women did not differ from men in patients with liver cirrhosis [12] & it was contrary to Patira NR et al., which showed increased prevalence of hypothyroidism in male cirrhotic patients [9].

Our study suggested that free T3 levels were found to be significantly inversely correlated with severe ascites. Similar results were observed in a study done by Al-Jarhi U et al., which showed significantly lower free T3 levels in patients with decompensated liver cirrhosis as compared to compensated liver cirrhosis [12].

Our study also showed that low free T3 were also found to be significantly related to hepatic encephalopathy. This observation is supported by Arafa M et al., who demonstrated lower T3 levels in patients with hepatic encephalopathy, the lowest level being found in patients with grade-4 hepatic encephalopathy [16].

No significant correlation was found between low free T3 levels and grading of varices or bleeding varices in our study. Contrary to our observations, Mansour-Ghanaei F et al., observed an increased risk of bleeding varices with decreasing total T3 levels (but not free T3) [1].

Free T4 and TSH levels were also found not to be related to any of the clinical indices of severity. This is in concordance with the previous studies demonstrating no relation of free T4 and TSH with clinical indices of severity [1].

We also did not found any relationship between etiology of cirrhosis and derangement of thyroid profile which was supported by previous studies [1,17].

In our study, significant correlation was also found between low free T3 levels and hyponatremia (p=0.004) and raised INR (p=0.038). Though sodium was significantly decreased in patients with low free T3 levels. This might represent increasing severity of liver dysfunction and the resultant dilutional hyponatremia or it might be due to the euvolemic hyponatremia observed in patients of hypothyroidism.

The coagulation parameters were also significantly deranged in patients with low free T3 levels as compared to patients with normal free T3 and similar findings were also observed by Dehghani SM et al., and Al-Jarhi U et al., [10,12].

Significant correlation was also found between low free T4 levels with serum bilirubin (p=0.049) and SGPT (p=0.008) levels in our study. Similar observations were made by Dehghani SM et al., [10].

None of the patients enrolled in our study had any clinical symptoms and signs suggestive of hypothyroidism. So, in patients with liver cirrhosis, the thyroid profile is altered but clinical euthyroidism was almost always maintained [1].

LIMITATION

There were some limitations in the present study. The present study was a cross-sectional study hence, it cannot show a causal relationship between thyroid abnormalities and cirrhosis of liver. Moreover, it is a single-centred study. In future, we need multi centric study involving patients of different geographical areas. As sample size was not adequate, so we need a study involving larger sample size to support our findings. Another limitation was lack of a liver biopsy to confirm cirrhosis. We avoided liver biopsy as it is an invasive procedure. Detailed work up for thyroid profile like reverse T3 and thyroid antibodies [thyroperoxidase (TPO) antibody, thyroglobulin] were also not carried out.

CONCLUSION

Derangement in thyroid profile is common in patients with cirrhosis of liver. Low free T3 and T4 levels are associated with more severe liver injury in patients with cirrhosis of liver. So, thyroid function test should be carried out in all cirrhotic patients to assess the severity and prognostication of such patients.

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