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Derangements of Thyroid Profile in Liver Cirrhosis

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Abstract

Background

Liver plays a crucial role in metabolism of thyroid hormones and secretion of thyroid binding globulin. Liver and thyroid functions are closely related to each other. Liver has enzyme Deiodinase-1 which helps in peripheral conversion of T4 to T3 and Deiodinase-3 which converts T4 to inactive reverse T3 (rT3). In liver cirrhosis, due to severe hepatocyte dysfunction, thyroid metabolism is disturbed and patients may present with features of hypo or hyperthyroidism. The aim of our study was to evaluate thyroid profile in patients with cirrhosis and establish its correlation with disease severity.

Materials and Methods

We conducted a prospective study and assessed thyroid profile in 100 patients (>18 years of age) suffering from liver cirrhosis. Clinical, biochemical and radiological evaluation was done for confirmation of diagnosis. Patients with pre-existing thyroid disease, consuming drugs known to alter thyroid profile, sepsis, cardiac failure, renal failure and pregnancy were excluded.

Result

We found that 68 patients had low free T3, 33 had low free T4 and 55 patients were found to have higher normal range for TSH. Disease severity was inversely proportional to free T3 and T4 levels. There was significant correlation between free T3, raised INR(p=0.03) and hyponatremia(p=0.004). Significant correlation was observed between free T4, SGPT(p=0.008) and bilirubin(p=0.04). We also depicted correlation of thyroid profile with Child Pugh and MELD score.

Conclusion

Cirrhotic patients have deranged thyroid profile with low free T3 and T4 levels, associated with more severe liver disease. Thus, free T3 and T4 can be used as prognostication marker in liver cirrhosis.

Keywords: cirrhosis, thyroid hormones, Child Pugh Turcotte Score, MELD Score, hepatic encephalopathy

Introduction

Liver is the depot for thyroid hormone metabolism. Many important enzymes required for thyroid hormone metabolism like Deiodinase-1, Deiodinase-3 are secreted by the liver along with thyroid binding globulin.[1] Thyroxine (T4) and triiodothyronine (T3) are secreted by the thyroid gland, T4 being secreted twenty times more than T3. These hormones are bound to plasma proteins like thyroxine-binding globulin, transthyretin, and albumin.[2] These hormones act through α and β receptors and are

responsible for cell differentiation during development, maintaining thermogenic and metabolic homeostasis and regulating basal metabolic rate of all cells, including hepatocytes, thereby modulating hepatic function. Liver and thyroid functions are intricately linked to each other.[3] Since liver cirrhosis is a diseased state where severe hepatocyte dysfunction disturbs thyroid metabolism, we conducted a study to evaluate thyroid profile in patients of liver cirrhosis to find correlation between thyroid profile derangements and clinical/biochemical parameters of liver disease.

Material And Method

This prospective study was conducted on 100 cirrhotic patients who presented to Department of Medical Gastroenterology, Mahatma Gandhi Hospital, Jaipur from May 2022- January 2023 after taking ethical clearance from Institutional Ethical Committee. Informed consent from each participant was taken.

Inclusion criteria

1. Patient age >18 years.
2. Clinical, biochemical and/or radiological evidence of liver cirrhosis.

Exclusion criteria

1. Pre-existing thyroid disease
2. Consuming drugs that alter thyroid profile
3. Sepsis
4. Cardiac failure
5. Renal failure
6. Cancer
7. Radiotherapy or chemotherapy exposure
8. Pregnancy

Criteria for analysis

1. Thyroid profile (free T3, free T4 and TSH) was evaluated by Cobas e411 thyroid immune analyzer.
2. Liver function tests (Bilirubin, SGPT, SGOT, ALP, GGT, PT/INR) were assessed.
3. Sonographic assessment for features of cirrhosis and grading of ascites was done. Ascites was classified as Mild - detectable only by sonography; Moderate - detected by clinical examination and; Severe - tense ascites.
4. Child Pugh Turcotte Score and MELD Score (Model of End Stage Liver disease) were calculated to estimate severity of liver disease.[4,5]

Statistical analysis was performed using SPSS version 22.0 (SPSS Inc. Chicago, USA). All parametric data were analysed using student's T-test. All non- parametric data were analysed by Chi-square test. p-value <0.05 was considered statistically significant.

Results

100 cirrhotic patients were enrolled in our study, 72 males and 28 females; mean age being 42 ± 13.1 years. These patients had liver cirrhosis due to variable causes, most common etiology being alcoholic cirrhosis (67%). Most common presenting symptom was ascites (78%).

63% patients had compensated and 37% had decompensated liver disease. 32% patients had hepatic encephalopathy.

We found that 68% patients had low FT3, 33% had low FT4 and TSH was found to be on the higher side of normal range in 55% patients.

Thyroid function test	Mean value in 100 cirrhotic patients	Normal reference range
Free T3 (pmol/L)	2.21± 0.14	3.10-6.80 pmol/L
Free T4 (pmol/L)	12.1± 0.31	12-22 pmol/L
TSH (mIU/ml)	5.57± 0.29	0.35-5.5 mIU/mL

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Out of 100, 4 patients with thyroid dysfunction were in Child Pugh Class A, 36 in Class B and 60 of patients in Class C.

Low FT3 was maximally seen in Child-Pugh Class C (81.6%) patients, followed by Child- Pugh Class B (60%) and Child Pugh Class A (50%) and this difference was statistically significant (table 2).

Free T3 levels	**CHILD – PUGH CLASS**			
	Child Pugh Class A (n=4)	Child Pugh Class B (n=36)	Child Pugh Class C (n=60)	Total (n=100)
	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Low	2 (50 %)	22 (60%)	49 (81.6%)	73 (73%)
Normal	2 (50%)	14 (40 %)	11 (18.3%)	27 (27%)
P value= 0.027				
Table 2: Correlation of FT3 levels with Child Pugh Class				

Out of 100, 62 patients had MELD score <20 and 38 patients had MELD score ≥ 20. Out of the 38 patients with more severe liver cirrhosis (MELD score ≥ 20), 33 patients had significantly lower FT3 levels as compared to patients with MELD score <20 (table 3).

FREE T3 LEVELS	**MELD SCORE < 20 (n=62)**	**MELD SCORE ≥ 20 (n=38)**	**TOTAL(n=100)**
	No. of patients (%)	No. of patients (%)	No. of patients (%)
Low	40 (64.5%)	33 (86.8%)	73 (73%)
Normal	22 (35.5%)	5 (13.1%)	27 (27%)
P value= 0.011			
Table 3: Correlation of FT3 levels with MELD score.			

Patients with low FT4 having MELD score ≥ 20 were significantly higher as compared to the patients having MELD score < 20 (table 4). However, majority (n=51) patients with low MELD score and 19 patients with high MELD score had normal FT4 levels.

FREE T4 LEVELS	**MELD score < 20 (n=63)**	**MELD score ≥ 20(n=37)**	**TOTAL (n=100)**
	No. of patients (%)	No. of patients (%)	No of patients (%)
High	1 (1.58%)	0	1 (1%)
Low	12 (19.04%)	17 (45.9%)	29 (29%)
Normal	51 (80.9%)	19 (51.3%)	70 (70%)

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P value=0.017
Table 4: Correlation of Free T4 levels with MELD score

Correlation of FT3 levels with complications of liver cirrhosis was also done. Significant correlation was seen between low FT3 levels and hepatic encephalopathy (p=0.017) and severe ascites (p=0.031) (table 5).

No significant correlation was seen between complications of cirrhosis and FT4 & TSH levels.

Complications of liver cirrhosis	**Low FT3 levels (n=71)**	**Normal FT3 levels (n=29)**	**Total (n=100)**		
	No. of patients (%)	No of patients (%)	No. of patients (%)	2 χ	P
Mild to moderate ascites	40 (56.33 %)	12 (41.3%)	52 (52%)	0.663	0.412
Severe ascites	17 (23.9%)	1 (3.44%)	18 (18%)	5.341	0.031
Hepatic encephalopathy	28 (39.4%)	4 (13.7%)	32 (32%)	6.812	0.017
Bleeding varices	12 (16.9%)	7 (24.1%)	19 (19%)	1.603	0.258
Table 5: Correlation of FT3 levels with complications of liver cirrhosis					

Discussion

Liver plays an important role in metabolizing thyroid hormones and regulating their systemic endocrine effects. It secretes Type 1 deiodinase responsible for peripheral conversion of T4 to T3 accounting for approximately 30%–40% of extrathyroidal production of T3.[6] It helps in both 5'-and 5-deiodination of T4 to T3. Liver is also involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin.[7]

Thyroid and liver functions are interlinked and clinical and laboratory associations have been seen between thyroid and liver diseases. Thyroid diseases affect liver function and vice versa and systemic diseases can affect both the organs.[3]

Since thyroid hormone metabolism is hampered due to severe hepatocyte dysfunction, altered thyroid hormone levels and thyroid binding proteins (also known as Low FT3 syndrome) is characterized by low T3, decreased T3:T4 ratio and increased rT3.[5,8] Low T3 may be an adaptive response of thyroid gland to reduce basal metabolic rate of hepatocytes to preserve liver function.[8] In our study, we found 68 (68%) patients had low FT3.

Following mechanisms are postulated for low FT3 levels in cirrhosis:

1. Loss of peripheral deiodination "sick euthyroid syndrome".[9,10,11]
2. Cytokine storm (predominantly IL-6) responsible for sick euthyroid syndrome.
3. Poor nutritional status in cirrhosis.
4. Alcohol consumption inhibits hepatic deiodinase activity.

We found inverse relation between FT3 and Child Pugh Score (p=0.027), as also shown by Patira et al, Dehghani et al and Tas et al in their study.[8,9,10] We also found inverse relation between FT3 levels and MELD score(p=0.011) similar to study by Tas et al.[10]

We also observed inverse relation between FT4 and MELD score (p=0.017) similar to study by Dehghani SM et al due to increased conversion of FT4 to rT3 by Deiodinase 3.[9]

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Our study showed no correlation between FT4 / TSH and Child-Pugh score.

No significant correlation between TSH and Child Pugh / MELD score was seen, similar to Mansour et al and Dehghani et al.[1,9]

FT3 levels were related to severity of ascites, as shown by Al- Jarhi et al.[11]

FT3 levels were significantly related to hepatic encephalopathy, as seen by Arafa et al who showed lowest FT3 levels in Grade 4 hepatic encephalopathy.[12]

No significant correlation was found between FT3 levels and bleeding varices, in contrast to study by Mansour et al where they observed increased risk of bleeding varices with decreasing FT3 levels.[1] There was no correlation of FT4 / TSH levels with clinical indices of liver disease severity.[1]

We found significant correlation between low FT3 levels and hyponatremia (p=0.007) and raised INR (p=0.047). This may be due to severity of liver dysfunction causing dilutional hyponatremia or due to euvolemic hyponatremia in patients of hypothyroidism.

Statistically significant correlation was found between low FT4 with ALT levels (p=0.004) and hyperbilirubinemia (p=0.044), similar to study by Dehghani SM et al and Al-Jarhi et al.9,11

There was no significant relation between gender and thyroid profile, in contrast to Patira et al who showed increased prevalence of hypothyroidism in male cirrhotic patients.[8]

Our study showed no relation between deranged thyroid profile and etiology of cirrhosis, similar to studies by Mansour et al and Zietz B et al.[1,13]

There were some limitations in our study. This was a cross-sectional study so causal relationship between thyroid abnormalities and liver cirrhosis was not established. We conducted a single-centred study with a small sample size of 100 patients. In future, multi centric study involving larger sample size may be required to support our findings. Another limitation was lack of histopathological evidence of cirrhosis. Work up for reverse T3 and thyroid antibodies [thyroperoxidase (TPO) antibody, thyroglobulin] were also not carried out.

Conclusion-

In our study, none of the patients had clinical sign and symptoms of hypothyroidism. Therefore, cirrhotic patients may be clinically euthyroid despite their deranged thyroid profile. FT3 and FT4 levels can be an indirect marker for severity of liver cirrhosis. Thus, it is very important to assess thyroid profile of patients with cirrhosis to assess severity and prognostication.

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