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Original Research Article

Study of Decreased Serum Total T3 Level in Hepatitis B and C Related Cirrhosis by Severity of Liver Damage

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Abstract:

Background: Thyroxin-binding globulin metabolism involves the liver significantly. Thyroxin-binding globulin, thyroxin-binding prealbumin, and albumin in plasma bind more than 99% of thyroid hormones. A healthy liver axis is necessary for thyroid function. In order to determine whether there is any correlation between thyroid hormones and the severity of liver damage, the thyroid hormone profile in patients with hepatic cirrhosis brought on by persistent HBV and HCV infections was examined.

Methods: The thyroid function status of patients with the diagnosis of hepatic cirrhosis brought on by hepatitis B or C was checked. Scores for Child-Pugh and the MELD model for end-stage liver disease were computed. Patients were separated into two groups, one for each thyroid function test, with lower than normal and normal range thyroid hormones (for TSH, normal and upper than normal). It was considered whether thyroid function tests and the severity of liver disease correlated.

Results: Along with an increase in Child-Pugh scores A, B, and C, the number of patients with T3 levels below the normal range (70-110 ng/dL) also increased dramatically. Child-Pugh scores and total serum T3 level were shown to be negatively correlated ($r = -0.453$, $P < 0.001$). Additionally, a negative connection ($r = -0.305$, $P = 0.14$) between the MELD score and T3 levels was found.

Conclusion: In conclusion, the degree of liver damage affects blood T3 levels, which is an excellent indicator of hepatic function.

Keywords: Cirrhosis, Thyroid hormones, Thyroid dysfunction, Hypothyroidism.

Introduction

Liver cirrhosis is one of the main causes of illness and mortality in the world. The liver produces thyroid binding globulin, which is essential for the metabolism and circulation of thyroid hormones. [1] The degenerative condition known as liver cirrhosis causes diffuse fibrosis and inflammation. Triiodothyronine (T3) and thyroxine (T4) are two hormones that are produced by the thyroid gland. These hormones, which act via the thyroid hormone receptors, are essential for cell differentiation during development and for adults' ability to maintain normal levels of metabolism and thermogenesis. Twenty times more T4 than T3 is secreted by the thyroid gland. Both hormones are associated with plasma proteins such as albumin, transthyretin, and thyroxine-binding globulin. [2] As the primary organ involved in the extrathyroidal conversion of T4 to T3 by Type 1 deiodinase, the liver is essential in the production of thyroid hormones. [3-5] The liver produces Type I deiodinase, which converts T4 to T3 by both the 5'- and 5-deiodination of T4 and is in charge of 30 to 40 Percent of extrathyroidal production of T3. The liver also contributes significantly to the metabolism and circulation of thyroid hormones by producing thyroid binding globulin [6]. The conjugation and excretion of thyroid hormone both take place in the liver. Thyroid stimulating hormone (TSH) metabolism and systemic endocrine effects are both regulated by the liver.

Material and Methods

All patients with the diagnosis of hepatic cirrhosis caused by hepatitis B or C who attended the outpatient departments of the Atal Bihari Vajpayee Institute of Medical Sciences and Ram Manohar Lohia Hospital in New Delhi from August 2021 to July 2022 were sequentially screened for thyroid function status. A liver biopsy, biochemical evidence of liver failure, or ultrasound evidence of portal hypertension and small liver size were all used to confirm the diagnosis of cirrhosis. Chronic

hepatitis was characterized as abnormal serum aminotransferase for more than six months; if this was accompanied by positive serum HBS antigen, it was thought to be caused by HBV, and if it was also accompanied by positive serum anti-HCV antibody and positive HCV RNA PCR, it was thought to be caused by HCV. Patients with clinical evidence of thyroid disease or thyroid dysfunction as well as those who tested positive for both HBV and HCV infections were not taken into account for the study. Patients on Carbamazepine, Phenytoin, Phenobarbitone, Salicylates, and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) were also excluded from the trial, and none of the patients were receiving treatment with thyroid stimulating or inhibitory drugs. Subjects having a history of alcohol use in the previous 6 months were excluded because we intended to examine the changes in thyroid hormones in individuals with HBV or HCV associated cirrhosis. Patients fulfilling the inclusion criteria were recruited in the study after taking informed written consent. The following clinical consequences were assessed: ascites, encephalopathy, bleeding varices, and spontaneous bacterial peritonitis (SBP). Thyroid and liver function were also assessed. A Child-Pugh score was obtained [7], and the MELD risk score (RS) was computed utilizing the formula below: [8]

RS = 0.957 × loge (creatinine mg/dL) + 0.378 × loge (bilirubin mg/dL) + 1.120 × loge (INR) + 0.643 × (cause of cirrhosis).

For which the value for cause of cirrhosis, as it was viral in all the patients, was considered 1. Radio immunological assay kits were used to measure the levels of circulating free T3 (reference, 1.5 to 4.1 ng/dL), free T4 (reference, 0.9 to 1.7 mcg/dL), total T3 (reference, 70 to 190 ng/dL), total T4 (reference, 4.8 to 12 mcg/dL), and TSH (reference, 0.3 to 5.5 mcIU/mL). Additionally, kits were used to check liver testing. Patients were split into several groups during analysis based on the type of hepatitis, comorbidities, Child-Pugh classes, and MELD score greater than or less than 20 in order to identify significant differences. In order to conduct the statistical analysis, SPSS 14.0 (SPSS Inc., Chicago, IL) was used. As necessary, the chi-square test, the Fisher exact test, and the univariate logistic regression model were applied. The correlations were reported using Spearman's rho because the child-Pugh and MELD scores were not regularly distributed. Statistical significance was defined as a P-value <0.05.

Results

During the study period, 72 cirrhotic individuals showed up; 3 were turned away due to chronic alcohol use, and 5 were turned away due to a history of hypothyroidism. The study included 64 patients in total (42 men and 22 women), with a mean age of 55.03±12.05 years. Prior to enrolment, cirrhosis had been present for an average of 25 months (range: 1 month to 6 years). HBV was identified as the cause of cirrhosis in 34 cases, whereas HCV was to blame in 30 patients. Ascites (n = 59), encephalopathy (n = 31), bleeding varices (n = 20), and SBP (n = 10) were some of the associated comorbidities. Table 1 presents the thyroid function test findings. According to the measurements, the levels of total albumin and TBG were 3.04± 0.6 (NL: 4-5.3 g/dL) and 1.02±0.9 (NL: 1.3-3.0 mg/dL), respectively.

Table 1: Thyroid function tests in the study population categorized according to normal ranges

Parameters	< Lower limit (n, %)	Normal range	>upper range (n, %)
TSH	5 (7.81%)	54 (84.38%)	5 (7.81%)
T3	52 (81.25%)	12 (18.75%)	0 (0.0%)
T4	22 (34.37%)	42 (65.63%)	0 (0.0%)
FT3	16 (25.0%)	48 (75.0%)	0 (0.0%)
FT4	10 (15.62%)	49 (76.57%)	5 (7.81%)

Significant differences were found in the number of patients with ascites, bleeding varices, and Child-Pugh scores when patients were divided into two groups with thyroid hormone levels that were lower than normal and normal range, separately for each thyroid hormone test (for TSH, normal and upper than normal), only for total T3. Of the patients who had ascites when they were first diagnosed, 16 had severe ascites (all with <T3 70 ng/dL), 31 moderate ascites (26 with T3 <70 ng/dL), and 12 mild ascites (2 with T3 <70 ng/dL). Patients with higher grade ascites had a higher likelihood of having a serum T3 level below the normal range (OR = 3.56, 95% CI = 1.54 to 8.23) in a logistic regression model adjusted only for ascites; as a result, the severity of ascites was correlated with the proportion of patients with a serum T3 level below the normal range (P = 0.011). Serum T3 levels were below 70 for all 20 patients with bleeding varices; this difference from the other 44 patients (32 had serum T3 levels below normal range) was significant (P = 0.012). However, there was no difference in TSH, T4, FT3, or FT4 across patients with and without comorbidities.

Scores A, B, and C of the Child-Pugh system were used to group patients. In subgroups of patients with thyroid function test results that were lower than normal and normal (for TSH, normal, and higher than normal), only T3 showed a significant difference (P <0.001); there were 2 (out of 5), 16

(out of 22), and 34 (out of 35) patients with T3 <70 ng/dL for Child-Pugh scores A, B, and C, respectively. Additionally, a negative connection (r = -0.453, P <0.001) between Child-Pugh scores and total serum T3 level was found. There was no discernible difference for any of the thyroid function test variables in the same analysis for MELD scores greater than 20 compared to less than 20. The MELD score and T3 levels did, however, show a reverse connection (r = -0.305, P = 0.014). TSH and Child-Pugh score also had a favourable connection (r = 0.294, P = 0.018) (Table 2).

Table 2: Correlation between thyroid profile and Child-Pugh score and MELD score

Grouping	TSH	Total T3	Total T4	Free T3	Free T4
Child-Pugh Score					
• r	0.294	-0.453	-0.172	-0.090	-0.060
• p	0.018	0.000	0.175	0.481	0.639
MELD Score					
• r	-0.016	-0.305	-0.204	-0.058	-0.138
• p	0.903	0.014	0.106	0.647	0.279

The thyroid test variables lower than normal/within normal range, individually for each thyroid hormone test (for TSH, normal and upper than normal), were used to categorize patients with HBV/HCV linked cirrhosis. No thyroid test variable showed a significant difference (TSH: P = 0.540; T3: P = 0.810; T4: P = 0.081; free T3: P = 0.583; free T4: P = 0.810).

Discussion

The current study that a more severe liver state was negatively correlated with serum total T3 levels. When classifying patients into Child-Pugh categories A, B, and C, we discovered that there was a significant relationship between the Child-Pugh score and the number of patients with serum T3 levels below the normal range; this relationship was absent when using a cutoff of 20 as the MELD risk score's indicator of the severity of hepatic status. Serum T3 levels exhibited a negative connection with the degree of ascites and the existence of bleeding varices, both of which are indications of cirrhosis severity. According to the viral etiology of cirrhosis (HBV/HCV), however, no appreciable difference was found. It has been demonstrated that liver disease-like symptoms, such as increased aspartate amino transferase and myxoedema ascites, are linked to hypothyroidism. [9,10] Patients having a history of treated or active hypothyroidism were therefore not included in this investigation. Patients with a history of alcohol use were also excluded because it is believed that alcohol is harmful for the thyroid gland parenchyma [11]. This study additionally looked at the relationship between the MELD score and thyroid function tests in addition to the Child-Pugh score. By grouping the patients into under normal/normal range T3 groups and determining the relationship between T3 and the severity of the liver illness, we also attempted to explore the reduction in serum T3 levels in cirrhotic patients in connection to the severity of liver damage. Along with all other bodily cells, thyroxine and tri-iodothyronine affect hepatic function through controlling the basal metabolic rate of hepatocytes. By metabolizing hormones, the liver also controls the levels of T3 and T4 in the blood, producing a controlled endocrine action. [6] Type 1 and type 3 deiodinases are the primary enzymes of the iodothyronine seleno-deiodinase enzyme system that function in the liver and are in charge of producing T3 extrathyroidally and inactivating thyroid hormones, respectively.12-14. Total T3 levels have likely dropped as deiodinase1 activity in the livers of cirrhotic patients has decreased. [2,6,13] However, a recent rise in rT3 values [16,17] linked to sick euthyroid syndrome is attributable to elements preventing rT3 to rT2 conversion, which were not present in our study. [6,18]

More than 99% of the lipophilic thyroid hormones in plasma are attached to albumin, thyroxine-binding prealbumin and thyroxine-binding globulin. A decreased blood total T3 after hepatocyte damage is justified by the liver's participation in the synthesis of these proteins; a negative connection between thyroxine-binding globulin and Child-Pugh score is noted. As a result, a lower serum T3 level is linked to a higher Child-Pugh score. [19,20] Although serum T3 levels have been reported to have changed, serum TSH and T4 levels have reportedly remained stable [2,3,6,15,20]. This suggests adaptive processes by which the body lowers basal metabolic rate to minimize caloric requirements while keeping the patient euthyroid. Additionally, decreased basal metabolic rates within hepatocytes and the ensuing maintenance of liver function and total body protein storage are attributed to lower total serum T3. [6]

Subclinical hypothyroidism was effective in experimental investigations on rats for both preventing future liver damage and causing established fibrosis in induced liver fibrosis to regress. [21] There is additional evidence to support the idea that hypothyroid individuals typically have greater liver function than euthyroid

controls. [22] Additionally, Oren et al. demonstrated that patients with euthyroid cirrhosis may benefit from a managed hypothyroidism. [23]

These studies, however, may point to a defense mechanism in the body whereby a decrease in the level of T3 that circulates helps to protect the liver from additional fibrosis and aids in healing the damage that has already been done. Although hepatitis C is reportedly more closely linked to hypothyroidism than hepatitis B [20,23], our findings of no significant correlation between hepatitis type and serum level of thyroid hormones were in line with those of Zietz et al [19].

Conclusion

Our findings support the findings of prior studies that blood T3 concentration is a reliable predictor of hepatic function. Regarding the cause of viral hepatitis, thyroid hormones showed no difference.

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