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To Investigate the Thyroid Function Profile in Individuals with Chronic Liver Illness and Determine its Association with the Child-Pugh Score

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Abstract

Background: The relationship between thyroid hormones and liver function is intricate and may be seen in both healthy and diseased states. The liver, in conjunction with the thyroid gland, has a crucial function in the conversion of inactive Thyroxine (T4) into active Triiodothyronine (T3). In cirrhosis of the liver, the most often seen thyroid hormone profile is characterized by low levels of total T3 and free T3. This is primarily due to decreased activity of deiodinase type 1 and an increased conversion to reverse Triiodothyronine (rT3). The aim is to investigate the thyroid function profile in individuals with chronic liver illness and determine its association with the Child-Pugh score. **Material and Methods:** The study group comprised patients over the age of 18, of any gender, who had evidence of chronic liver disease (CLD) and provided informed consent to participate. Following the evaluation of eligible patients based on specific inclusion and exclusion criteria, we obtained a sample size of 120 patients. The individuals were categorized based on the child Pugh score system after a clinical evaluation and investigations according to a predetermined working proforma. Measurements of serum TSH, FT3, and FT4 levels were conducted for all patients. TSH was quantified using a Sandwich chemiluminescent immunoassay (CLIA), whilst FT3 and FT4 were quantified using a competitive CLIA. **Results:** The CTP score was computed for all 120 patients, revealing that 22 (18.33%) patients were classified as CTP class A, 45 (37.5%) patients had a CTP score corresponding to class B, and the highest number, 53 (44.17%) patients, fell into CTP class C. The mean CTP score was computed and determined to be 9.57±2.25. A strong positive correlation was seen between CTP class and TSH (μIU/mL) values ($p<0.001$). The mean (SD) TSH values for CTP class A, B, and C were 2.51±0.65, 4.03±0.87, and 6.03±1.12, respectively. There was a strong negative correlation between CTP class and FT3 (pg/ml) values ($p<0.001$). The mean (SD) FT3 values for CTP class A, B, and C were 3.53±0.64, 2.63±0.45, and 2.31±0.33, respectively. There was a strong negative correlation between CTP class and FT4 (ng/ml) values ($p<0.001$). The mean (SD) values for CTP class A, B, and C were 1.51±0.47, 1.11±0.33, and 0.92±0.26, respectively. An analysis was conducted to determine the association between the thyroid profile (TSH, FT3, FT4) and the child Pugh score. The Pearson correlation scores were computed and found to be 0.81, -0.47, and 0.38 for TSH, FT3, and FT4, respectively. The p-values for all three variables were less than 0.001. **Conclusion:** Our findings indicate that the levels of S. TSH rose in correlation with the severity of chronic liver illness, as determined by the CTP score. Conversely, the levels of FT3 and FT4 reduced in correlation with the severity of liver disease, as determined by the CTP score. Therefore, thyroid hormone levels might be regarded as an indicator of the extent of liver dysfunction and the prognosis in individuals with chronic liver disease (CLD).

Keywords: Chronic liver disease, CTP score, TSH, FT3, FT4.

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Introduction

Liver cirrhosis is a leading cause of illness and death globally, and its incidence has risen by 74.53% between 1990 and 2017.[1,2] In 2017, it caused 1.32 million fatalities, making it the 11th most common cause of death and the 15th most common cause of illness. It is categorized in clinical terms as either "compensated" or "decompensated". Ascites is the most common first symptom.[3] The avoidable factors include the intake of alcohol, viral hepatitis, and non-alcoholic fatty liver disease. In simple terms, the thyroid hormones help regulate the body's metabolism and temperature balance. They do this by attaching to thyroid hormone receptors, which are crucial for cell specialization throughout growth and development.[4] The liver plays a vital role in the peripheral conversion of tetraiodothyronine (T4) to tri-iodothyronine (T3) by the action of the type 1 deiodinase enzyme. This process is critical for the metabolism of thyroid hormones.[5] The Type I deiodinase enzyme, which is mostly found in the liver, is responsible for synthesizing around 30% to 40% of T3 hormone outside of the thyroid gland. It catalyzes the conversion of T4 to T3 by the process of 5' and 5 deiodination. The most common thyroid hormone abnormalities seen in persons with cirrhosis are elevated levels of TSH, decreased levels of free T3, and increased amounts of reverse T3. When T4 is converted into T3, the level of free T4 is the first to exhibit these anomalies, making it clinically significant to assess. The reduced activity of the type 1 deiodinase enzyme leads to a reduction in the conversion of T4 to T3, which is the main cause of these abnormalities.[6] Therefore, individuals with liver cirrhosis often have hypothyroidism and low T3 syndrome. As a result, the levels of T3 and T4 decrease because the liver does not convert them properly and the liver cells do not absorb them well. The drop in T4 levels is most likely due to either the presence of peripheral-binding inhibitors or a deficiency in the production of thyroid-binding globulin (TBG).[7] Acute liver illness and primary biliary cirrhosis may lead to elevated levels of T4, TBG, and acute phase proteins. An study of many studies found that lower levels of free T3 (fT3) and free T4 (fT4) were strongly linked to an increased risk of liver cirrhosis. Conversely, higher levels of TSH were positively correlated with the risk of liver cirrhosis.[8]

Thyroid disorder may disrupt liver function, whereas liver illness affects the metabolism of thyroid hormones. There is an intricate connection between the thyroid and liver in both normal and pathological conditions. The liver has a crucial physiological function in the activation and deactivation, transportation, and metabolism of thyroid hormones. Therefore, any malfunction of the thyroid gland may lead to a decline in liver function, while any liver illness can affect the metabolism and levels of thyroid hormones in the blood.[9] The liver and kidneys play a significant role in regulating the levels of thyroid hormones and their byproducts in the bloodstream. Therefore, the proper functioning of these organs is crucial for the normal and effective functioning of thyroid hormones.[10] Several scoring systems have been used to evaluate the prognosis of individuals with chronic liver disease (CLD), including the Child Turcotte Pugh (CTP) score and the model for end stage liver disease (MELD) score. Child and Turcotte first introduced the Child-Pugh score as a means of assessing the surgical risk in patients having portosystemic shunt surgery for variceal hemorrhage. The score included the following parameters: ascites, nutritional state, total bilirubin, hepatic encephalopathy (HE), and albumin. Pugh et al proposed a change by replacing the assessment of clinical nutrition status with the measurement of prothrombin time. The point ranges for CTP class A are 5-6 points, for CTP class B are 7-9 points, and for CTP class C are 10-15 points.[11-13] This research aims to investigate the thyroid function profile in individuals with chronic liver disease (CLD) and its relationship with the child Pugh score.

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Material and Methods

This analytical cross-sectional research was undertaken in the department of General Medicine of a hospital, after ethical approval from the ethical board. The study group comprised patients over the age of 18, of any gender, who had evidence of chronic liver disease (CLD) and provided informed consent to participate. Pregnant women, individuals with known thyroid disorders, those with a history of thyroid or major neck surgery, patients taking medications that affect thyroid function (such as dopamine, levodopa, bromocriptine, steroids, or amiodarone), individuals with sepsis, and those who declined to participate were excluded from the study. Following the evaluation of eligible patients based on specific inclusion and exclusion criteria, we obtained a sample size of 120 patients. These patients then received a comprehensive assessment of their medical history and a complete clinical examination, after providing written informed permission. The individuals were categorized based on the child Pugh score system after a clinical evaluation and investigations according to a predetermined working proforma. Measurements of serum TSH, FT3, and FT4 levels were conducted for all patients. TSH was quantified using a Sandwich chemiluminescent immunoassay (CLIA), whilst FT3 and FT4 were quantified using a competitive CLIA.

Statistical Analysis

The data was analyzed using SPSS version 24.0. The continuous variables were represented by their means and standard deviations. Percentages were used to represent categorical variables. Statistical tests of significance were used to compare variables. A statistical association between variables was deemed significant if the p-value was below 0.05.

Results

Out of the total of 120 patients, 96 (80%) were male and 24 (20%) were female. The average (standard deviation) age of all patients was 46.34±3.47 years, ranging from 24 to 71 years. Among the 120 patients with CLD, the majority (61.67%) had alcoholic liver disease as the cause, followed by 15.83% with hepatitis B, 14.17% with hepatitis C, and 8.33% with other causes [Table 1].

Table 1: Demographic Parameter of the Participants

Demographic parameter	Number	Percentage
Gender		
Male	96	80
Female	24	20
Age		
Below 25	3	2.5
25-35	17	14.17
35-45	50	41.67
45-55	39	32.5
Above 55	11	9.17
Mean Age		

Table 2: Aetiology of Liver Disease

Aetiology of liver disease	Number	Percentage
Alcohol	74	61.67
Hepatitis B	19	15.83
Hepatitis C	17	14.17
Others	10	8.33

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Out of the total number of patients, 63 (52.5%) did not have any hepatic encephalopathy (grade 0). On the other hand, 8 (6.67%) patients had grade I HE, 30 (25%) patients had grade II HE, 11 (9.17%) patients had grade III HE, and 6 (5%) patients had grade IV HE.
Among the 120 patients, 43 (35.83%) had no ascites, 25 (20.83%) had mild ascites, 31 (25.83%) had moderate ascites, and 21 (17.50%) had severe ascites.
The mean International Normalized Ratio (INR) of prothrombin time was determined to be 2.25, with a standard deviation (SD) of 0.74. The INR range was 1.11-5.14. The average serum bilirubin level was determined to be 3.41 mg/dl, with a standard deviation of 1.21. The spectrum of S. bilirubin ranged from 0.51 to 21.04. The mean serum albumin concentration was determined to be 3.11 grams per deciliter, with a standard deviation of 0.43. The S. bilirubin levels ranged from 1.57 to 4.32.

Table 3: Grade of Hepatic Encephalopathy

	Number	**Percentage**
Grade of hepatic encephalopathy		
0	63	52.5
I	8	6.67
II	30	25
III	11	9.17
IV	6	5
Ascites		
No	43	35.83
Mild	25	20.83
Moderate	31	25.83
Severe	21	17.5

The CTP score was computed for all 120 patients, revealing that 22 (18.33%) patients were classified as CTP class A, 45 (37.5%) patients had a CTP score corresponding to class B, and the highest number, 53 (44.17%) patients, fell into CTP class C. The mean CTP score was computed and determined to be 9.57±2.25. A strong positive correlation was seen between CTP class and TSH (µIU/mL) values ($p<0.001$). The mean (SD) TSH values for CTP class A, B, and C were 2.51±0.65, 4.03±0.87, and 6.03±1.12, respectively. There was a strong negative correlation between CTP class and FT3 (pg/ml) values ($p<0.001$). The mean (SD) FT3 values for CTP class A, B, and C were 3.53±0.64, 2.63±0.45, and 2.31±0.33, respectively. There was a strong negative correlation between CTP class and FT4 (ng/ml) values ($p<0.001$). The mean (SD) values for CTP class A, B, and C were 1.51±0.47, 1.11±0.33, and 0.92±0.26, respectively [Table 4].

Table 4: Association between thyroid hormones and CTP

	CTP A	**CTP B**	**CTP C**	**r**	**P value**
TSH (µIU/mL)	2.51±0.65	4.03±0.87	6.03±1.12	0.81	0.001
FT3 (pg/ml)	3.53±0.64	2.63±0.45	2.31±0.33	-0.47	0.001
FT4 (ng/ml)	1.51±0.47	1.11±0.33	0.92±0.26	0.38	0.001

An analysis was conducted to determine the association between the thyroid profile (TSH, FT3, FT4) and the child Pugh score. The Pearson correlation scores were computed and found to be 0.81, -0.47, and 0.38 for TSH, FT3, and FT4, respectively. The p-values for all three variables were less than 0.001. Subgroup analysis was conducted on all CTP classes to compare the levels of serum TSH, FT3, and FT4 values among patients with diverse

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etiologies of chronic liver disease (CLD), including alcohol-related, hepatitis B-related, hepatitis C-related, and unknown etiology. No significant correlation was seen between any cause of chronic liver disease (CLD) and levels of serum thyroid-stimulating hormone (S.TSH), free triiodothyronine (FT3), and free thyroxine (FT4).

Discussion

Patients with higher Child-Pugh scores had lower levels of mean total T4 and free T3. Upon evaluating the disparity in average thyroid hormone levels, it was noted that there was a notable difference in the average T4 and free T3 levels across the three kid pugh classes, which indicate the severity of liver illness. This discovery indicates a correlation between the average T4 and free T3 levels across the different Child-Pugh groups. However, there was no statistical correlation seen between T3, free T4, and TSH levels across the kid pugh groups. Multiple studies have been conducted to examine the levels of thyroid hormones in individuals with chronic liver disease (CLD) and cirrhosis. Agha et colleagues discovered a substantial drop in the average blood levels of T3, FT3, and FT4 in individuals with cirrhosis. However, there was no significant change seen in the levels of serum T4 and TSH.[14] Sanul et al demonstrated a substantial drop in the average blood concentration of T3 and the T3 / T4 ratio in individuals with cirrhosis ($p<0.01$). However, there was no significant alteration seen in serum T4 and TSH levels.[15] In their investigation, Mansour-Ghanaei et al. discovered a negative association between child-Pugh scores and total serum T3 level ($r=-0.453$, $p<0.001$).[16]

Vincken et al found a substantial decrease in fT3 and fT4 levels in patients with cirrhosis compared to healthy individuals ($p=0.001$ and 0.002, respectively). There was no significant statistical difference in TSH levels between the two groups.[17] In their study, Hong-Ling et al discovered that the chronic hepatitis group had substantially lower levels of FT3 (2.79±0.71 vs. 4.43±0.75 pmol/L, $p<0.001$) and TSH [0.618 (0.186-1.185) vs. 1.800 (1.570-2.590) mIU/L, $p<0.001$], and higher levels of FT4 (19.51±6.26 vs. 14.47±2.19 pmol/L, $p<0.001$) compared to the control group.[18] Liu et colleagues discovered that the levels of free triiodothyronine (FT3) and free thyroxine (FT4) in the liver cirrhosis group were significantly lower than those in the control group ($p<0.001$). Additionally, the levels of thyroid-stimulating hormone (TSH) in the liver cirrhosis group were significantly greater than those in the control group ($p<0.001$).[19]

Prior research has consistently shown a reduction in blood levels of FT3 and FT4, accompanied by an elevation in serum TSH levels, in individuals suffering from chronic hepatitis and cirrhosis. Several investigations have shown that when liver failure becomes more severe, there is a reduction in FT3 levels and an increase in serum TSH levels.

The findings of our investigation indicated a strong positive association ($r=0.81$, $p<0.001$) between serum TSH values and CTP score. Additionally, we observed substantial negative correlations between serum FT3 levels and CTP scores ($r=-0.47$, $p<0.001$), as well as between serum FT4 levels and CTP scores ($r=-0.38$, $p<0.001$).

There was a strong positive correlation between CTP class and TSH (μIU/mL) values ($p<0.001$). The mean (SD) TSH levels for CTP class A, B, and C were 2.51±0.65, 4.03±0.87, and 6.03±1.12, respectively. A strong negative correlation was observed between CTP class and FT3 (pg/ml) values ($p<0.001$). The mean (SD) FT3 values for CTP class A, B, and C were 3.53±0.64, 2.63±0.45, and 2.31±0.33, respectively. A strong negative correlation was observed between CTP class and FT4 (ng/ml) values ($p<0.001$). The mean (SD) FT4 values for CTP class A, B, and C were 1.51±0.47, 1.11±0.33, and 0.92±0.26, respectively.

Our investigation demonstrated a positive correlation between the degree of liver dysfunction, as measured by CTP scores, and an increase in S.TSH values. Additionally, we observed a negative correlation between the severity of chronic liver disease (CLD) and

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serum FT3 and FT4 values, indicating a reduction in these values with increasing severity of CLD. A drawback of the current investigation was its restriction to a solitary tertiary health center. Future research endeavors may use a multi-centred approach, including a greater sample size. Patients may be monitored to see changes in thyroid hormone levels when liver function and CTP score fluctuate in patients with chronic liver disease (CLD) over time.

Conclusion

Our investigation revealed a positive correlation between the degree of thyroid dysfunction and the severity of liver malfunction in individuals with chronic liver disease (CLD). Our findings indicate that the levels of S. TSH rose in correlation with the severity of chronic liver illness, as determined by the CTP score. Conversely, the levels of FT3 and FT4 reduced in correlation with the severity of liver disease, as determined by the CTP score. Therefore, thyroid hormone levels might be regarded as an indicator of the extent of liver dysfunction and the prognosis in individuals with chronic liver disease (CLD).

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