Original Article

The Relationship between Thyroid Hormones Levels and Liver Cirrhosis Prognosis Criteria and Complications: a Cross-Sectional Study

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ABSTRACT

Background:
The impact of thyroid function on the prognosis and complications of liver cirrhosis remains unclear. Therefore, this study aimed to determine the relationship between thyroid hormones and cirrhosis prognosis and complications.

Materials and Methods:
This cross-sectional study was conducted from March 2021 to March 2022 at Imam Khomeini Hospital in Iran. A total of 100 patients with cirrhosis, aged 18 to 80 years, were recruited. The questionnaire designed for collecting data included patients' demographics, laboratory data, and criteria for cirrhosis progression.

Results:
The study revealed a significant correlation between the model for end-stage liver disease (MELD) and free tri-iodothyronine (FT3) (P=0.019). For each unit increase in FT3, the MELD score is expected to decrease by approximately 2.268 units. In men, there was a correlation between MELD and FT3 (P=0.033). Additionally, in women, there was a correlation between MELD and FT4 (P=0.03). MELD had a significant correlation with ascites and hepatic encephalopathy. Furthermore, a significant relationship was found between FT3 and ascites and esophageal varices. Results of analysis of the relationship between FT3 and MELD components revealed a significant correlation between FT3 and bilirubin (P=0.001). Moreover, an inverse relationship was found between thyroid stimulating hormone (TSH) and international normalized ratio (INR) (P=0.03). High FT3 levels were found to be 15 times more frequent in Child-Pugh A and B patients compared to Child-Pugh C patients.

Conclusion:
FT3 is correlated with the MELD score and complications of cirrhosis. The value of FT3 can serve as a prognostic criterion. It is recommended to monitor thyroid levels in patients with cirrhosis and provide treatment if any disorder is detected.

Keywords: Liver cirrhosis, Thyroid hormones, Prognosis

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INTRODUCTION

Chronic liver damage can lead to a condition known as cirrhosis, which is characterized by regenerative nodules and diffuse liver fibrosis (1,2). Cirrhosis is the end stage of chronic liver disease (3). It is often the result of various diseases, such as alcohol consumption, non-alcoholic fatty liver disease (NAFLD), hepatitis viruses, and autoimmune diseases (4,5). Progression of cirrhosis includes asymptomatic stages such as compensated cirrhosis or decompensated stages, which could cause several complications, including ascites, gastroesophageal variceal hemorrhage, and hepatic encephalopathy (6,7). Child-Pugh and model for end-stage liver disease (MELD) scores are commonly used to evaluate the outcome of cirrhosis (8,9). In severe cases, cirrhosis can lead to liver failure and death, which is a significant burden on global public health due to the high mortality and morbidity rates (10,11).

There is an important relationship between the liver and the thyroid gland. So, disorders of these two organs interact with each other (12,13). Thyroid hormones are crucial for cell growth, differentiation, and metabolism in the body, especially in the liver, and they have effects on liver fat homeostasis and bilirubin metabolism (14). Hypothyroidism increases the risk of diseases such as NAFLD. A low level of free tri-iodothyronine (FT3) is considered an independent criterion for mortality in diseases like myocardial infarction, renal disease, and NAFLD (15,16). On the other hand, the liver has a vital impact on the metabolism of thyroid hormones like synthesis, excretion, peripheral deiodination, and thyroid-binding globulin (TBG) production (17). A cirrhotic liver reduces the conversion of thyroxine (T4) to tri-iodothyronine (T3), due to the decrease in the activity of the deiodinase enzyme in the liver (18).

Until now, many studies have investigated the relationship between chronic liver disease and thyroid hormone levels. However, limited data on patients with cirrhosis are available, especially on the prognosis of cirrhosis and complications such as esophageal varices, hepatic encephalopathy, and ascites (19). Therefore, we assessed the relationship between FT3 and MELD, Child-Pugh score, hepatic encephalopathy, ascites, and esophageal varices. If there was an association with MELD score, we would conduct further analysis to specify which component of MELD score had an association with FT3.

MATERIALS AND METHODS

Study design

This was a cross-sectional study conducted from March 2021 to 2022 in Imam Khomeini Hospital Complex, Gastroenterology and Liver Disease Clinic, Tehran, Iran.

Data collection

A researcher designed a questionnaire to collect data for this study. The questionnaire includes patients' demographics as well as laboratory data such as thyroid hormone levels, liver enzymes, and criteria for liver disease progression.

Cirrhosis diagnosis

Cirrhosis was verified by two gastroenterologists by evaluating complete blood count (CBC), liver function test, and radiological testing like ultrasonography.

In the case of incomplete information in the patients' medical records, we contacted the patients by phone. The study was approved by the Ethics Committee of the Hospital. The ethics code is IR.TUMS.IKHC.REC.1400.165. Informed consent was obtained from the study participants.

Participants

All patients with cirrhosis aged 18 to 80 years were eligible to be recruited for this study. Patients were excluded from the study if they were younger than 18 years old or older than 80 years old, had a history of thyroid malignancy, had taken thyroid hormone medications in the last 3 months, had taken anti-thyroid medications in the last 3 months, or had a history of simultaneous severe disease in other organs.

Statistical analysis

The data were analyzed using IBM SPSS software version 26. The qualitative data were analyzed using the Chi-square test and the quantitative data were analyzed using the t test. The Pearson correlation test was used to measure the strength and direction of the linear relationship between MELD score and thyroid stimulating hormone (TSH), T3, T4, FT3, and FT4. Multilinear regression is a statistical modelling technique used to understand the relationship between MELD score and TSH, T3, T4, FT3, and FT4.

RESULTS

100 subjects were included in the study; 63 were men, and 37 were women. The mean age of the patients was 48 years. The age, MELD score, and laboratory data details are described in table 1.

26 subjects had Child-Pugh A, 46 had Child-Pugh B, and 28 had Child-Pugh C. 35 participants had no history of ascites, 27 had a history of mild ascites, and 38 had a history of moderate to severe ascites leading to paracentesis. 39 patients had no history of varices, 18 had grade F1 varices, and 43 had grade F2 to F3 varices leading to band ligation. 66 patients had no history of encephalopathy, 22 had a history of grade 1 and 2 of encephalopathy, and 12 had a history of grade 3 and 4 of encephalopathy.

Table 1. Demographics, laboratory data, and MELD score in patients

Variables	Mean±standard deviation
Age	48.05±13.284
MELD	14.26±5.080
TSH (mIU/L)	2.78742±1.739656
T3 (nmol/L)	1.3130±0.56467
T4 (µg/dL)	7.9349±2.35014
FT3 (pg/mL)	2.5978±0.61616
FT4 (ng/dL)	1.0932±0.25799
Bilirubin (mg/dL)	2.9000±2.55887
international normalized ratio (INR)	1.4074±0.37615
Albumin (g/dL)	3.6321±0.62981
Creatinine (mg/dL)	1.1509±1.29087
Na (meq/dL)	138.742±3.2861

The study showed a significant correlation between MELD and FT3 (P=0.019), whereas the correlations between MELD and FT4, total T3, total T4, and TSH were not significant. Based on sex classification, there was a significant correlation between MELD and FT3 in men, with (P=0.0330). In women, there was a correlation between MELD and FT4 (P=0.03). Other hormones had no significant correlation with MELD in men and women (table 2). Subjects were divided into two groups based on the MELD score: those over 16 who were candidates for liver transplantation and those under 16. Among thyroid hormones, there was a significant correlation only between FT3 and MELD (P=0.03).

Table 2. Association between thyroid hormones and MELD in the total population, men, and women

Thyroid hormones	P value		
	All (n=100)	Male (n=63)	Female (n=37)
FT3	0.019	0.033	0.301
FT4	0.140	0.680	0.030
T4	0.246	0.824	0.060
T3	0.990	0.093	0.069
TSH	0.658	0.593	0.863

P<0.05 was considered statistically significant

Among the components of MELD, a strong correlation was found between FT3 and bilirubin (P=0.001). There was also an inverse relationship between TSH and international normalized ratio (INR) (P=0.03) (table 3). For MELD score and FT3, a statistically significant small negative correlation was found (r=-0.292, P=0.019). This means that as the MELD score increases, there is a tendency for FT3 levels to decrease, albeit to a modest degree.

Table 3. Relationship between thyroid hormones and components of MELD

	Bilirubin	INR	Albumin	Creatinine	MELD
FT3	0.001	0.615	0.088	0.387	0.019
TSH	0.423	0.030	0.572	0.647	0.658
T3	0.089	0.917	0.492	0.379	0.990
T4	0.200	0.651	0.260	0.110	0.246
FT4	0.851	0.951	0.972	0.480	0.140

P value<0.05 was considered statistically significant

There was a significant relationship between FT3 and ascites and varices, but no significant relationship with encephalopathy (table 4).

Table 4. Association between FT3 and cirrhosis complications

Cirrhosis complications	P value
Ascites	0.033
Varices	0.046
Encephalopathy	0.248

P <0.05 was considered statistically significant

MELD was significantly correlated with ascites and hepatic encephalopathy, but there was no significant association with varices (table 5).

Table 5. Association between MELD and cirrhosis complications

cirrhosis complications	Subgroups*	P value
Ascites	None and moderate to severe	0.003
Varices	None and F2 to F3	0.170
Hepatic encephalopathy	None and grades 3 to 4	0.002

P <0.05 was considered statistically significant. *subgroups whose means were compared and their association with MELD analyzed.

There was no significant association between thyroid hormones and Child-Pugh. For more assessment of the association between FT3 and Child-Pugh, FT3 was first divided into four categories. In Child A, the group with a low FT3 was the lowest, and in Child C, the group with a high FT3 was the lowest. When the association between Child-Pugh and FT3 was assessed based on age and sex adjustment, high FT3 was 15 times more common in Child-Pugh A and B than in Child C.

Table 6. Multiple linear regression to predict MELD score

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Overall model	18.187	4.190		4.341	<0.001	9.772	26.603
TSH	-0.204	0.384	-0.072	-0.531	0.598	-0.976	0.568
T3	0.804	1.465	0.088	0.549	0.586	-2.138	3.746
T4	-0.361	0.321	-0.155	-1.125	0.266	-1.007	0.284
FT3	-2.268	1.078	-0.330	-2.104	0.040	-4.433	-0.103
FT4	3.404	2.751	0.169	1.238	0.222	-2.121	8.930

The multilinear regression analysis (table 6) suggests that there is a statistically significant negative relationship between FT3 and the MELD score. Specifically, for each unit increase in FT3, the MELD score is expected to decrease by approximately 2.268 units after controlling for the other independent variables in the model. On the other hand, the P values for the other independent variables (TSH, T3, T4, and FT4) were greater than 0.05. This indicates that there was insufficient evidence to suggest a significant relationship between these variables and the MELD score in this analysis. Figure 1 demonstrates the relationship between MELD scores and FT3.

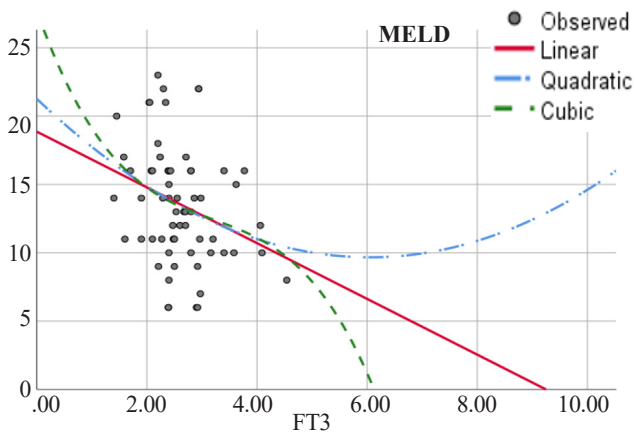

Figure 1. Linear relationship between MELD scores and FT3, then MELD scores = 18.86 – 2.04 (FT3) level, R2=0.085, P=0.019.

DISCUSSION

Thyroid hormone levels are associated with chronic disease, with both overproduction and underproduction contributing to the development of chronic diseases. They have effects on several metabolic pathways in the body, including insulin resistance, lipid metabolism, and inflammation. The exact mechanism by which thyroid hormones affect chronic diseases has still not been studied (20,21).

Previous studies have shown that thyroid dysfunction is associated with liver disease, lung and kidney malignancies, severe systemic diseases, fasting, malnutrition, trauma, and acute infections (22). Individuals with hypothyroidism and hyperthyroidism are at higher risk for developing cardiovascular disease. This could be the result of high blood pressure and inflammation (23). Subclinical hypothyroidism, particularly in individuals with TSH > 10 mIU/L, is associated with an increased risk of coronary heart disease and mortality (24). The regulation of glucose metabolism is a crucial function of the thyroid hormone, and its imbalances contribute to the development of metabolic disorders such as type 2 diabetes (25). During pregnancy, thyroid dysfunction and autoantibodies can predict pregnancy complications and maternal morbidity in later life (26). Additionally, both hyperthyroidism and hypothyroidism have been associated with an increased risk of fractures, particularly in the hip and spine (27). Dysregulation of the thyroid-brain axis may also contribute to mood disorders in individuals with thyroid disorders (28). Hypothyroidism can lead to neuropsychiatric symptoms, such as depression, anxiety, and cognitive impairment. However, appropriate treatment can reverse these symptoms (29).

Patients suffering from chronic liver disease commonly experience thyroid dysfunction, which poses a higher risk of morbidity and mortality (17,30). Additionally, subclinical hypothyroidism raises the risk of NAFLD, while higher levels of thyroid-stimulating hormone lower the risk of NAFLD. Hence, conducting thyroid function tests can help identify individuals who are at risk of developing NAFLD (31). Moreover, Borzio and colleagues evaluated thyroid function tests in chronic liver disease. In this study, the severity of liver dysfunction was correlated with T3 (32).

Cirrhosis is the end stage of chronic liver disease, and cirrhotic portal hypertension results in the progression of decompensation complications like ascites, varices bleeding, and hepatic encephalopathy (33). According to pieces of evidence, thyroid disorders are related to chronic liver disorders, including cirrhosis (30). Because of the impact of thyroid hormones on the liver and vice versa, this study was performed in patients with cirrhosis to evaluate the relationship between FT3 and cirrhosis prognosis.

In this study, there was an inverse correlation between MELD and FT3 hormone levels. Considering that the MELD scoring system is one of the scoring systems designed to predict mortality in patients with cirrhosis, FT3 can be used as a prognostic factor. Bilirubin was determined as the reason for the relationship between FT3 and MELD, and there was a strong inverse relationship between FT3 and bilirubin. The lowest number of patients with low FT3 in Child-Pugh class A and the lowest number of patients with high FT3 in Child-Pugh class C were present.

In our study, there was an inverse relationship between FT3 and complications of portal hypertension, including ascites and esophageal varices, but there was no significant relationship with hepatic encephalopathy. While Bajaj and co-workers showed that at the time of admission to the hospital, if there were low levels of thyroxine and certain metabolites linked to the gut microbiota, it could indicate the possibility of developing advanced hepatic encephalopathy in the future, regardless of other clinical biomarkers. Thus, it could be used as a prognosis index (34). The study performed by Huang and colleagues in 2020 showed that a low FT3 level was related to the poor prognosis of cirrhotic portal hypertension, which is in accordance with our results (15).

Rink and others demonstrated that a low T3 level was a sensitive factor for predicting cirrhosis prognosis (35). According to Walfish's study in 1979, there is a relationship between the severity of liver dysfunction in alcoholic liver disease and low admission serum T3 and FT3 levels when accompanied by normal serum T4, FT4, and TSH levels. In addition, these factors are associated with increased mortality risk (36). Results of the study done in 1989 by F Agha and colleagues demonstrated that changes in T3 and FT3 were related to cirrhosis progression and could be used as a prognostic value (19). Sikarwar and others found a significant relationship between Child-Pugh score and levels of T3, T4, and TSH. Among these hormones, total T3 is believed to be the most accurate predictor of the severity of cirrhosis (37). Punekar and colleagues claimed that there was a negative correlation between FT3 and FT4 levels, but a positive correlation between TSH levels and several markers such as leukocyte counts, bilirubin levels, liver enzymes, globulin levels, blood clotting time, urea levels, creatinine levels, Child–Turcotte–Pugh score, and MELD score in cirrhosis. The most common abnormality observed in these patients was low T3 (low FT3) syndrome, which occurred in 41% of cases overall, 50% of cases with HE in cirrhosis, and 32% of non-survivors (38).

Several studies have found that patients with cirrhosis commonly exhibit abnormal levels of serum thyroid hormones, specifically low levels of serum T3, high levels of rT3, and normal levels of TSH. Multiple factors could contribute to these abnormalities, including changes in the plasma levels of thyroid-binding proteins, alterations in the binding of T4 and T3 to their carrier proteins, impaired clearance of reverse T3 (rT3) by the liver, and reduced conversion of T4 to T3 outside the thyroid gland. In patients with cirrhosis, extensive inflammation and fibrosis in the liver inhibit type 1 (D1) deiodinase enzymes, leading to decreased conversion of T4 to T3. As a result, most of the remaining T4 is converted into rT3, resulting in increased rT3 levels, while type 2 (D2) deiodinase enzymes remain active (39). This is the first time this issue has been analyzed at a referral hospital. Although the subjects were from one center, this may be indicative of the Iranian population because it is a referral center.

Further studies are recommended to compare thyroid hormone tests between patients with cirrhosis and patients with acute complications of cirrhosis. In addition, further studies are recommended to evaluate the score improvement of these prognostic systems when thyroid abnormalities are corrected. Classification of cirrhosis into categories based on etiology to analyze the relationship between thyroid function and cirrhosis prognosis is suggested.

CONCLUSION

This study has shown the association of FT3 with MELD score and the complications of cirrhosis. FT3 can be used as a prognostic criterion. It is recommended to check thyroid levels in patients with cirrhosis; if there is a disorder, treatment must be given.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this work.

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