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Thyroid Function in Liver Cirrhosis: Is It affected? A Case Control Study

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ABSTRACT

Background: Cirrhosis of the liver may be compensated with no obvious complications or decompensated which accompanied by ascites, hematemesis, or renal impairment. Liver disease affects thyroid hormone metabolism, thyroid problems can impair liver functions, and several systemic diseases can affect both organs.

Objectives: The aim of the current work was to study level of thyroid hormones in patients with liver cirrhosis and to evaluate the significance of thyroid hormone level and severity of liver cirrhosis.

Patients and methods: This case control study included a total of 25 cirrhotic patients and equal number of age and gender matched controls, attending at Hepatology and Gastroenterology unit, Department of Internal Medicine, Faculty of Medicine, Mansoura University. Thyroid hormones were measured and correlated with child Pugh score, model for end-stage liver disease (MELD) score and degree of hepatic encephalopathy (HE).

Results: The mean age of the liver cirrhotic patients was54.08±15.14 and for control subjects was 49.32±13.02. There was positive correlation between TSH level, Child score and MELD score (P value <0.001). Also, there was positive correlation between TSH level and degree of hepatic encephalopathy (p value <0.001).

Conclusions: Thyroid dysfunction is well established as liver cirrhosis progressed. So, it could be concluded that thyroid levels could be utilized as a prognostic indicator in cirrhotic patients.

Keywords: liver cirrhosis; thyroid dysfunction; TSH level; degree of encephalopathy; Child Pugh score.

INTRODUCTION

Either "compensated" or "decompensated" liver cirrhosis could be described. Cirrhosis that has become decompensated refers to it being accompanied by one or more of the following signs: ascites, hepatic encephalopathy (HE), jaundice or bleeding varices. Decompensation also includes hyponatremia, the hepatorenal syndrome and spontaneous bacterial peritonitis, however in these individuals, ascites always develops first. None of these traits are present in compensated cirrhotic patients [(1).]

Thyroxine (T4) and triiodothyronine, two related hormones, are produced by the thyroid gland (T3). By acting on the receptors α and β, these hormones control cell growth and keep thermogenic and metabolic equilibrium in adults. T4 is secreted by the thyroid gland in excess of T3 by around 20 times. The plasma proteins to which T3 and T4 are linked are thyroxine-binding globulin, transthyretin (formerly known as thyroxine binding prealbumin), and albumin [(2).]

Tetraiodothyronine (T4) is peripherally converted to T3 by Type 1 deiodinase, which gives the liver a crucial role in the metabolism of these thyroid hormones [(3, 4)] The primary enzyme in the liver, type I deiodinase, converts both the 5'- and 5-deiodination of T4 to T3, which accounts for 30% to 40% of additional thyroidal synthesis of T3.

In addition, the liver participates in the conjugation, excretion, and production of thyroid binding globulin [(3, 5)]. T4 and T3 impact hepatic function via controlling the baseline metabolic rate of all cells, including hepatocytes. The liver is in charge of metabolizing THS and managing their endocrine effects throughout the body. Liver disease affects thyroid hormone metabolism, thyroid disorders can impair liver function, and several systemic illnesses can have an impact on both organs [(6).]

Thyroid and liver diseases have clinical and laboratory associations. Overall abnormal thyroid hormone levels were seen in 39.1 % patients with liver cirrhosis [(7).] Chronic liver disease patients may have type of hyperthyroidism, thyroiditis, or hypothyroidism. Also, patients having hyperthyroidism or subacute thyroiditis or could have deteriorations in liver function tests, and when thyroid condition improve, these abnormalities improve [(6).] Also,

Studies that are currently available showed that variations in total and free T3 concentrations at the plasma level of thyroid hormones are typically associated with the severity of hepatic dysfunction. However, no study explicitly linked liver cirrhosis severity to FT4 and thyroid-stimulating hormone (TSH) levels. Serum T4 levels are either stable or marginally low. Serum TSH levels, however, continue to be normal or slightly elevated. Because of how well-established these fluctuations in thyroid hormone levels are, several researchers have pushed for their use as a sensitive indicator of liver function [(8, 9).]

The aim of this work was to study level of thyroid hormones (TSH, Free T3 and Free T4) in patients with liver cirrhosis and to evaluate the significance of thyroid hormone level and severity of liver cirrhosis.

PATIENTS AND METHODS

This case control study included a total of 25 cirrhotic patients and equal number of age and gender matched controls, attending at Hepatology and Gastroenterology unit, Department of Internal Medicine, Faculty of

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Medicine, Mansoura University. This study was conducted over 14 months study period from March 2020 to May 2021.

Liver cirrhosis was evidenced by history taking, clinically based, ultrasound, presence of liver dysfunction (decrease albumin level, increased bilirubin level or prolonged prothrombin time). Evidence of varices was done by endoscope and of hepatic encephalopathy clinically.

Exclusion criteria: Subjects < 18 or > 80 years, known thyroid disorders without cirrhosis of the liver, patients with a history of cancer, organ failure, chemotherapy, or radiation therapy, and people with active infections like muscle and bone disease, chronic kidney disease, diabetes, nephrotic syndrome, or people taking thyroid-interfering medications like propylthiouracil, levothyroxine, iodine, carbimazole, beta-blockers and amiodarone.

Based on the case history, the clinical examination, and biochemical tests (albumin, ALT, AST, bilirubin, INR, and CBC) liver cirrhosis was diagnosed, 4 patients underwent endoscopic evaluation (endoscopic band ligation was done to 1 case, 2 cases with small esophageal varices and the last with no varices) and ultrasound evaluations to all cases. Also control cases underwent biochemical testing and ultrasound evaluation to exclude liver disease. The Child-Pugh grading scale and model for end-stage liver disease were used to assess the severity of the liver injury in patients with cirrhosis (MELD). There were four grades of encephalopathy, ranging from Grade 1 to Grade 4. All cases and controls underwent thyroid function testing (TFT) [(10)] by electrochemiluminescence immunoassay.

Ethical Consideration:

The research was ethically approved by Scientific Research Ethics Commission, Mansoura University (Institutional Research Board "IRB" number R.21.10.1495). Written informed consent of all the participants (or the participants' parents) was obtained with keeping the patients records confidential in all stages of the study. This work has been carried out in accordance with Clinical trials Register NCT05250401. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical methods

The machine was supplied with data, and IBM SPSS Corp.'s 2013. release was used to analyze it. Version 22.0 of IBM SPSS Statistics for Windows. IBM Corp., Armonk, New York Number and percentage were used to describe qualitative data. After determining the normality of the quantitative data using the Kolmogrov-Smirnov test, the median (interquartile range), mean, and standard deviation were used to summarize the data. The acquired results' significance was assessed at the (0.05) level.

RESULTS

The Present Study Included 50 cases, 25 Patients with liver cirrhosis (15 males and 10 females with mean age 54.08±15.14 and 25 control (15 males and 10 females with mean age 49.32±13.02 admitted at Specialized Medical hospital, Mansoura University. The clinical and demographic of data are shown in (table 1): high TSH level (p value < 0.001), low free T3 (p value 0.001) and low free T4 (p value 0.04) were found in cases of cirrhosis compared with control.

Table (1): demographic and clinical characteristics of the studied groups

	Cases (N=25)	Control (N=25)	Test of significance
Age/years	54.08±15.14	49.32±13.02	t=1.19 P=0.239
ALT (U/L)	25(15-48.5)	16(13.5-23)	Z=1.97 P=0.048*
AST (U/L)	54(32.5-91.5)	20(15.5-26.5)	Z=4.84 P<0.001*
Bilirubin (mg/dl)	2.8(2.09-6.6)	0.6(0.5-0.8)	Z=5.57 P<0.001*
Albumin (g/dl)	2.56±0.48	3.95±0.67	t=5.33 p<0.001*
Creatinine (mg/dL)	1.0(0.7-1.35)	0.7(0.6-0.9)	Z=1.81 P=0.071
TSH (µIU/ml)	6.8 (2.68-8.35)	1.6(0.675-2.50)	Z=4.59 P<0.001*
FT3 (pg/ml)	2.50 (0.715-3.75)	4.9(2.72-6.4)	Z=3.25 P=0.001 *
FT4 (ng/dl)	1.3(0.51-2.05)	1.22(0.975-1.75)	Z=2.06 P=0.04*

Results were nonparametric.

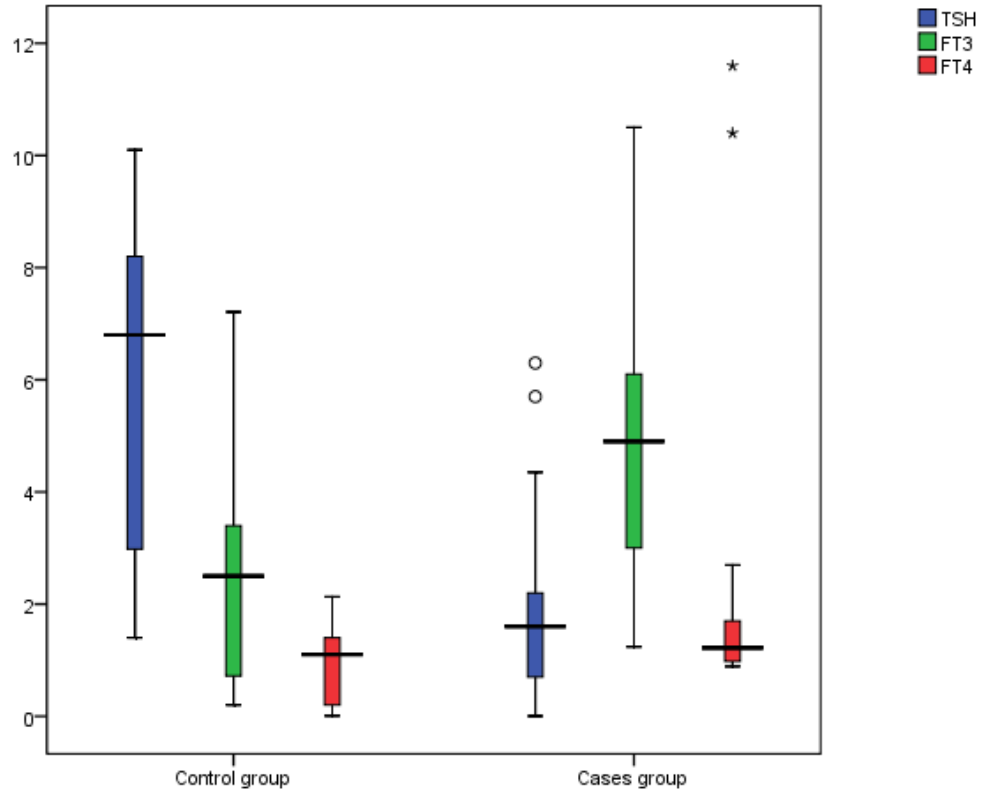

Figure (1): Box & Whisker plot of median thyroid profile among studied groups.

Correlation of Child score and MELD score with thyroid profile among studied cases.

According to Child Pugh classification, patients were classified as 1patient with child A (4%), 12 patients with Child B (48%), 12 patients with child C (48%). According to MELD score 16 patients (64%) with MELD above 20 and 9 patients (36%) with MELD below 20, There was positive correlation between TSH level, Child, and MELD score (p value <0.001). TSH level increases as long as MELD score or Child score progress. Also, there was negative correlation between free T3 level and Child score (p value 0.005) and MELD score (p value 0.012). Free T3 level decreases as long as MELD score or Child score progress.

Table (2): correlation of MELD, Child score with thyroid profile among studied cases.

		MELD	Child score
TSH	R	0.941	0.902
	P	<0.001*	<0.001*
FT3	R	-0.493	-.545
	P	0.012*	0.005*
FT4	R	-0.321	-.429
	P	0.118	.032*

Table (3): Thyroid profile distribution among child scores

	Child Score		**Test of Significance**
	A&B N=13	C N=12	
TSH	1.4(0.57-3.09)	2.0(0.88-7.48)	Z=0. 190 P=0.849
FT3	4.2(3.25-5.2)	3.16(1.1-6.53)	Z=1.42 P=0.157
FT4	1.40(0.91-2.06)	1.165(0.14-2.09)	Z=1.55 P=0.121

Results were nonparametric.

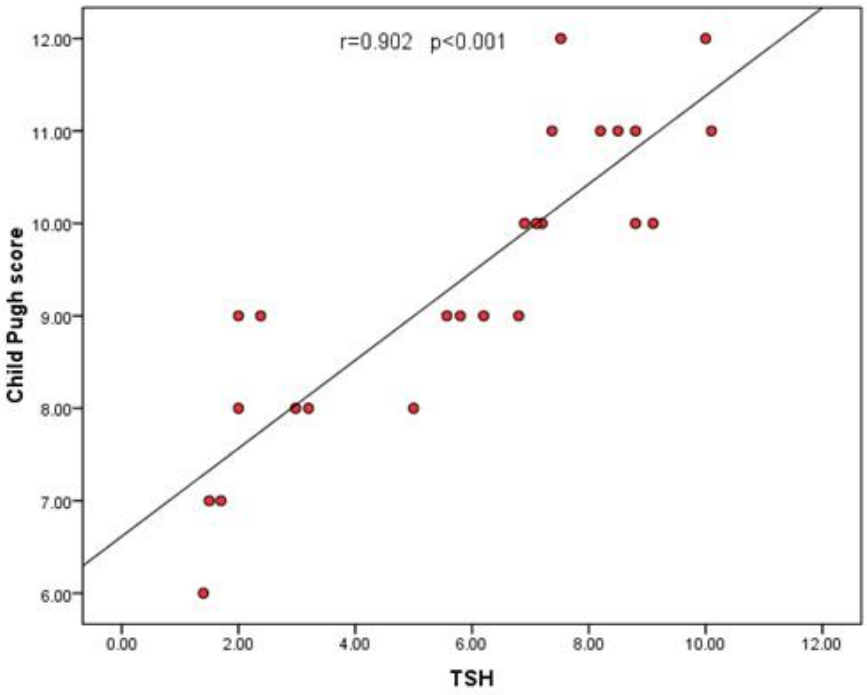

Figure (2): Correlation between TSH level and Child Pugh score

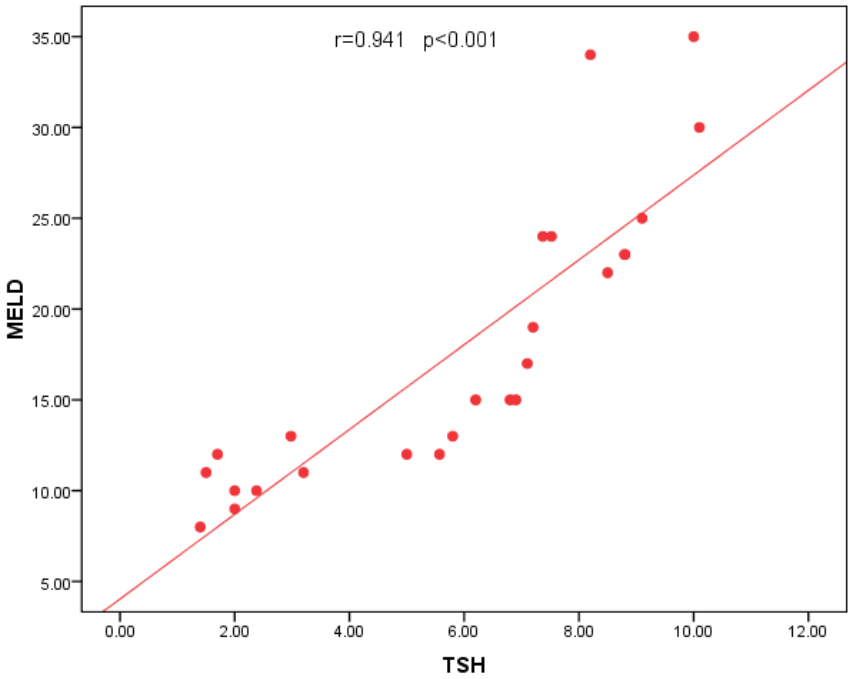

Figure (3): Correlation between TSH level and MELD score

Table (4) shows **Correlation between thyroid profile and encephalopathy.**

5 patients (20 %) presented with hepatic encephalopathy (1 patient with G1, 3 patients with G2 and 1 patient with G4). There was positive correlation between TSH level and degree of encephalopathy. TSH median in group with no encephalopathy 5.69 (2.095-7.18) and the group with encephalopathy 9.1 (8.65-10.05) with p value P=0.001*

Table (4): Correlation between thyroid profile and encephalopathy.

		Encephalopathy
TSH	R	0.680
	P	<0.001*
FT3	R	-0.300
	P	0.146
FT4	R	-0.367
	P	0.071

Table (5): thyroid profile distribution according to incidence of encephalopathy among studied cases.

	Encephalopathy		Test of sig.
	None N=20	Present N=5	
TSH	5.69(2.095-7.18)	9.1(8.65-10.05)	Z=3.29 P=0.001*
FT3	2.91(1.10-3.93)	0.71(0.36-2.70)	Z=1.43 P=0.153
FT4	1.255(0.230-1.85)	0.40 (0.0875-0.90)	Z=1.73 P=0.083

Results were nonparametric.

Adverse events

The study was completed without any significant negative outcomes.

DISCUSSION

Out of 25 cases and according to Child Pugh classification, 12 patients (48%) were classified as child C, 12 patients (48%) were classified as child B, only 1 patient (4%) was classified as Child A. This demonstrated that most patients presented with advanced liver cirrhosis.

As illustrated in Table 1, the most common abnormality seen was low FT3 median 2.5 (0.715 -3.75) in cases with liver cirrhosis and 4.9 (2.72-6.4) in controlled group (P=0.001).

As illustrated in Table 3, When FT3 mean serum levels in Child A, B, and C were compared, Child C had the lowest levels 3.16 (1.1-6.53), followed by Child A and B group 4.2 (3.25-5.2).

Numerous processes have been suggested as the causes of the decreased free T3 levels in patients with liver cirrhosis and their inverse correlation with the severity of liver injury. The most prevalent theory claims that ill euthyroid syndrome, or low free T3, is primarily caused by a lack of peripheral deiodination [11-17]. In patients with liver cirrhosis, poor diet may contribute to a reduction in free T3 [15]. Interleukin-6 (IL-6) and other cytokine release may also be to blame for sick euthyroid syndrome. Additionally, alcohol consumption has been directly linked to decreased hepatic deiodinase activity [18]. This may explain elevated TSH levels and decreased free T3 and T4 levels in cirrhotic patients with refractory ascites [19].

When 20 was chosen as a threshold to distinguish between more severe and less severe disease, there was a strong inverse association between the MELD score and free T3 levels in our study (p=0.013), and this was also corroborated by Tas A et al [13]. In our study, 2 groups were determined based on MELD scoring; 36% (n = 9) of patients fit into group 1 with a MELD score >20 and 64% (n = 16) into group 2 with a MELD score 20.

A correlation between the prevalence of low FT3 and the severity of liver disease and HE grades was also found [Table 4]. These findings supported those of El-Feki and Abdalla [20].

Low FT3 levels were the most common finding across numerous trials. The levels of FT3 were noticeably low in patients with liver cirrhosis in Deepika et al., [21] D'costa and Dhume, [22] Saleem and Wadea, [23] Kayacetin et al., [5] El-Sawy and Tawfi, [24] etc.

In our study, the prevalence of hypothyroidism was 16%. According to Joeimon et al. [25] and our study, the prevalence of hypothyroidism was 21.6 %, however Patira et al. [26] found that the prevalence of subclinical hypothyroidism was 62%. The sample size, sex, age and regional variations in thyroid illness could all play a role in this disparity.

In instances of liver cirrhosis, the median TSH level was 6.8 (2.68-8.35), compared to 1.6 (0.675-2.50) in the control group (P 0.001).

According to the study's findings [Table 1], all cirrhotic patients had statistically significantly higher TSH levels than healthy controls (P 0.0001) did. El Feki and Abdalla [20] reached similar conclusions. According to Punekar et al and [27,28] research, patients with

cirrhosis had considerably higher TSH levels. Our findings agree with those of these investigations.

As shown in Table 3, when comparing the mean serum levels of TSH in Child A, B, and C, it was discovered that Child C had the highest levels, 2.0(0.88-7.48), while Child A, B group had the lowest levels, 1.4. (0.57-3.09).

Contrary to what was observed by earlier investigations, we discovered a strong association between TSH and MELD score (p0.001) [11, 13, 14].

Compared to cirrhosis without HE, cirrhosis with HE had a higher TSH of 9.1(8.65-10.05) (P 0.0001), although the level of FT4 (P 0.083) was not statistically significant.

Our investigation also demonstrated that hepatic encephalopathy and low free T3 levels were not substantially associated. This finding is Contrary to Arafa M et al. [29], who found lower T3 levels in individuals with hepatic encephalopathy, none of the participants in our study had any clinical symptoms or signs that were suggestive of hypothyroidism. Therefore, although the thyroid profile was different in patients with liver cirrhosis, clinical euthyroidism is almost always preserved [11].

CONCLUSIONS

When compared to healthy controls, liver cirrhosis cases showed significantly lower mean FT3 and FT4 levels and significantly higher mean TSH levels. Low FT3 levels also associated with the Child Pugh score or MELD, a measure of the severity of liver disease.

Thyroid dysfunction is well established as liver cirrhosis progressed. So, it could be concluded that thyroid levels could be utilized as a prognostic indicator in cirrhotic patients.

Low FT3 and high TSH may be used to predict mortality in patients with liver cirrhosis, even though death in cirrhotic patients is multifactorial. Low FT3 may be used to predict patients for underlying HE.

Trial registration: Clinical trials Register
NCT05250401

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