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ORIGINAL ARTICLE

Thyroid Dysfunction in Cirrhotic Patients and its Correlation With Severity of Liver Disease

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Abstract

Background: **Liver disease modifies thyroid hormone metabolism, as well as several systemic disorders can affect both the thyroid as well as the liver.**

Aim and objectives: **To assess the thyroid derangements in cirrhotic individuals and their relationship to the severity of the liver disease.**

Patients and methods: **This case-control study included 150 cases of liver cirrhosis and 50 healthy controls recruited from ward and outpatient clinics at Al-Hussin and Bab Al Sharia Hospitals, Department of Hepatology, Gastroenterology, and Infectious Diseases between January 2023 and June 2023.**

Results: **We found that cirrhotic patients have higher thyroid stimulating hormone (TSH) level, lower free triiodothyronine (FT3) and free thyroxine (FT4), and higher thyroid volume compared with control group. The lowest level of FT3 was among the Child C group, followed by the Child B group, the lowest level of FT4 found was in the Child C group followed by the Child B group, The highest level of TSH was found in the Child C group followed by the Child B group. There was a statistically significant negative correlation between FT3 and FT4 level and model for end-stage liver disease score, between thyroid volume by ultrasound and post cibum% and albumin level, and between TSH level and post cibum% and albumin level.**

Conclusion: **Thyroid measures have the potential to be exploited as a prognostic indicator in cirrhotic individuals. A low FT3 level can be employed in predicting which patients are more prone to develop hepatic encephalopathy.**

Keywords: Liver cirrhosis, Hepatic encephalopathy, Thyroid-stimulating hormone, Thyroxine

1. Introduction

Cirrhosis of the liver is the final phase of chronic liver disease and is characterized by fibrosis and architectural distortion of the liver along with the production of regenerating nodules. It is a major contributor to morbidity and mortality rates all around the world. More than 160 million people suffered from cirrhosis in 2017 around the world, and more than 0.8 million patients with cirrhosis died every year. Among the etiologies, more than half of the patients were attributed to hepatitis B (HBV) and hepatitis C virus (HCV).[1]

Cirrhosis is classified as 'compensated' or 'decompensated' in the medical field. Decompensated cirrhosis is marked by ascites, jaundice, hepatorenal syndrome, or variceal bleeding, hepatic encephalopathy, as well as is an immediate decline in liver function in an individual with cirrhosis.[2]

Thyroid hormones, including thyroxin (T4) as well as triiodothyronine (T3), are synthesized by the thyroid gland. These hormones are responsible for cell differentiation, thermogenesis, along with metabolic regulation in adults. The amount of T4 produced is bigger than that of T3.[3]

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Transthyretin, albumin, as well as thyroxine-binding globulin are just few of the plasma proteins that are connected to both hormones. Type-1 deiodinase, found in the liver, converts tetraiodothyronine to T3, then T3 is transported to the peripheral nervous system.[4]

Thyroid hormones are metabolized in the liver because Type 1 deiodinase converts tetraiodothyronine to T3 in the periphery. The liver also has a role in the creation of thyroid-binding globulin and conjugation and excretion of thyroid hormone.[5,6]

Liver disease modifies thyroid hormone metabolism, as well as several systemic disorders can affect both the thyroid and the liver.[7]

This research aimed to assess the thyroid derangements in cirrhotic individuals and their relationship to the severity of liver disease.

2. Patients and methods

This case-control study included 150 cases of liver cirrhosis and 50 healthy controls. All our patients were recruited from the ward and outpatient clinic at Al-Hussin and Bab Al Sharia Hospitals, Department of Hepatology, gastroenterology and infectious diseases. From the period between January 2023 and June 2023.

2.1. Inclusion criteria

Age more than 18 years male and female, known and established cases of liver cirrhosis by clinical, radiological (abdominal ultrasound), and biochemical studies, and patients who were willing to be part of the study after signing written informed consent.

2.2. Exclusion criteria

Known cases of thyroid disorder, patient with a history of organ failure apart from liver cirrhosis, patients with cancer, under radio or chemotherapy, patients with an active infections such as bone and muscle disease, chronic diseases that affect thyroid function as cardiac patients, diabetes, chronic kidney disease and patients with nephrotic syndrome and a patient who had not met up inclusion criteria were excluded from this study.

2.3. Methods

Patients were subjected to the following: history taking, clinical examination, general examination (jaundice, spider telangiectasia, palmer erythema, gynecomastia, cachexia, and other stigmata of chronic liver disease), local abdominal examination, local thyroid examination, laboratory investigations, full thyroid profile, abdominal ultrasound, Neck ultrasound, upper gastrointestinal tract endoscopy and assessment of severity of liver cirrhosis by the scoring system.

2.4. Modified child-pugh score

According to the modified Child–Pugh score, the patients with liver cirrhosis were divided into three groups: group A: patients with liver cirrhosis (Child A, 50 persons), group B: patients with liver cirrhosis (Child B, 50 persons) and group C: patients with liver cirrhosis (Child C, 50 persons).

2.5. Model of end-stage liver disease (MELD) score

The present version of the model of end-stage liver disease (MELD) score incorporated three objective variables, including total bilirubin, creatinine, and international normalized ratio (INR). Currently, it has been used to rank the priority of liver transplantation candidates.[8]

$$3.8*\mathrm{Ln}\,[\text{serum bilirubin}\,(\text{mg}/\text{dL})] + 11.2*\ln[\text{INR}] + 9.57*\mathrm{Ln}[\text{serum creatinine}\,(\text{mg}/\text{dL})] + 6.4$$

Where: LN-natural logarithm, INR-international normalized ratio

Modified MELD score included the MELD-Na score which was calculated by

$$\text{MELD} + 1.59 \times (135 - \text{Na}\,(\text{mmol/l})).$$[9]

2.6. Measurement of serum TSH, FT3 and FT4 level

Full thyroid profile included: serum TSH, FT3 and FT4 level were estimated by enzyme linked immunosorbent assay (ELISA) kits.

The following kits were used: TSH (catalogue number: BDTS03, company: Bioactivia diagnostic, country: Germany). FT3 (catalogue number: BDTE06, company: Bioactivia diagnostic, country: Germany). And FT4 (catalogue number: BDFT05, company: Bioactivia diagnostic, country: Germany).

2.7. Statistical methods

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons

between quantitative variables were done using the nonparametric Kruskal–Wallis and Mann–Whitney tests.[10] For comparing categorical data, χ^2 test was performed. Exact test was used instead when the expected frequency is less than 5.[11] Correlations between quantitative variables were done using Spearman correlation coefficient.[12] *P* values less than 0.05 were considered as statistically significant.

3. Results

Table 1.

This table displayed that there was no statistically significant variance in the age, sex and BMI among cirrhosis cases and healthy controls (Table 2).

This table exposed that there was a statistically significant higher liver enzyme, higher bilirubin level, prolonged PT, international normalized ratio (INR), higher TSH and larger thyroid volume and lower albumin, Hb, and platelets in the cirrhosis patients than healthy controls, while there was no statistically significant as regard Urea, creatinine, HB and TLC (Table 3).

This table displayed that there was a statistically significant lower FT3, FT4, and higher TSH, larger thyroid volume, higher heterogeneity, vascularity, and nodule formation in subjects with encephalopathy (Table 4).

This table presented that the lowest level of FT3 were between the Child C group 2.10 ± 1.76, followed by the Child B group 2.75 ± 2.58, while the Child A group was 3.57 ± 2.64, the lowest level of FT4 observed were in the Child C group 0.92 ± 0.52, followed by the Child B group 1.09 ± 0.56, while the Child A group was 1.25 ± 0.61. The highest TSH was found in the Child C group 7.55 ± 4.24, followed by the Child B group 6.03 ± 3.80, while the Child A group was 5.16 ± 3.42. There was a statistically significant lower FT3, FT4 and larger thyroid volume, higher heterogeneity, vascularity, and nodule formation in patients with Child C than Child B and A (Fig. 1, Table 5).

This table showed a statistically significant negative correlation between FT3 and FT4 level as regards MELD score. TSH level has a statistically significant negative correlation with PC% and albumin level and a statistically significant positive correlation with alanine transaminase (ALT), and aspartate aminotransferase (AST). Total and direct bilirubin, PT, INR, and MELD score. Thyroid

Table 1. Comparison of demographic data of the groups under the study.

	Cirrhosis $N = 150$		Normal control $N = 50$		Independent student *t* test/chi square test	
	Mean	SD	Mean	SD	t	*P* value
Age	45.32	9.69	48.22	10.33	−1.746	0.085
BMI	33.35	5.89	34.65	6.61	−1.239	0.219
Sex	*N* (%)		*N* (%)		χ^2	*P* value
Male	100 (66.7)		33 (66)		0.007	0.931
Female	50 (33.3)		17 (34)			

BMI, body mass index.

Table 2. Comparison of laboratory data and thyroid volume of the studied groups.

	Cirrhosis $N = 150$		Normal control $N = 50$		Independent student *t* test	
	Mean	SD	Mean	SD	t	*P* value
AST (IU)	64.69	6.74	27.04	6.40	35.535	0.000
ALT (IU)	78.28	5.05	40.12	6.10	39.922	0.000
T.bilirubin mg/dl	3.74	0.57	0.69	0.23	53.842	0.000
D.bilirubin mg/dl	1.87	0.28	0.38	0.13	51	0.000
PT sec	25.83	3.42	22.01	4.07	5.97	0.000
PC%	68.74	10.75	92.96	5.62	−20.454	0.000
INR	1.68	0.22	1.26	0.24	11.02	0.000
Albumin (mg/dl)	2.75	0.43	3.31	0.29	−10.359	0.000
Urea (mg/dl)	53.69	21.21	54.69	22.75	−0.274	0.785
Createnine (mg/dl)	1.20	0.18	1.19	0.17	0.182	0.856
HB (gm/dl)	10.52	2.75	12.28	2.37	−2.888	0.042
TLC $\times 10^3/mm^3$	4.63	0.97	4.53	0.89	0.675	0.501
platelets $\times 10^3/mm^3$	119.65	64.71	400.07	668.42	−5.091	0.000
FT4 (ng/dl)	1.09	0.58	1.28	0.27	−2.234	0.027
FT3 (pmol/l)	2.81	2.42	3.59	0.77	−2.238	0.026
TSH (mIU/l)	6.25	3.94	3.01	1.46	8.475	0.000
Thyroid volume by US (mm^3)	19.90	10.16	15.16	2.97	5.105	0.000

ALT, alanine transaminase; AST, aspartate aminotransferase; FT3, free triiodothyronine; FT4, free thyroxine; HB, hemoglobin; INR, international normalized ratio; PC, post cibum; PT, prothrombin time; TLC, total leucocyte count; TSH, thyroid stimulating hormone.

Table 3. Thyroid function and thyroid US in relation to encephalopathy of the studied groups.

	Encephalopathy $N = 31$		No encephalopathy $N = 119$		Independent student t test/chi square test	
	Mean	SD	Mean	SD	T	P value
FT4 (ng/dl)	0.87	0.67	1.14	0.54	−2.129	0.039
FT3 (pool/l)	2.08	3.17	2.30	2.15	−1.523	0.136
TSH (mIU/l)	8.75	4.30	5.59	3.57	3.766	0.001
Thyroid volume by US (mm^3)	30.06	9.56	17.26	8.54	6.789	0.0001
	N (%)		N (%)		χ^2	P value
FT4						
High	2 (6.5)		5 (4.2)		22.402	0.0001
Low	21 (67.7)		29 (24.4)			
Average	8 (25.8)		85 (71.4)			
FT3						
High	2 (19.4)		5 (4.2)		19.981	0.0001
Low	23 (74.2)		38 (31.9)			
Average	6 (19.4)		76 (63.9)			
TSH						
High	25 (80.6)		53 (44.5)		13.013	0.001
Low	1 (3.2)		6 (5)			
Average	5 (16.1)		60 (50.4)			
Enlarged thyroid	25 (80.6)		18 (15.1)		51.628	0.00001
Heterogeneity	18 (58.1)		11 (9.2)		37.586	0.00001
High vascularity	21 (67.7)		12 (10.1)		47.645	0.00001
Thyroid nodule	15 (48.4)		11 (9.2)		26.298	0.00001

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

Table 4. Thyroid function and thyroid US in relation to CHILD scale of the studied patients.

	Child A $N = 50$		Child B $N = 50$		Child C $N = 50$		One way ANOVA test/chi square test	
	Mean	SD	Mean	SD	Mean	SD	t	P value
FT4 (ng/dl)	1.25	0.61	1.09	0.56	0.92	0.52	4.338	0.015
FT3 (pmol/l)	3.57	2.64	2.75	2.58	2.10	1.76	4.869	0.009
TSH (mIU/l)	5.16	3.42	6.03	3.80	7.55	4.24	4.969	0.008
Thyroid volume by US (mm^3)	15.92	6.69	19.88	8.83	23.91	12.59	8.532	0.0001
	N (%)		N (%)				χ^2	P value
FT4								
High	3 (6)		3 (6)		1 (2)		10.917	0.028
Low	10 (20)		15 (30)		25 (50)			
Average	37 (74)		32 (64)		24 (48)			
FT3								
High	3 (6)		3 (6)		1 (2)		12.380	0.015
Low	12 (24)		20 (40)		29 (58)			
Average	35 (70)		27 (54)		20 (40)			
TSH								
High	21 (42)		25 (50)		32 (64)		8.464	0.076
Low	5 (10)		1 (2)		1 (2)			
Average	24 (48)		24 (48)		17 (34)			
Enlarged thyroid	8 (16)		12 (24)		23 (46)		11.802	0.003
Heterogeneity	2 (4)		9 (18)		18 (36)		16.500	0.00001
High vascularity	6 (12)		9 (18)		18 (36)		9.091	0.011
Thyroid nodule	2 (4)		6 (12)		18 (36)		19.355	0.00001

FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

volume by the US has a statistically significant negative association with PC% and albumin level and a statistically significant positive correlation with age, ALT, and AST. Total and direct bilirubin, PT, INR in addition to MELD score.

4. Discussion

Our study showed that 150 cases with liver cirrhosis (100 males and 50 women with an average age 45.32 ± 9.69 and 50 control (33 men and 17

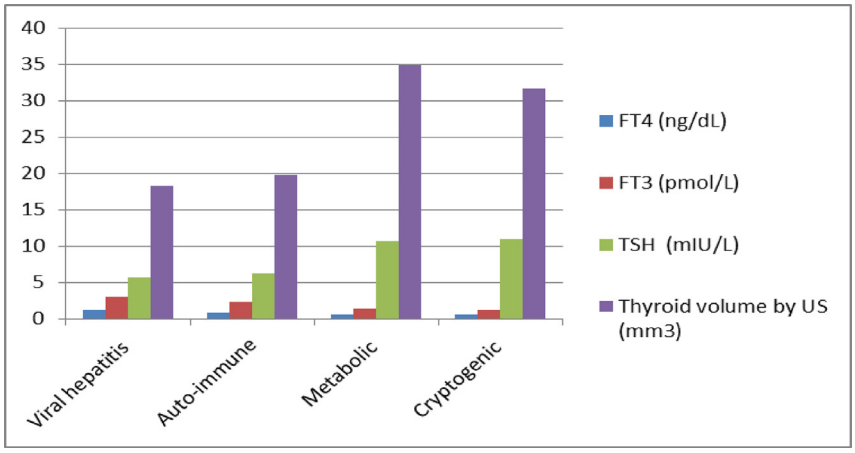

Fig. 1. Thyroid function and thyroid ultrasound in relation to CHILD scale of the studied patients. FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid stimulating hormone.

Table 5. Association amongst thyroid function and thyroid volume by ultrasound and clinical and laboratory data of the studied population.

	FT4		FT3		TSH		Thyroid volume	
	r	*P* value	R	*P* value	R	*P* value	r	*P* value
Age	−0.060	0.398	−0.049	0.492	−0.120	0.09	0.147	0.037
BMI	−0.048	0.496	−0.037	0.601	−0.013	0.852	0.033	0.642
ALT	−0.130	0.067	−0.136	0.054	0.446	0.0001	0.306	0.0001
AST	−0.046	0.515	−0.030	0.673	0.403	0.0001	0.212	0.003
T.bil	−0.027	0.701	−0.072	0.313	0.344	0.0001	0.228	0.001
D.bil	−0.030	0.675	−0.070	0.326	0.341	0.0001	0.229	0.001
PT	−0.097	0.171	0.013	0.856	0.257	0.0001	0.201	0.004
PC	0.023	0.748	−0.054	0.448	−0.359	0.0001	−0.229	0.001
INR	−0.084	0.235	−0.004	0.951	0.326	0.0001	0.235	0.001
Alb	0.021	0.764	−0.066	0.354	−0.290	0.0001	−0.198	0.005
MELD	−0.339	0.0001	−0.259	0.001	0.369	0.0001	0.419	0.0001

Alb, serum albumin; ALT, alanine transaminase; AST, aspartate aminotransferase; D.bil, direct bilirubin; INR, international normalized ratio; MELD, end-stage liver disease. PC, post cibum; PT, prothrombin time; T.bil, total bilirubin.

women with average age 48.22 ± 10.33) and there was no statistically significant variance in the age, sex and BMI amongst cirrhosis cases and healthy controls.

Our findings agreed with those of Gameel as well as Elbialy, whose objectives were to investigate the level of thyroid hormones in individuals with liver cirrhosis along with determining the importance of thyroid hormone level in connection with the degree of liver cirrhosis. They had a total of 50 cases, with 25 patients suffering from liver cirrhosis 15 men and 10 women with an average age of 54.08 ± 15.14 as well as 25 controls, with 15 males and 10 females having a mean age of 49.32 ± 13.02. Regarding age, they discovered that there was not a statistically significant distinction ($P = 0.239$) amongst any of the groups that were investigated.[11]

Regarding clinical presentation of our studied patients, we detected that 69.3% of cases with cirrhosis presented with ascites, 62% presented with GIT bleeding, 53.3% presented by LL edema, 40% presented by jaundice, and 16.7% presented by encephalopathy.[13]

Our results agreed with Mansour–Ghanaei *et al.* who aimed to assess thyroid hormones profile in individuals with hepatic cirrhosis because of chronic HBV and HCV infections. Clinical comorbidities in the included individuals were ascites ($n = 59$), encephalopathy ($n = 31$) and bleeding varices ($n = 21$).[14]

Our study showed that the mean TSH levels in cases and controls 6.25 ± 3.94 and 3.01 ± 1.46, AST 64.69 ± 6.74 and 27.04 ± 6.40, PT sec 25.83 ± 3.42 and 22.01 ± 4.07, INR levels 1.68 ± 0.22 and 1.26 ± 0.24, albumin levels 2.75 ± 0.43 and 3.31 ± 0.29, platelets 119.65 ± 64.71 and 400.07 ± 668.42 and thyroid volume 19.90 ± 10.16 and 15.16 ± 2.97. Also, there were statistically significant higher liver enzymes, higher bilirubin levels, prolonged PT, INR, higher TSH and larger thyroid volume, and lower albumin, Hb, and

platelets in the cirrhosis patients than healthy controls.

Our results were in concordance with Gameel and Elbialy,[13] who found that there was a statistically significant alteration amongst cirrhosis cases and healthy controls with higher liver enzymes, bilirubin level, TSH and lower albumin levels in the cirrhosis patients than healthy controls.

In the context of studying the association between this thyroid derangement and severity of liver disease we found that in 29 patients of Child C that was 58% of the individuals had low FT3, 20 patients of Child B that were 40% of patients had low FT3 and 24% of the patient with child A had low free triiodothyronine, 46% of the patient with child C had larger thyroid volume. Also, there was statistically significant lower FT3, FT4 and larger thyroid volume, higher heterogeneity, vascularity, and nodule formation in patients with Child C than Child B and A. These results may be due to the variety in patients.

And we found that the lowest level of FT3 was between the Child C group 2.10 ± 1.76, followed by the Child B group 2.75 ± 2.58, while the Child A group was 3.57 ± 2.64, the lowest level of FT4 obtained were in the Child C group 0.92 ± 0.52, followed by the Child B group 1.09 ± 0.56, while the Child A group was 1.25 ± 0.61. The highest TSH was found in the Child C group 7.55 ± 4.24, followed by the Child B group 6.03 ± 3.80, while the Child A group was 5.16 ± 3.42.

Our research concurred with the findings of Samarthana and Mamatha,[15] who found that 30 instances of Child C, which was 96% of the patients, had low FT3, 34 patients of Child B, which was 75% of the patients, and 20 cases of Child A had low FT3. Child A had normal levels of FT3 in 55% of the cases that were examined. With a *P* value of less than 0.001, they were able to demonstrate that free triiodothyronine was a sensitive marker for the severity of liver disease. This finding was statistically significant. The degree of cirrhosis progressed from Child–Pugh A to C, and the serum level of TSH began to rise over the normal range. The *P* value was 0.001, which indicated that the results were statistically significant.

Also, our outcomes displayed that there was a statistically significant negative connection between FT3 and FT4 level and MELD score. Moreover, we found that TSH level had statistically significant negative correlation with PC% and albumin level and a statistically significant positive correlation with ALT, and AST. Total in addition to direct bilirubin, PT, INR and MELD score this may be due to the small sample size.

Regarding thyroid volume by US had a statistically significant negative relationship with PC% and albumin level and a statistically significant positive correlation with age, ALT, AST, total and direct bilirubin, PT, INR and MELD scores.

Our results are consistent with Punekar *et al.*[7] who described that there was statistically significant negative association between FT3 and FT4 level and MELD score. TSH level had a statistically significant negative correlation with platelets and albumin level and TSH levels were positively associated with blood urea, ST bilirubin, total leukocyte counts, alanine transaminase, aspartate transaminase, INR, PT, serum creatinine, in addition to the severity of liver cirrhosis (MELD score).

4.1. Limitation of the study

This study was conducted on small sample size, in single center and need longer period for patients follow-up.

4.2. Conclusion

Thyroid dysfunction is more obvious and well established with progression of severity in cirrhotic patients. It is possible to draw the following conclusion: thyroid measures have the potential to be exploited as a prognostic indicator in cirrhotic individuals. Also FT3 may be used to predict patients more prone to hepatic encephalopathy.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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