Original Article

A Study of Thyroid Dysfunction in Cirrhosis of Liver and Correlation with Severity of Liver Disease

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Abstract

Introduction: Liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by Type 1 deiodinase. **Materials and Methods:** This case–control study included 100 decompensated liver cirrhosis patients (71 males and 29 females) and 100 apparently healthy controls (71 male and 29 female). Serum FT3, FT4, and thyroid-stimulating hormone (TSH) levels were measured using electrochemiluminescence immunoassay and analyses between cases versus healthy controls (Group 1) and further analyses in subgroups, cirrhosis with hepatic encephalopathy (HE) cases ($n = 38$) versus cirrhosis without HE cases (Subgroup 1), cirrhosis survivors ($n = 84$) versus cirrhosis nonsurvivors (Subgroup 2), HE survivors ($n = 23$) versus HE nonsurvivors (Subgroup 3). Results were also analyzed for severity of liver disease according to Child–Turcotte–Pugh (CTP) (Class A, B, and C), model for end-stage liver disease (MELD) score, and HE grades. **Results:** Most common etiology was alcohol (46%) and presentation was gross ascites (74%). Cirrhosis patients had statistically significant lower level of FT3 ($P < 0.0001$) and FT4 ($P < 0.0001$) but had higher level of TSH ($P < 0.0001$) compared with the controls. Cirrhosis with HE ($n = 38$) had significantly lower lever of FT3 ($P < 0.0001$) compared with cirrhosis without HE ($n = 62$), whereas there was no statistically significant difference in FT4 ($P < 0.09$) and TSH ($P < 0.60$) levels. FT3 level significantly low in HE Grade 4 patients compared with HE Grade 1 patients ($P = 0.0001$). In all cirrhotic patients, FT3 and FT4 were negatively correlated, but TSH level was positively correlated with total leukocyte counts, serum total bilirubin, aspartate transaminase, alanine transaminase, globulin, prothrombin time (PT), blood urea, serum creatinine, CTP, and MELD score. Overall, the most common abnormality seen was low T3 (low FT3) syndrome 41% (41 out of 100) in cases, 50% (19 out of 38) in cirrhosis with HE, and 32% (5 out of 16) in Non-survivors cases. **Conclusion:** The mean FT3 and FT4 levels were significantly decrease and mean TSH levels were significantly increase in liver cirrhosis patients compared to healthy controls. Level of FT3, FT4, and TSH also correlate with the severity of liver disease, level of FT3 can be used as prognostic marker for liver cirrhosis patients.

Keywords: Child–Turcotte–Pugh, FT3, FT4, hepatic encephalopathy grade, liver cirrhosis, model for end-stage liver disease score, thyroid stimulating hormone

Introduction

In clinical terms, cirrhosis is described as are either "compensated" or "decompensated." Decompensation means cirrhosis complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy (HE), or bleeding varices. Ascites is the usual first sign.[1] Hepatorenal syndrome, hyponatremia, and spontaneous bacterial peritonitis are also features of decompensation, but in these patients, ascites invariably occurs first. Compensated cirrhotic patients have none of these features.[1]

The thyroid gland produces two-related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors α and β, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. T4 is secreted from the thyroid gland in about twenty-fold excess over T3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin, transthyretin (formerly known as thyroxine binding prealbumin), and albumin.[2]

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_25_18

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How to cite this article: Punekar P, Sharma AK, Jain A. A study of thyroid dysfunction in cirrhosis of liver and correlation with severity of liver disease. Indian J Endocr Metab 2018;22:645-50.

The liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to T3 by Type 1 deiodinase.[3,4] Type I deiodinase is the major enzyme in the liver and accounts for approximately 30%–40% of extrathyroidal production of T3, it can carry out both 5'-and 5-deiodination of T4 to T3. Moreover, the liver is involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin.[3,5] T4 and T3 regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. The liver metabolizes the THS and regulates their systemic endocrine effects. Thyroid diseases may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both the organs.[6] There are clinical and laboratory associations between thyroid and liver diseases. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests, which return to normal as the thyroid condition improves.[6]

Till date, available studies showed most frequent change in plasma level of thyroid hormones is decreased total T3 and free T3 concentration which is reported to be associated with severity of hepatic dysfunction. But no study clearly mentioned FT4 and thyroid-stimulating hormone (TSH) levels with severity of liver cirrhosis. Serum T4 levels either remain normal or slightly low. However, serum TSH levels remain normal or slightly raised. These changes in thyroid hormone levels are so well established that some workers have advocated its use as a sensitive index of liver function.[7,8]

Aims and objectives

The aims of this study were:

Primary – To study thyroid hormone level (FT3, FT4, and TSH) in the liver cirrhosis patient.

Secondary – To find out the significance of thyroid hormone level and severity of cirrhosis of the liver.

Materials and Methods

Study Design

This was a case–control study.

Study population

This case–control study included 100 apparently healthy controls and 100 liver cirrhosis patients (case) from wards, outpatient department, and Intensive Care Unit in Department of Medicine with clinical, biochemical, and radiological evidence of cirrhosis of liver. All patients were subjected to medical examination as per the fixed pro forma.

Inclusion criteria

Case – Age >18–80 years male and female. Known and established cases of cirrhosis liver by clinical, radiological (ultrasound abdomen), and biochemical study. Patients who were willing to part of study after consent.

Control – Apparently healthy age- and sex-matched individuals between 18 and 80 years.

Exclusion criteria

Known cases of thyroid disorder without liver cirrhosis. Patient with history of organ failure, cancer, radio or chemotherapy and individual with active infection such as bone and muscle disease, cardiac, pancreatic (diabetes), chronic kidney disease, nephrotic syndrome, and patient who had not meet up inclusion criteria are excluded from this study. Patient using drugs that interfere with thyroid metabolism such as levothyroxine, propylthiouracil, carbimazole, iodine, amiodarone, and beta-blockers.

Study period

The study period was March 2016–August 2017.

Ethical aspects

The protocol for the study was approved by the Ethical and Research Committee. Data were collected only after patient informed and written consent.

Diagnostic tool

The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic and ultrasound findings, or liver biopsy. Liver biopsies were not performed if coma, reduced coagulability or extensive ascites was present. The functional severity of the liver injury was determined on the basis of the Child–Pugh grading system and model for end-stage liver disease (MELD). The degree of encephalopathy was defined on the basis of previously reported criteria ranked between Grade 1 and Grade 4.

Thyroid function tests (TFT)[9] was done by electrochemiluminescence immunoassay. The normal range of thyroid profile as a following: FT3 is (2.1–4.4 pg/ml), FT4 is (0.8–2.7 ng/dl), and TSH is (0.35–5.5 μIU/ml).

Statistical analysis

All the statistical analysis was performed using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp) and Microsoft Excel 2016. A statistical value <0.05 was considered as significant. The results were expressed in the form of tables. Student's *t*-test was used to compare the continued variables between two groups. The analysis of variance was used to test the significance of continued variables within groups. All values are reported as mean ± standard deviation.

Results

A total of 100 liver cirrhosis cases (71 males and 29 females) and 100 apparently healthy controls (71 male and 29 female) were included in the final analysis. The mean age was 43 ± 14 years for cases and 42 ± 15 years for controls. All cases were decompensated liver cirrhosis. During study, gross

ascites (74%) was found most common presentation and other complications were anemia (87%), thrombocytopenia (53%), coagulation abnormality (65%), HE (38%), jaundice (32%), upper gastrointestinal bleed (34%), azotemia (17%), pleural effusion (16%), sepsis (22%), shock (14%). Constipation was found in 49% patients. Alcohol was found most common etiology (46%) followed by hepatitis B (19%), hepatitis C (3%), Wilson disease (1%), and others.

Discussion

As illustrated in Table 1, the most common abnormality seen was low FT3 syndrome 41% (41 out of 100) in cases, 50% (19 out of 38) in cirrhosis with HE, and 32% (5 out of 16) in nonsurvivor group of liver cirrhosis cases. Hypothyroidism (high TSH level) was observed in 20% (20 out of 100) of decompensated liver cirrhosis patients, 26.3% (10 out of 38) in decompensated liver cirrhosis with HE, and 50% (8 out 16) in nonsurvivor cases. Nonthyroidal illness with low T4 was observed in 15% (15 out of 100) of decompensated liver cirrhosis patients, 16% (6 out of 38) in decompensated liver cirrhosis with HE, and 12% (2 out 16) in nonsurvivor group. All cirrhosis patients did not have clinical signs of hypothyroidism and their TSH levels were also in the subclinical range of hypothyroidism.

Joeimon *et al*.[10] reported the prevalence of hypothyroidism was 21.6% (similar to our study), but this prevalence was contradicts to Patira *et al*.,[11] in which prevalence of subclinical hypothyroidism was 62%. This difference may be due to sample size, age, sex, and regional variation in thyroid disease.

When we looked for individual parameter of thyroid function, the most common abnormality seen was low free T3 level (71%), low free T4 (21%), and high TSH level (20%). Mobin *et al*.[12] reported that in all decompensated cirrhotic patients (sample size n = 76), 76.3% (our study 71%) had low serum T3 levels, 14.47% (our study 21%) had low serum T4 levels, and 2.63% (our study 20%) had raised TSH levels. The results of our study for FT3 levels and FT4 levels are consistent with Mobin et al study, but contradict for TSH levels. This difference may be due to sample size ,age ,sex ,severity of liver disease and regional variation of thyroid disorders.

In several studies, the most common abnormalities of serum thyroid hormone concentration in cirrhotic patients observed were, low serum T3 level, raised rT3 level, and a normal TSH levels. There are many factors those may be responsible for these abnormalities, which includes alteration in plasma level of thyroid binding proteins, altered binding of T4 and T3 to their carrier protein, impaired hepatic clearance of reverse T3 (rT3), hyperglucagonemia, and reduced extrathyroidal conversion of T4 to T3. In cirrhotic patients, because of extensive hepatic inflammation and fibrosis, there is inhibition of Type 1 (D1) deiodinase enzymes that lead to decreased conversion of T4 to T3. Since the type 2 (D2) deiodinase enzymes remain active, now most of the T4 is converted into rT3 leading to increased rT3 levels.

As illustrated in Table 2 (Group 1), all liver cirrhosis patients (n = 100) had low FT3 ($P < 0.0001$), low FT4 ($P < 0.0001$), and high TSH ($P < 0.0001$) levels compared to apparently healthy controls (n = 100). Table 2 (Subgroup 1) also showed significantly low FT3 levels ($P < 0.0001$) in cirrhosis with HE compared to cirrhosis without HE, but level of FT4 ($P < 0.09$) and TSH ($P < 0.60$) were not statistically significant. In several studies, low FT3 levels were the most consistent finding. In Deepika *et al*.,[13] D'costa and Dhume,[14] Saleem and Wadea,[15] Kayacetin *et al*.,[5] El-Sawy and Tawfi,[16] etc., the levels of FT3 were significantly low in liver cirrhosis patients. FT3 levels were significantly low also in all cirrhotic nonsurvivors compared to all cirrhotic survivors (P = 0.005). However, there was no significant difference in cirrhosis with HE nonsurvivors compared to cirrhosis with HE survivor (P = 0.42), because mortality in cirrhotic patients is multifactorial.

The results of the present study [Table 2] showed a statistically significant decrease in FT4 levels in all cirrhotic patients compared to controls ($P < 0.0001$). In comparison of cirrhosis with HE and cirrhosis without HE, mean FT4 level were low but statistically not significant (P = 0.09). Kayacetin *et al*.[5] reported that serum levels of FT3 and total T4 were significantly lower in all cirrhotic patients with HE compared to cirrhosis without HE. Our results are consistent with this study.

The results of the present study [Table 2] showed a statistically highly significant increase in TSH levels in all cirrhosis patients compared to healthy controls ($P < 0.0001$). El-Feki and Abdalla[17] concluded the same results. Antonelli *et al*.[18] found that the level of TSH was significantly higher in patients with cirrhosis. Our results are consistent with these studies.

Increased level of TSH also statistically significant in cirrhosis nonsurvivors compared to cirrhosis survivors (Subgroup 2) and HE nonsurvivors compared to HE survivors (Subgroup 3) liver cirrhosis patients [Table 2]. Joeimon *et al*.[10] reported similar results, but Kayacetin *et al*.[5] observed no significant difference in TSH Level in liver cirrhosis patients.

As illustrated in Table 3, on comparing the mean serum levels of FT3 in Child A, B, and C, the lowest levels were among the Child C group (1.80 ± 0.53), followed by the Child B group (2.20 ± 0.55), while the Child A group was 1.9 ± 0.00. Prevalence of low FT3 also correlated with the severity of liver disease as per Child–Turcotte–Pugh (CTP), MELD score [Table 3], and HE grades [Table 4]. These results were consistent with El-Feki and Abdalla.[17]

As illustrated in Table 3, on comparing the mean serum level of FT4 between Child A, B, and C, the lowest levels found were in the Child C group (1.17 ± 0.51), followed by the Child B group (1.44 ± 0.54), while the Child A group was (0.76 ± 0.00). The mean levels FT4 was also correlated

Table 1: Incidence of thyroid dysfunction in cirrhosis of liver

Thyroid dysfunction pattern	Case (n=100)		Cirrhosis with hepatic encephalopathy (n=38)		Nonsurvivors cirrhosis cases (n=16)	
Low FT3, normal FT4, normal TSH (low T3 syndrome)	41 (41%)		19 (50%)		5 (32%)	
Low FT3, high TSH, normal FT4, (hypothyroid)	12 (12%)	20 (20%)	6 (16%)	10 (26%)	6 (38%)	8 (50%)
Low FT3, low FT4, high TSH (hypothyroid)	6 (6%)		4 (10%)		2 (12%)	
Normal FT3, normal FT4, high TSH (hypothyroid)	1 (1%)		-		-	
Low FT3, high FT4, high TSH (hypothyroid)	1 (1%)		-		-	
Low FT3, Low FT4, normal TSH (NTIS with low T4)	11 (11%)	15 (15%)	6 (16%)	6 (16%)	1 (6%)	2 (12%)
Low FT4, normal FT3, normal TSH (NTIS with low T4)	4 (4%)		-		1 (6%)	
Normal FT3, normal FT4, low TSH (hyperthyroid)	1 (1%)		-		-	
Normal FT3, normal FT4, normal TSH (euthyroid)	23 (23%)		3 (8%)		1 (6%)	
Total	100		38		16	

FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone, NTIS: Nonthyroidal illness syndrome

Table 2: Comparison of thyroid functions in various groups

Thyroid profile	Group 1 cases versus controls			Subgroup analysis								
				Subgroup 1 Cirrhosis with HE versus cirrhosis without HE			Subgroup 2 Cirrhosis survivors versus cirrhosis nonsurvivors			Subgroup 3 HE survivors versus HE nonsurvivors		
	Case (n=100) all cirrhotic	Control (n=100) all healthy	t-test (P)	Cirrhosis without HE (n=62)	Cirrhosis with HE (n=38)	t-test (P)	Cirrhosis nonsurvivors (n=16)	Cirrhosis survivors (n=84)	t-test (P)	HE nonsurvivors (n=15)	HE Survivors (n=23)	t-test P
FT3 (mean±SD)	1.95±0.57	3.13±0.59	<0.0001	2.15±0.49	1.63±0.53	<0.0001	1.59±0.72	2.02±0.51	0.005	1.54±0.71	1.68±0.38	0.42
FT4 (mean±SD)	1.27±0.54	1.86±0.36	<0.0001	1.34±0.53	1.15±0.54	<0.09	1.10±0.55	1.30±0.53	0.16	1.13±0.56	1.17±0.53	0.80
TSH (mean±SD)	4.09±1.70	3.15±1.20	<0.0001	4.02±1.52	4.21±1.97	<0.60	4.89±2.29	3.94±1.53	0.04	5.10±2.20	3.63±1.60	0.025

HE: Hepatic encephalopathy, TSH: Thyroid stimulating hormone, SD: Standard deviation, FT3: Free triiodothyronine, FT4: Free thyroxine

Table 3: Comparison of thyroid functions in all cirrhotic patients according to severity of liver disease

Thyroid profile	CTP classification Group A				MELD Score Group B				
	Class A (n=1)	Class B (n=37)	Class C (n=62)	P (one-way ANOVA)	≤9 (n=7)	10-19 (n=58)	20-29 (n=27)	30-39 (n=8)	P (one-way ANOVA)
FT3 (mean±SD)	1.9±0.00	2.20±0.55	1.80±0.53	0.002	2.11±0.75	2.07±0.61	1.74±0.38	1.63±0.28	0.0225
FT4 (mean±SD)	0.76±0.00	1.44±0.54	1.17±0.51	0.03	1.48±0.65	1.32±0.54	1.17±0.52	1.04±0.33	0.27
TSH (mean±SD)	4.41±0.00	3.68±1.64	4.34±1.71	0.17	3.25±1.34	3.63±1.54	4.87±1.55	5.56±1.94	0.0003

CTP: Child-Turcotte-Pugh, MELD: Model for end-stage liver disease, SD: Standard deviation, FT3: Free triiodothyronine, FT4: Free thyroxine, ANOVA: Analysis of variance, TSH: Thyroid-stimulating hormone

Table 4: Comparison of thyroid functions according to grades of hepatic encephalopathy

Thyroid profile	None (n=62)	Grade 1 (n=13)	Grade 2 (n=13)	Grade 3 (n=4)	Grade 4 (n=8)	F-statistics	P (one-way ANOVA)
FT3 (mean±SD)	2.15±0.49	1.74±0.38	1.46±0.34	1.75±0.27	1.65±0.97	6.77	0.0001
FT4 (mean±SD)	1.34±0.53	1.08±0.36	1.28±0.65	1.17±0.35	1.15±0.69	1.12	0.35
TSH (mean±SD)	4.02±1.52	3.81±2.04	4.50±1.59	5.26±1.86	3.85±2.53	0.81	0.52

SD: Standard deviation, FT3: Free triiodothyronine, FT4: Free thyroxine, ANOVA: Analysis of variance, TSH: Thyroid-stimulating hormone

Table 5: Correlation between thyroid hormones levels and different parameters in liver cirrhosis patients

Variables	Mean±SD	FT3		FT4		TSH	
		r	*P*	*r*	*P*	*r*	*P*
Age	43±14	−0.10	0.18	0.04	0.62	0.08	0.23
Hb	8.05±2.2	0.57	<0.0001	0.38	<0.0001	−0.27	0.0001
TLC	8744±6134	−0.22	0.002	−0.15	0.03	0.25	0.0004
DLC (*n*)	73±11	−0.24	0.0008	−0.14	0.05	0.10	0.17
Platelets	1.17±0.78	0.48	<0.0001	0.46	<0.0001	−0.18	0.01
Bilirubin	4.75±5.21	−0.39	<0.0001	−0.34	<0.0001	0.24	0.0008
SGOT	106.03±105	−0.33	<0.0001	−0.27	0.0001	0.17	0.02
SGPT	57.99±62.4	−0.22	0.002	−0.16	0.02	0.19	0.005
Protein	6.14±0.84	0.41	<0.0001	0.34	<0.0001	−0.18	0.01
Albumin	2.61±0.71	0.65	<0.001	0.51	<0.0001	−0.28	<0.0001
Globulin	3.53±0.75	−0.45	<0.0001	−0.34	<0.0001	0.20	0.005
PT	25±13.86	−0.20	0.05	−0.05	0.59	0.30	0.003
INR	1.67±0.58	−0.17	0.08	−0.09	0.37	0.38	0.0001
Blood urea	44.74±43	−0.27	0.0001	−0.18	0.009	0.18	0.009
Serum creatinine	1.28±1.12	−0.18	0.009	−0.17	0.02	0.30	<0.0001
Na+	139±4	−0.58	<0.0001	0.40	<0.0001	−0.24	0.0005
K+	4.51±0.55	−0.26	0.0002	−0.10	0.17	0.14	0.04
MELD	18±7	−0.30	0.003	−0.23	0.02	0.39	0.0001

Hb: Hemoglobin, TLC: Total leukocyte count, DLC: Differential leukocyte count, SGPT: Serum glutamate pyruvate transaminase, SGOT: Serum glutamic-oxaloacetic transaminase, PT: Prothrombin time, INR International normalized ratio, MELD: Model for end-stage liver disease, SD: Standard deviation, FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid-stimulating hormone

with MELD score [Table 3] and HE grades [Table 4], but statistically not significant.

As illustrated in Table 3, when comparing the mean serum levels of TSH in Child A, B, and C, it was found the highest in the Child C group (4.34 ± 1.71), followed by the Child B group (3.68 ± 1.64), while the Child A group was (4.41 ± 0.00).

As illustrated in Table 4, levels of FT3 were significantly low in HE Grade 4 compared to HE Grade 3, HE Grade 2, HE Grade 1, and cirrhotic patients without HE. Level of FT4 and TSH were statistically not significant.

As illustrated in Table 5, in all cirrhotic patients, FT3 and FT4 were negatively correlated but TSH levels were positively correlated with total leukocyte counts, ST bilirubin, aspartate transaminase (AST), alanine transaminase, globulin, PT, blood urea, serum creatinine, and severity of liver cirrhosis (CTP and MELD score). Mansour-Ghanaei *et al*.[19] reported negative correlation of T3 levels with MELD as well as CTP. Yadav *et al*.[20] reported TSH showed significant positive correlation with AST and ALP values, whereas FT3 and FT4 had a negative correlation with AST in overt hypothyroidism. Results of our study were consistent with these studies.

Conclusion

The mean FT3 and FT4 levels were found to be significantly decreased and the mean TSH levels were significantly increased in liver cirrhosis cases compared to healthy controls. Low levels of FT3 also correlated with the severity of liver disease in the form of CTP or MELD. Level of FT4 decreases as CTP Class (A–C) increases. Level of TSH increases with MELD score. Therefore, thyroid levels in cirrhotic patients may be used as a prognostic marker. Low FT3 might be used as a predictor of patients for underlying HE, while low FT3 and high TSH might be used as a predictor of mortality in liver cirrhosis patients, although death in cirrhotic patient is multifactorial.

Impact on society

Thyroid function test should be done regularly in liver cirrhosis patients to reduce morbidity and mortality.

Acknowledgment

We would like to thanks entire faculty of Department of Medicine, NSCB Medical College and Hospital, Jabalpur, for their generous assistance to complete this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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