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Original Research Article

Thyroid Dysfunction in Patients of Liver Cirrhosis and Any Association between Severity of Liver Cirrhosis and Thyroid Profile

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Abstract

Aim: This study was conducted to study thyroid dysfunction in patients of liver cirrhosis and any association between severity of liver cirrhosis and thyroid profile.

Methods: This case-control study was conducted in the Department of Medicine, GMC, Azamgarh, Uttar Pradesh, India. A total of 200 liver cirrhosis patients (case) and equal number (200) of healthy controls were included in this study. The study was conducted for the period of two years.

Results: A total of 200 liver cirrhosis cases (150 males and 50 females) and 200 apparently healthy controls (120 males and 80 females) were included in the final analysis. The mean age was 46.34 ± 8.24 years for cases and 47.23 ± 6.34 years for controls. Controls as compared to cases had higher free T3 (fT3) (2.48 ± 0.44 vs. 1.64 ± 0.52 pg/ml) and free T4 (fT4) (1.28 ± 0.32 vs. 1.16 ± 0.46 ng/ml), although the difference was significant only for freeT3. On the contrary, TSH values of cases were found to be significantly higher as compared to that of controls (3.57 ± 0.90 vs. 3.02 ± 0.64 µIU/ml). Low T3 syndrome and hypothyroidism were common thyroid disorders (24% and 18%), normal thyroidal illness syndrome with low T4 and high T4 were observed among 16% and 12% cases, whereas out of 200 controls, 180 (90%) did not have any abnormality in thyroid functions. Only 14 (7%) cases were diagnosed as normal thyroidal illness syndrome with high T4 abnormality. The difference in thyroid dysfunctions between cases and controls was found to be significant statistically.

Conclusion: Liver disease cases as compared to controls had significantly lower fT3 levels and significantly higher TSH levels. Mortality rate of liver disease cases with thyroid dysfunction was also found to be significantly higher.

Keywords:fT3, fT4, liver cirrhosis, thyroid dysfunction; 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]

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] Some of the lipogenic enzymes that are regulated are malic enzyme, glucose-6-phosphate dehydrogenase, and fatty acid synthase. Thus, the nature of relationship between the thyroid and liver is a mutual one with each one affecting the function of other. Evidence of an association between chronic diseases of the liver andthyroid alterations has often been reported. [6] However, most of the time, this association is traced among liver cirrhosis patients and other conditions are ignored. Recent studies have traced a reverse relationship between thyroid dysfunction and liver disease too. [7,8] Given this bidirectional relationship, it is of interest to understand and evaluatethe relationship between liver diseaseand thyroid functions under all possible conditions.

This study was conducted to study thyroid dysfunction in patients of liver cirrhosis and any association between severity of liver cirrhosis and thyroid profile.

Materials and Methods

This case-control study was conducted in the Department of Medicine, GMC, Azamgarh, Uttar Pradesh, India. A total of 200 liver cirrhosis patients (case) and equal number (200) of healthy controls were included in this study. The study was conducted for the period of two years.

Inclusion Criteria

Case

All patients with cirrhosis of liver aged >18 years with evidence of hepatocellular dysfunction and portal hypertension as evident clinically and by portal vein diameter >13 mm on ultrasonography (USG) and presence of esophageal varices on endoscopy or evidence of cirrhosis of the liver on fibro scan

Control

Apparently, healthy age-and sex-matched individuals of age >18

Exclusion Criteria

Known cases of thyroid disorder without liver cirrhosis, patient with a history of organ failure, cancer, radio or chemotherapy, individual with active infection, nephrotic syndrome, pregnancy, and history of drugs intake (amiodarone, NSAIDs, etc.).

Ethical Aspects

The protocol for the study was approved by the ethical and research committee. Data were collected only after the patient informed and written consent.

Diagnostic Tool

The diagnosis of cirrhosis was based on the case history, clinical examination, biochemical, endoscopic and ultrasound findings, and elastography. The functional severity of the liver injury was determined on the basis of the Child–Pugh–Turcotte (CPT) grading system and Model for End-Stage and Liver-Stage Disease (MELD). The etiology of cirrhosis was determined on the basis of case history and biochemical tests. Thyroid function test was done by electrochemiluminescence immunoassay. Normal range of thyroid parameters were fT3 = 1.71–3.71 pg/ml, fT4 = 0.70–1.48 ng/ml, and thyroid- stimulating hormone (TSH) = 0.5–4.94 μIU/ml.

Statistical Analysis

The statistical analysis was done using the SPSS (Statistical Package for the Social Sciences) version 21.0 statistical analysis Software. The values were represented in number (%) and mean ± standard deviation.

Results

Table 1: Distribution of patients according to gender

Gender	N	%
Case		
Male	150	75
Female	50	25
Mean age	46.34 ± 8.24 years	
Control		
Male	120	60
Female	80	40
Mean age	47.23 ± 6.34 years	

A total of 200 liver cirrhosis cases (150 males and 50 females) and 200 apparently healthy controls (120 males and 80 females) were included in the final analysis. The mean age was 46.34 ± 8.24 years for cases and 47.23 ± 6.34 years for controls.

Table 2: Comparison of thyroid function parameters between cases and controls

Examined characteristic	Mean±SD/n (%)		P
	Case n=200	Control n=200	
fT3 (pg/ml)	1.64±0.52	2.48±0.44	<0.001
Below normal	130 (65)	0	<0.001
Normal	70 (35)	200 (100)	
fT4 (ng/ml)	1.16±0.46	1.28±0.32	0.070
Below normal	60 (30)	0	<0.001
Normal	100 (50)	180 (90)	
Above normal	40 (20)	20 (10)	
TSH (µIU/ml)	3.57±0.90	3.02±0.64	<0.001
Normal	160 (80)	200 (100)	<0.001
Above normal	40 (20)	0	

Controls as compared to cases had higher free T3 (fT3) (2.48 ± 0.44 vs. 1.64 ± 0.52 pg/ml) and free T4 (fT4) (1.28 ± 0.32 vs. 1.16 ± 0.46 ng/ml), although the difference was significant only for freeT3. On the contrary, TSH values of cases were found to be significantly higher as compared to that of controls (3.57 ± 0.90 vs. 3.02 ± 0.64 µIU/ml).

Table 3: Comparison of type of thyroid disorder between cases and controls

Thyroid status	Study group (n=100), n (%)	Controls (n=100), n (%)	P
Euthyroid	52 (26)	180 (90)	<0.001
Thyroid dysfunction	140 (70)	20 (10)	<0.001
Low T3 syndrome	48 (24)	0	<0.001
NTIS with low T4	32 (16)	0	<0.001
Hypothyroidism	36 (18)	0	<0.001
NTIS with high T4	24 (12)	14 (7)	<0.001

Low T3 syndrome and hypothyroidism were common thyroid disorders (24% and 18%), normal thyroidal illness syndrome with low T4 and high T4 were observed among 16% and 12% cases, whereas out of 200 controls, 180 (90%) did not have any abnormality in thyroid functions. Only 14 (7%) cases were diagnosed as normal thyroidal illness syndrome with high T4 abnormality. The difference in thyroid dysfunctions between cases and controls was found to be significant statistically.

Table 4: Association of thyroid function parameters with severity of liver disease

Child-Pugh score	Mean±SD/n (%)			P
	Category A (n=20)	Category B (n=100)	Category C (n=80)	
fT3 (pg/ml)	2.28±0.72	1.64±0.44	1.38±0.34	<0.001
fT4 (ng/ml)	1.34±0.36	1.25±0.52	1.05±0.36	0.164
TSH (µIU/ml)	3.26±0.82	3.57±0.87	3.72±1.03	0.414
Euthyroid	16 (80)	35 (35)	8 (10)	0.001
Thyroid dysfunction	4 (20)	65 (65)	72 (90)	0.001

A subsequent decline with severity of liver disease according to CPT score was observed in fT3 and fT4 levels, while a subsequent increment in TSH with severity of liver disease was observed. However, the associationof severity of liver disease was found to be significant only for fT3 levels while a significant increment in proportion of cases with thyroid dysfunction was observed with increase in severity of the disease, i.e., Category A (20%), Category B (65%), and Category C (90%).

Table 5: Association of thyroid function parameters with mortality risk (model for end-stage and liver-stage disease)

	Mean±SD/n (%)				P
	Very low risk (≤9)	Mild risk (10-19)	Moderate risk (20-29)	Very high risk (30-39)	
fT3 (pg/ml)	2.22±0.58	1.56±0.44	1.46±0.36	1.18±0.32	0.001
fT4 (ng/ml)	1.12±0.48	1.18±0.58	1.16±0.44	0.86±0.34	0.518
TSH (μIU/ml)	3.48±0.70	3.57±0.93	3.86±1.64	3.89±1.51	0.835
Euthyroid	8	20	8	0	0.120
Thyroid dysfunction	6	60	28	8	0.105

A subsequent significant decline with increase in mortality risk (MELD) was observed in fT3 levels, and this association was found to be significant statistically. Association of mortality risk with fT4 level and TSH levels were not found to be significant. Increment in proportion of cases with thyroid dysfunction with increase in mortality risk was observed, i.e., very low risk followed by mild risk, moderate risk, and very high risk, this association was not found to be significant statistically.

Discussion

Cirrhosis of liver is a leading cause of morbidity and mortality worldwide. Liver plays a vital role in thyroid hormone metabolism and circulation of thyroid hormone by producing thyroid binding globulin. [9] Liver also plays a role in the production of triiodothyronine (T3) by the action of selenium dependent 5' deiodinase. Moreover, another selenium independent deiodinase acts on the phenolic ring of thyroxine (T4) to produce the hormonally inactive reverse T3 (rT3). [10] The levels of thyroid hormone and thyroid binding proteins are altered in patients of chronic liver disease. Low free T3 syndrome is frequently described in patients with cirrhosis of liver and is characterized by increased rT3, low T3 and decreased T3:T4 ratio. [11] Low T3 may be an adaptive thyroid response to reduce the basal metabolic rate of hepatocytes and preserve liver function. [12]

A total of 200 liver cirrhosis cases (150 males and 50 females) and 200 apparently healthy controls (120 males and 80 females) were included in the final analysis. Controls as compared to cases had higher free T3 (fT3) (2.48 ± 0.44 vs. 1.64 ± 0.52 pg/ml) and free T4 (fT4) (1.28 ± 0.32 vs. 1.16 ± 0.46 ng/ml), although the difference was significant only for freeT3. On the contrary, TSH values of cases were found to be significantly higher as compared to that of controls (3.57 ± 0.90 vs. 3.02 ± 0.64 μIU/ml). Similarly, Vincken et al. [13] reported that the mean fT3 and fT4 was significantly lower in cases (2.80 ± 0.59 ng/L and 11.80 ± 1.92 ng/L) as compared to controls (3.30 ± 0.45 ng/L, 13.00 ± 1.57 ng/L). Moreover, the mean TSH was not significantly different between cases (1.60 ± 0.74 mIU/L) and controls (1.77 ± 1.23 mIU/L). In another study, Punekar et al. [14] observed mean fT3, fT4, and TSH levels as 1.95 ± 0.57, 1.27 ± 0.54, and 4.09 ± 1.70, respectively, in cases as compared to 3.13 ± 0.59, 1.86 ± 0.36, and 3.15 ± 1.20, respectively, in controls, thus showing mean fT3 and fT4 values of cases to be significantly lower while that of TSH to be significantly higher in cases as compared to that in controls.

In the present study, only 25% of cases as compared to 90% of controls were euthyroid, thus showing that thyroid disorders were highly prevalent in patients with liver cirrhosis. Among cases, low T3 syndrome was the most common thyroid dysfunction (25%), followed by hypothyroidism (18%), normal thyroidal illness syndrome with low T4 (16%), and normal thyroidal illness syndrome with high T4 (13.9%), respectively, whereas among controls all the 9.7% of cases had normal thyroidal illness syndrome with highT4. Compared to the present study, Punekar et al. [14] intheir study had only 23% euthyroid cases. The most common thyroid dysfunction pattern was low T3 syndrome (41%) followed by hypothyroidism (20%), normal thyroidal illness syndrome with low T4 (15%), and hyperthyroidism (1%), respectively.

As far as severity is concerned, in the present study, we used two criteria to grade the severity, one of themwas clinical staging (Child–Pugh Scoring [CPS]) andother was prognostic score (MELD). In the present study, according to CPS, half (50%) patients were in Class B followed by Class C (40%) and Class A (10%), respectively. According to the MELD score, majority had score 10–19 followed by score 20–29,<9, and 30–39 respectively. On theassessment of association between thyroid function hormones and severity scores, a significant decreasing trend of fT3 was observed with increasing CPS class and MELD score, the prevalence of thyroid dysfunction also showed an incremental trend with increasing CPS class and MELD score, thus implying that thyroid function, especially fT3 levels are affected by severity of liver cirrhosis. These results are in agreement with the findings of the previous studies. [15-17]

Low T3 syndrome and hypothyroidism were common thyroid disorders (24% and 18%), normal thyroidal illness syndrome with low T4 and high T4 were observed among 16% and 12% cases, whereas out of 200 controls, 180 (90%) did not have any abnormality in thyroid functions. Only 14 (7%) cases were diagnosed as normal thyroidal illness syndrome with high T4 abnormality. The difference in thyroid dysfunctions between cases and controls was found to be significant statistically.However, the associationof severity of liver disease was found to be significant only for fT3 levels while a significant increment in proportion of cases with thyroid dysfunction was observed with increase in severity of the disease, i.e., Category A (20%), Category B (65%), and Category C (90%). Patira et al. [16] in their study found that all the three thyroid function hormones (fT3, fT4, and TSH) show a significant association with CPS classes. Verma et al. [17] in their study reported both fT3 and fT4 levels to be significantly associated with MELD scores. They also showed a significant association between Child–Pugh class and fT3 levels. However, they did not find a significant association of TSH levels with either Child–Pugh class or MELD score and fT4 with Child–Pugh class. In the present study too, we found that for mean thyroid functions, only fT3 levels showed a significant association with CPS class and MELD scores. In fact, almost all the previous studies have shown a significant inverse association of fT3 levels with increasing severity of liver disease as observed in the present study.

A subsequent significant decline with increase in mortality risk (MELD) was observed in fT3 levels, and this association was found to be significant statistically. Association of mortality risk with fT4 level and TSH levels were not found to be significant. Although increment in proportion of cases with thyroid dysfunction with increase in mortality risk was observed, i.e., very low risk followed by mild risk, moderate risk, and very high risk, this association was not found to be significant statistically.

Conclusion

In this study, the mean fT3 was significantly lower and TSH was significantly higher in liver disease cases as compared to controls. Among cases of liver disease as compared to controls, abnormal fT3, fT4, and TSH levels were observed in significantly higher proportion. Thyroid dysfunction was observed in significantly higher among cases. A trend of significant decline in fT3 levels with increase in severity was observed. Thyroid dysfunction was also observed in higher proportion of higher category of cases, and this association was significant. Duration of hospital stay ofliver disease cases was not found to be associated withthyroid dysfunction. The fT3 levels of expired caseswere significantly lower and TSH levels significantlyhigher. Mortality rate of liver disease cases with thyroiddysfunction was also found to be significantly higher.

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