

Assessment of the Association between Severity of Liver Cirrhosis and Thyroid Profile in Patients with Reported with Thyroid Dysfunction

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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, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India. A total of 100 liver cirrhosis patients (case) and equal number (100) of healthy controls were included in this study. The study was conducted for the period of one year.

Results: A total of 100 liver cirrhosis cases (70 males and 30 females) and 100 apparently healthy controls (65 males and 35 females) were included in the final analysis. The mean age was 49.22 ± 7.22 years for cases and 49.14 ± 6.27 years for controls. Controls as compared to cases had higher free T3 (fT3) (2.45 ± 0.40 vs. 1.60 ± 0.50 pg/ml) and free T4 (fT4) (1.26 ± 0.21 vs. 1.15 ± 0.48 ng/ml), although the difference was significant only for free T3. On the contrary, TSH values of cases were found to be significantly higher as compared to that of controls (3.61 ± 0.95 vs. 3.01 ± 0.66 μ IU/ml). Low T3 syndrome and hypothyroidism were common thyroid disorders (23% and 18%), normal thyroidal illness syndrome with low T4 and high T4 were observed among 16% and 12% cases, whereas out of 100 controls, 90 (90%) did not have any abnormality in thyroid functions. Only 8 (8%) cases were diagnosed as normal thyroidal illness syndrome with high T4 abnormality. The association of 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 (70%), and Category C (90.0%).

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.

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Introduction

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. [1] 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). [2]

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. [3] Low T3 may be an adaptive thyroid response to reduce the basal metabolic rate of hepatocytes and preserve liver function. [4]

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. [5] 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. 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]

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 and thyroid alterations has often been reported. [7] 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. [8,9] Given this bidirectional relationship, it is of interest to understand and evaluate the relationship between liver disease and 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, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India. A total of 100 liver cirrhosis patients (case) and equal number (100) of healthy controls were included in this study. The study was conducted for the period of one year.

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 $ft3 = 1.71\text{--}3.71$ pg/ml, $ft4 = 0.70\text{--}1.48$ ng/ml, and thyroid-stimulating hormone (TSH) = $0.5\text{--}4.94$ μ IU/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 \pm standard deviation.

Results

Table 1: Distribution of patients according to gender

| Gender | N | % |
|----------------|------------------------|----|
| Case | | |
| Male | 70 | 70 |
| Female | 30 | 30 |
| Mean age | 49.22 \pm 7.22 years | |
| Control | | |
| Male | 65 | 65 |
| Female | 35 | 35 |
| Mean age | 49.14 \pm 6.27 years | |

A total of 100 liver cirrhosis cases (70 males and 30 females) and 100 apparently healthy controls (65 males and 35 females) were included in the final analysis. The mean age was 49.22 ± 7.22 years for cases and 49.14 ± 6.27 years for controls.

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

| Examined Characteristic | Mean \pm SD/n (%) | | P |
|-------------------------|---------------------|-----------------|--------|
| | Case n=100 | Control n=100 | |
| ft3 (pg/ml) | 1.60 \pm 0.50 | 2.45 \pm 0.40 | <0.001 |
| Below normal | 64 (64) | 0 | <0.001 |
| Normal | 36 (36) | 100 (100) | |
| ft4 (ng/ml) | 1.15 \pm 0.48 | 1.26 \pm 0.21 | 0.070 |
| Below normal | 25 (25) | 0 | <0.001 |
| Normal | 55 (55) | 90 (90) | |
| Above normal | 20 (20) | 10 (10) | |
| TSH (μ IU/ml) | 3.61 \pm 0.95 | 3.01 \pm 0.66 | <0.001 |
| Normal | 80 (80) | 100 (100) | <0.001 |
| Above normal | 20 (20) | 0 | |

Controls as compared to cases had higher free T3 (fT3) (2.45 ± 0.40 vs. 1.60 ± 0.50 pg/ml) and free T4 (fT4) (1.26 ± 0.21 vs. 1.15 ± 0.48 ng/ml), although the difference was significant only for free T3. On the contrary, TSH values of cases were found to be significantly higher as compared to that of controls (3.61 ± 0.95 vs. 3.01 ± 0.66 μ IU/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 | 25 (25) | 90 (90) | <0.001 |
| Thyroid dysfunction | 72 (72) | 10 (10) | <0.001 |
| Low T3 syndrome | 23 (23) | 0 | <0.001 |
| NTIS with low T4 | 16 (16) | 0 | <0.001 |
| Hypothyroidism | 18 (18) | 0 | <0.001 |
| NTIS with high T4 | 12 (12) | 8 (8) | <0.001 |

Low T3 syndrome and hypothyroidism were common thyroid disorders (23% and 18%), normal thyroidal illness syndrome with low T4 and high T4 were observed among 16% and 12% cases, whereas out of 100 controls, 90 (90%) did not have any

abnormality in thyroid functions. Only 8 (8%) 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 \pm SD/n (%) | | | P |
|---------------------|---------------------|-------------------|-------------------|--------|
| | Category A (n=10) | Category B (n=50) | Category C (n=40) | |
| fT3 (pg/ml) | 2.25 \pm 0.75 | 1.68 \pm 0.47 | 1.36 \pm 0.32 | <0.001 |
| fT4 (ng/ml) | 1.32 \pm 0.39 | 1.23 \pm 0.55 | 1.03 \pm 0.38 | 0.170 |
| TSH (μ IU/ml) | 3.24 \pm 0.84 | 3.55 \pm 0.92 | 3.75 \pm 1.01 | 0.420 |
| Euthyroid | 8 (80) | 15 (30) | 4 (10) | 0.001 |
| Thyroid dysfunction | 2 (20) | 35 (70) | 36 (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 association of 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 (70%), and Category C (90.0%).

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

| | Mean \pm SD/n (%) | | | | P |
|---------------------|----------------------------|-------------------|-----------------------|------------------------|-------|
| | Very low risk (≤ 9) | Mild risk (10-19) | Moderate risk (20-29) | Very high risk (30-39) | |
| fT3 (pg/ml) | 2.20 \pm 0.61 | 1.59 \pm 0.47 | 1.48 \pm 0.37 | 1.17 \pm 0.33 | 0.001 |
| fT4 (ng/ml) | 1.13 \pm 0.43 | 1.19 \pm 0.51 | 1.17 \pm 0.45 | 0.84 \pm 0.31 | 0.510 |
| TSH (μ IU/ml) | 3.46 \pm 0.72 | 3.60 \pm 0.98 | 3.91 \pm 1.61 | 3.91 \pm 1.61 | 0.870 |
| Euthyroid | 4 | 10 | 4 | 0 | 0.140 |
| Thyroid dysfunction | 3 | 30 | 14 | 4 | 0.120 |

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 levels and TSH levels were not found to be significant. Although an 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

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. 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. [10]

In the present study, observed mean fT3, fT4, and TSH levels as 1.60 ± 0.50 pg/ml, 1.15 ± 0.48 ng/ml, and 3.61 ± 0.95 μ IU/ml, respectively, in cases as compared to 2.45 ± 0.40 pg/ml, 1.26 ± 0.21 ng/ml, and 3.01 ± 0.66 μ IU/ml, respectively, in controls. However, only differences in fT3 and TSH levels were found to be significant. Similarly, Vincken et al. [11] 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. [12] 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 high T4. Compared to the present study, Punekar et al. [12] in their 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 them was clinical staging (Child–Pugh Scoring [CPS]) and other 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 the assessment 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. [13-15]

Patira et al. [14] 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. [15] 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. [16]

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 of liver disease cases was not found to be associated with thyroid dysfunction. The fT3 levels of expired cases were significantly lower and TSH levels significantly higher. Mortality rate of liver disease cases with thyroid dysfunction was also found to be significantly higher. The above findings indicate that thyroid dysfunction was more common in patients of liver disease as compared to healthy counterparts and the risk of thyroid dysfunction increases with severity of the

disease and is associated with poor outcomes.

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