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EVALUATION OF THYROID FUNCTION AND ITS ASSOCIATION WITH SEVERITY IN PATIENTS WITH CHRONIC LIVER DISEASE

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ABSTRACT

Background: The liver is the most biochemically complex organ. It is necessary for the metabolism, elimination, detoxification, and storage of hazardous chemicals. Since the liver is the primary organ involved in the peripheral conversion of tetraiodothyronine (T4) to triiodothyronine (T3) by Type 1 deiodinase, which leads to the 5-deiodination of T4, it contributes significantly to thyroid hormone metabolism.

Materials and Methods: This is an observational case–control study that included clinically diagnosed cases of chronic liver disease 50 and 50 healthy individuals. Serum FT3, FT4, and thyroid-stimulating hormone (TSH) levels were measured using chemiluminescent immunoassay (CLIA), and results were also analysed for severity of liver disease according to Child–Turcotte–Pugh (CTP) (Class A, B, and C), and model for end-stage liver disease (MELD) scores.

Results: Chronic liver disease patients had statistically significantly lower levels of FT3 ($P < 0.0001$) and had higher levels of TSH ($P < 0.0001$) compared with the controls. Overall, the mean FT3 levels were significantly lower in cases as compared to controls, while the mean FT4 levels in cases were marginally lower than those in controls, and TSH levels were significantly elevated in cases compared to controls. A decrease in FT3 levels was observed with an increasing CP Score of Chronic Liver Disease; i.e., CP Score A had the highest mean FT3 levels, while in MELD scoring, the highest percentage of cases, i.e., lowest severity, were in the ≤ 9 category (52%).

Conclusion: The mean FT3 levels were significantly decreased, and the mean TSH levels were significantly increased in chronic liver disease patients compared to healthy controls. The levels of FT3, FT4, and TSH also correlate with the severity of liver disease; the level of FT3 can be used as a prognostic marker for liver cirrhosis patients.

KEYWORDS: Child–Turcotte–Pugh; Model for end-stage liver disease; Thyroid dysfunction; FT3

1. INTRODUCTION

The liver is the largest metabolic organ and one of the most biochemically complex organs in the human body. It performs a wide range of essential physiological functions, including the metabolism of carbohydrates, proteins, and lipids; synthesis of plasma proteins and clotting factors; storage of vitamins and minerals; detoxification of endogenous and exogenous substances; and excretion of metabolic waste products. These diverse functions are fundamental to maintaining systemic metabolic and endocrine homeostasis.

Among its many endocrine functions, the liver plays a central role in the metabolism, transport, and clearance of thyroid hormones. Approximately 80% of circulating triiodothyronine (T3), the biologically active thyroid hormone, is generated through peripheral deiodination of thyroxine (T4), with the liver serving as one of the principal sites for this conversion via type 1 iodothyronine deiodinase. In addition, the liver synthesizes thyroid hormone-binding proteins, including thyroid-binding globulin, transthyretin, and albumin, which regulate hormone transport, distribution, and bioavailability. Hepatic conjugation and biliary excretion are also essential for maintaining normal thyroid hormone homeostasis.

Chronic liver disease (CLD) represents a progressive spectrum of hepatic disorders characterized by persistent inflammation, fibrosis, and gradual deterioration of liver function, ultimately culminating in cirrhosis and liver failure. The major aetiologies of CLD include chronic viral hepatitis, alcohol-related liver disease, metabolic dysfunction-associated steatotic liver disease, autoimmune liver diseases, hereditary metabolic disorders, and hepatocellular carcinoma. As liver disease advances, profound disturbances occur in multiple metabolic and endocrine pathways, including those regulating thyroid hormone synthesis, metabolism, transport, and clearance.

The liver and thyroid gland share a complex and reciprocal physiological relationship. Hepatic dysfunction may impair peripheral conversion of T4 to T3, reduce the synthesis of thyroid hormone-binding proteins, and alter hormone metabolism and clearance, resulting in characteristic abnormalities in thyroid function tests. Conversely, thyroid disorders can adversely affect hepatic metabolism and liver function. Consequently, patients with chronic liver disease frequently

exhibit alterations in thyroid hormone concentrations, particularly reduced serum T3 levels with relatively preserved or mildly decreased T4 concentrations, while thyroid-stimulating hormone (TSH) levels may remain normal or vary depending on the severity of liver dysfunction. Hypothyroidism, hyperthyroidism, and autoimmune thyroid disorders may also coexist in patients with chronic liver disease, highlighting the intricate interplay between these two organs.

In addition to its metabolic role, the liver is an important immunological organ that contains a diverse population of resident immune cells and is a major source of acute-phase proteins, complement components, cytokines, and chemokines involved in both innate and adaptive immune responses. Laboratory assessment of liver function commonly includes measurements of serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, and prothrombin time. These biochemical markers provide valuable information regarding hepatocellular injury, cholestasis, and hepatic synthetic function, while scoring systems such as the Child–Pugh and Model for End-stage Liver Disease (MELD) scores are widely used to assess disease severity and prognosis. Thus, the study aims to evaluate thyroid hormone levels (FT3, FT4, and TSH) in chronic liver disease patients and to determine the significance of thyroid hormone levels and chronic liver disease, and to compare levels of the above parameters with those of normal subjects.

2. METHODS

This case–control observational study included 50 healthy controls and 50 chronic liver disease patients (cases) from the outpatient department and Intensive Care Unit in the Department of Hepatology with clinical, biochemical, and radiological evidence of chronic liver disease. It included all genders with a diagnosis of chronic liver disease between the age group of 18-65 years and informed consent from the patient. Known cases of thyroid disorder without liver cirrhosis were excluded. Patients with a history of organ failure, cancer, radiotherapy, or chemotherapy, and patients who had not met the inclusion criteria were excluded from this study. Patient is using drugs that interfere with thyroid metabolism, such as levothyroxine, propylthiouracil, carbimazole, iodine, amiodarone, and beta-blockers, were also excluded. The study was conducted between April 2024 and October 2024. The Institutional Ethical Committee approved the protocol for the study. Data were collected only after the patient was informed and provided written consent. The diagnosis of chronic liver disease was based on case history, clinical examination, biochemical, endoscopic, and ultrasound findings, or liver biopsy. The functional severity of the liver injury was determined based on the Child–Pugh grading system and model for end-stage liver disease (MELD). The thyroid function test (TFT) was done by chemiluminescence immunoassay. The normal range of thyroid profile is as follows: FT3 is 2.27-5.27 pg/ml, FT4 is 0.78-2.19 ng/dl, and TSH is 0.465–4.68 μIU/ml. Results obtained from various parameters were presented as mean ± SD among the two groups, i.e., cases (n=50) and controls (n=50). The result of the case group was compared with that of the control group by applying the Student's t-test. To evaluate the thyroid functions in patients with chronic liver disease, Pearson's correlation test was also applied. A p-value of ≤ 0.05 was considered significant for all statistical tests.

3. RESULTS

When cases were categorized by gender, the majority were male (56%) compared to females (44%). The highest proportion (40%) was observed in the 30–40-year age group, followed by 22% in the 41–50-year range. The 51–60 and 61–65-year groups each accounted for 14% of cases. The smallest share (10%) was in the 18–29-year age group. The average FT3 levels were found to be notably lower in patients with CLD compared to healthy controls. The mean FT4 levels in cases were marginally lower than those in controls. TSH levels were found to be significantly higher in patients compared to controls **(Table 1)**. When a total of 50 patients with CLD were distributed based on severity using the CP Score, it was observed that the highest percentage of cases were in the CP-C category (54%), followed by the CP-B category (38%), and the CP-A category (6%). A decrease in FT3 levels was observed with an increasing CP Score of CLD, i.e., CP Score A had the highest mean FT3 levels, followed by CP Score B and CP Score C. T4 levels showed a downward trend, but this change did not reach statistical significance, while a statistically significant rise in TSH levels was detected with CP Score **(Table 2).** Based on severity using the MELD Score, it was observed that the highest percentage of cases, i.e., lowest severity, were in the ≤ 9 category (52%), followed by the 10-19 category (20%), and then the 20-29 category and 30-39 category (14%), respectively. FT3 levels decreased significantly with higher MELD scores. TSH levels exhibited a clear upward trend with increasing MELD scores **(Table 3).**

Table 1: FT3, FT4, TSH Levels in Cases and Control Groups

PARAMATER	CASES	CONTROL	P-value
FT3 (pg/ml)	1.87±0.59	3.17 ± 0.87	<0.0001
FT4 (ng/ml)	1.39 ± 0.51	1.57 ± 0.61	NS
TSH (μIU/ml)	3.59 ± 1.85	1.97 ± 1.06	<0.0001

Table 2: CP Score Distribution in Cases

CP SCORE	A (4)	B (19)	C (27)	P-value
FT3 (pg/ml)	2.35±0.72	2.12±0.42	1.58 ±0.57	< 0.001
FT4 (ng/ml)	1.23±0.05	1.14±0.21	1.63±0.61	0.004
TSH (μIU/ml)	2.57±1.85	2.49±1.12	4.68±1.74	< 0.001

Table 3: MELD Score Distribution in Cases

MELD SCORE	30-39 (7)	20-29 (7)	10-19 (10)	≤ 9 (26)	P-value
FT3 (pg/ml)	1.18±0.37	1.56±0.49	1.83±0.50	2.15± 0.52	<0.0001
FT4 (ng/ml)	2.11±0.74	1.67±0.67	1.26±0.19	1.18±0.19	<0.0001
TSH (µIU/ml)	6.33±0.94	5.31±0.44	4.13±0.67	2.18±1.09	<0.0001

No cases have been observed in category 40.

4. DISCUSSION

When total cases were distributed by gender, most were male (56%) compared with female (44%). A similar predominance of males (60%) over females (40%) was observed in the control group. **Vijaykumar et al., 2020** (21). also show a high occurrence of Liver Cirrhosis among males in their study, i.e., 78% of males out of a total of 100 cases. When the distribution of cases was done based on age, most cases, i.e., 40%, were in the age group of 30-40 years, followed by 22% in the age group of 41-50 years. Age groups of 51-60 years and 61-65 years show similar percentages of cases, i.e., 14% respectively. The least number of cases, i.e., 10%, were in the age group of 18-29 years. Similar patterns were reported by **Mobin A et. al., 2016** (22). A study by **Vijaykumar et al., 2020** (21) also reported the major percentage of patients (83%) between the age group of 30-40 years.

The mean FT3 levels were significantly lower in cases as compared to controls. The mean FT4 levels in cases were marginally lower than those in controls. TSH levels were significantly elevated in cases compared to controls, as shown in **Table 1.** Thyroid hormone abnormalities in chronic liver disease were also demonstrated by **Harischandra P et.al., 2020** (25), **Joeimon J L et.al., 2017** (24), and **Mobin A et.al., 2016** (22). They concluded in their studies that the level of FT3 decreased and TSH levels increases in Chronic Liver Disease patients.

In the present study, when a total of 50 patients with Chronic Liver Disease were distributed based on severity by using CP Score, it was observed that the highest percentage of cases were in CP-C category (54%), which is followed by - CP B category (38%) and only CP-A category (6%)

When the levels of serum FT3 were distributed among the subgroups of CP score A, B, C, by applying a one-way ANOVA test, a decrease in FT3 levels was observed with an increasing CP Score of Chronic Liver Disease; i.e., CP Score A had the highest mean FT3 levels, followed by CP Score B and CP Score C. **Ghanaei F M et.al., 2012 (2)** reported that FT3 levels in Chronic Liver Disease patients is a good index of hepatic function, and it is inversely related to the severity of liver damage

When the levels of FT4 were distributed among the subgroups of CP Score A, B, C, by applying a one-way ANOVA test, a decrease in T4 levels was observed with an increase in the severity of Chronic Liver Disease, but the observed decrease was not significant. FT4 levels were found to be insignificantly reduced or unchanged in studies conducted by **Vijaykumar S et. al., 2020** (21).

Based on severity, when the TSH levels were compared and sub-grouped in 3 classes of CP Score, with an increase in the severity of the disease, a slight significant increase in the levels of TSH was observed. Mean levels of TSH were compared by applying one-way ANOVA test as shown in **Table 2**. A study by **Verma S K et.al.,2017** (23), also demonstrated the increase in TSH levels among Chronic Liver Disease patients and concluded that the derangement in thyroid profile is common and may be used for prognosis in patients with Chronic Liver Disease

In the present study, when a total of 50 patients with Chronic Liver Disease were distributed based on severity by using the MELD Score, it was observed that the highest percentage of cases i.e. lowest severity were in the ≤ 9 category (52%), followed by the 10-19 category (20%) and then 20-29 category and 30-39 category (14%) respectively. FT3 levels decreased significantly with higher MELD scores. Cases with a MELD score ≤9 had the highest FT3 levels, while those with 30-39 had the lowest levels. It represents a strong correlation between declining FT3 levels and increasing disease severity, highlighting FT3 as a sensitive marker of disease progression. **Punekar P et.al. (1)**, **2018** also concluded that serum total FT3 levels as biomarkers for liver disease might be a beneficial tool, helping in monitoring the state of liver disease patients.

FT4 levels showed significant variability with MELD scores. Cases with a MELD score ≤9 had the lowest levels, while those with 30-39 had the highest levels. Similar patterns were also seen in the study of **Punekar P et.al. (1)**, **2018,** suggesting a complex interplay between FT4 levels and disease severity, warranting further investigation. TSH levels exhibited a clear upward trend with increasing MELD scores. Cases with a MELD score ≤9 had the lowest mean TSH level as compared to those with scores of 30-39, which had the highest levels, as shown in **Table 3**. Similar results were seen in the study of **Punekar P et.al. (1)**, **2018,** which concluded that TSH levels correlate with the severity of the disease. The highly significant result reinforces the relationship between elevated TSH levels and advanced disease, positioning TSH as a key marker for monitoring disease progression and severity.

CONCLUSION:

Increasing TSH and declining FT3 levels are observed with progressive CLD stages. The association of TSH and FT3 with systemic inflammation suggests a liver disease-associated non-thyroidal illness syndrome. Lower FT3 levels in patients with CLD indicate increased risk for decompensation, acute-on-chronic liver failure, and liver-related death**.**

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