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THYROID DYSFUNCTION IN PATIENTS WITH CHRONIC LIVER DISEASE: A CROSS-SECTIONAL STUDY

General Medicine

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ABSTRACT

Background: Chronic liver disease frequently disrupts thyroid hormone metabolism, yet systematic evaluation across different etiologies remains limited. To evaluate thyroid dysfunction prevalence and patterns in chronic liver disease patients and assess correlations with disease severity. **Methods:** This cross-sectional study at Chettinad Hospital enrolled 200 chronic liver disease patients and 50 healthy controls. Patients aged 18-75 years with confirmed chronic liver disease (>6 months) were included. Those with known thyroid disease, pregnancy, or thyroid-affecting medications were excluded. Primary outcomes included thyroid dysfunction prevalence and correlation with Child-Pugh and MELD scores. **Results:** Mean age was 52.3±12.8 years (68% males). Thyroid dysfunction prevalence was significantly higher in liver disease patients versus controls (64.5% vs 8.0%, p<0.001). Low T3 syndrome was most common (38.5%), followed by subclinical hypothyroidism (16.0%). Prevalence increased with severity: Child-Pugh Class A (45.2%), B (72.8%), C (89.1%) (p<0.001). T3 levels showed negative correlations with Child-Pugh (r=-0.68, p<0.001) and MELD scores (r=-0.52, p<0.001). **Conclusions:** Thyroid dysfunction is highly prevalent in chronic liver disease, correlating with disease severity. Routine thyroid screening is recommended for these patients.

KEYWORDS

chronic liver disease, thyroid dysfunction, hepatic cirrhosis, thyroid hormones, cross-sectional study

INTRODUCTION

Chronic liver disease affects over 1.5 billion individuals worldwide, ranking among leading causes of morbidity and mortality [1]. The spectrum includes chronic hepatitis, cirrhosis, and end-stage liver disease, with increasing prevalence attributed to viral hepatitis, non-alcoholic fatty liver disease, and alcohol-related conditions [2]. The liver plays a fundamental role in thyroid hormone metabolism through synthesis of thyroid-binding proteins (thyroxine-binding globulin, transthyretin, albumin), peripheral conversion of thyroxine (T4) to triiodothyronine (T3) via hepatic deiodinases, and hormone clearance through hepatic conjugation and biliary excretion [3-5]. Hepatic dysfunction significantly disrupts thyroid homeostasis, causing complex hormone alterations that may not reflect true thyroid pathology [6]. Thyroid dysfunction prevalence in chronic liver disease varies from 13% to 76%, depending on population, etiology, and severity [7,8]. The most common pattern is euthyroid sick syndrome, characterized by low T3 with normal/elevated reverse T3, often with normal/low TSH and variable T4 levels. However, true thyroid disorders occur with increased frequency in these patients [9].

This bidirectional hepato-thyroid relationship has important clinical implications. Thyroid dysfunction affects liver metabolism, cardiovascular function, and prognosis in chronic liver disease. Distinguishing between liver-induced thyroid alterations and true thyroid pathology poses diagnostic challenges requiring systematic evaluation [10].

Despite clinical importance, comprehensive studies evaluating thyroid dysfunction across different liver disease etiologies and severity stages remain limited, particularly in tertiary settings. This knowledge gap hampers development of evidence-based screening protocols.

This cross-sectional study aimed to evaluate thyroid dysfunction prevalence and patterns in chronic liver disease patients, assess correlations with disease severity, and identify etiologies associated with higher thyroid abnormality risk.

METHODS

Study Design and Setting

This cross-sectional observational study was conducted at the Gastroenterology Department, Hepatology Clinic, and Internal Medicine Department of a tertiary care center in Chennai, India. The study protocol was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki principles.

Participants

Inclusion Criteria: Patients aged 18-75 years with confirmed diagnosis of chronic liver disease (duration >6 months) of any etiology, stable clinical condition without acute hepatic decompensation, and willingness to provide written informed consent were eligible.

Exclusion Criteria: Patients were excluded if they had known pre-existing thyroid disease or thyroid medication use, history of thyroid surgery or radioiodine therapy, current use of medications significantly affecting thyroid function (amiodarone, lithium, interferon), acute liver failure or hepatic decompensation, pregnancy or lactation, severe psychiatric illness affecting consent capacity, concurrent malignancy or severe systemic illness, or unwillingness to participate.

Sample Size Calculation

Sample size was calculated using nMaster software Version 2.0. Based on literature reporting 25-45% prevalence of thyroid dysfunction in chronic liver disease patients, with 95% confidence interval, 5% margin of error, and accounting for 10% non-response rate, the minimum required sample size was 200 chronic liver disease patients and 50 healthy controls.

Data Collection And Laboratory Assessments
Comprehensive clinical evaluation included detailed medical history, physical examination, and assessment of liver disease etiology, duration, and severity. Standardized data collection forms captured demographic variables, liver disease characteristics, concurrent medications, and clinical findings.

Thyroid Function Assessment:
Thyroid function testing included serum TSH, free T4, and free T3 measured using chemiluminescent immunoassays. Normal reference ranges were: TSH 0.4-4.0 mIU/L, free T4 9.0-19.0 pmol/L, and free T3 3.5-6.5 pmol/L. Thyroid dysfunction was defined as any abnormality in these parameters.

Liver Function Assessment:
Liver biochemistry included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, and international normalized ratio (INR). Liver disease severity was assessed using Child-Pugh score (Class A: 5-6 points, Class B: 7-9 points, Class C: 10-15 points) and Model for End-Stage Liver Disease (MELD) score [11,12].

Additional Assessments:
Complete blood count, comprehensive metabolic panel, hepatitis B and C serology, and relevant imaging studies were performed as clinically indicate.

Statistical Analysis
Continuous variables were expressed as mean ± standard deviation or median with interquartile range based on distribution normality assessed by Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Prevalence of thyroid dysfunction was calculated with 95% confidence intervals. Between-group comparisons employed independent t-tests or Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables. Correlations between liver disease severity scores and thyroid parameters were assessed using Pearson's or Spearman's correlation coefficients. Multiple logistic regression analysis identified independent predictors of thyroid dysfunction. Statistical significance was set at $p < 0.05$. Data analysis was performed using SPSS version 28.0.

RESULTS

Participant Characteristics
A total of 250 participants were enrolled, with 200 patients with chronic liver disease and 50 healthy controls completing the study (Table: 1). The chronic liver disease group had a mean age of 52.3 ± 12.8 years compared to 48.6 ± 11.2 years in controls ($p = 0.081$). Male predominance was observed in the liver disease group (68.0% vs 54.0% in controls, $p = 0.089$).

The distribution of liver disease etiologies included viral hepatitis (42.0%, n=84), non-alcoholic fatty liver disease (31.5%, n=63), alcoholic liver disease (18.5%, n=37), and other causes (8.0%, n=16). Regarding disease severity, 62 patients (31.0%) had Child-Pugh Class A, 81 patients (40.5%) had Class B, and 57 patients (28.5%) had Class C disease. The median MELD score was 16.8 ± 8.4 (range 6-35).

Prevalence of Thyroid Dysfunction
Thyroid dysfunction was significantly more prevalent in chronic liver disease patients compared to healthy controls (129/200, 64.5% vs 4/50, 8.0%; $p < 0.001$; OR 21.8, 95% CI 7.4-64.2). Among liver disease patients, the most common abnormality was low T3 syndrome, observed in 77 patients (38.5%), followed by subclinical hypothyroidism in 32 patients (16.0%), overt hypothyroidism in 20 patients (10.0%), and subclinical hyperthyroidism in 8 patients (4.0%). Only 2 patients (1.0%) had overt hyperthyroidism (Table:2).

Table 1. Baseline Characteristics of Study Participants

Characteristic	Chronic Liver Disease (n=200)	Healthy Controls (n=50)	P Value
Age, mean (SD), y	52.3 (12.8)	48.6 (11.2)	.081
Male sex, No. (%)	136 (68.0)	27 (54.0)	.089
BMI, mean (SD), kg/m²	24.8 (4.2)	23.9 (3.1)	.182
Liver Disease Etiology, No. (%)			
Viral hepatitis	84 (42.0)	NA	NA
NAFLD	63 (31.5)	NA	NA
Alcoholic liver disease	37 (18.5)	NA	NA
Other causes	16 (8.0)	NA	NA
Disease Severity			
Child-Pugh Class A, No. (%)	62 (31.0)	NA	NA
Child-Pugh Class B, No. (%)	81 (40.5)	NA	NA
Child-Pugh Class C, No. (%)	57 (28.5)	NA	NA
MELD score, mean (SD)	16.8 (8.4)	NA	NA

Table 2. Thyroid Function Parameters In Study Participants

Parameter	Chronic Liver Disease (n=200)	Healthy Controls (n=50)	P Value
TSH, median (IQR), mIU/L	2.8 (1.6-4.9)	2.1 (1.4-3.2)	.031
Free T4, mean (SD), pmol/L	13.2 (4.8)	14.8 (2.9)	.036
Free T3, mean (SD), pmol/L	3.8 (1.4)	5.2 (0.8)	<.001
Thyroid Dysfunction, No. (%)			
Any thyroid dysfunction	129 (64.5)	4 (8.0)	<.001
Low T3 syndrome	77 (38.5)	0 (0)	<.001
Subclinical hypothyroidism	32 (16.0)	2 (4.0)	.032
Overt hypothyroidism	20 (10.0)	0 (0)	.014
Subclinical hyperthyroidism	8 (4.0)	1 (2.0)	.695
Overt hyperthyroidism	2 (1.0)	1 (2.0)	.468

Correlation with Liver Disease Severity
Thyroid dysfunction prevalence increased significantly with liver disease severity. Among Child-Pugh Class A patients, 28/62 (45.2%) had thyroid dysfunction, compared to 59/81 (72.8%) in Class B and 51/57 (89.1%) in Class C patients ($p < 0.001$ for trend).

Strong negative correlations (Table:3) were observed between free T3 levels and liver disease severity scores: Child-Pugh score ($r = -0.68$, $p < 0.001$) and MELD score ($r = -0.52$, $p < 0.001$). TSH levels showed a weak positive correlation with Child-Pugh scores ($r = 0.23$, $p = 0.001$), while free T4 levels demonstrated a moderate negative correlation ($r = -0.41$, $p < 0.001$).

Table 3. Thyroid Function By Liver Disease Severity

Child-Pugh Class	A (n=62)	B (n=81)	C (n=57)	P Value
Any thyroid dysfunction, No. (%)	28 (45.2)	59 (72.8)	51 (89.1)	<.001
Low T3 syndrome, No. (%)	12 (19.4)	35 (43.2)	30 (52.6)	<.001
TSH, median (IQR), mIU/L	2.2 (1.4-3.8)	2.9 (1.8-4.6)	3.6 (2.1-6.2)	.002
Free T4, mean (SD), pmol/L	15.1 (3.2)	13.2 (4.1)	11.8 (6.1)	.001
Free T3, mean (SD), pmol/L	4.6 (1.1)	3.8 (1.2)	2.9 (1.3)	<.001

Etiology-Specific Analysis
Thyroid dysfunction prevalence varied significantly across liver disease etiologies. Viral hepatitis patients had the highest prevalence (60/84, 71.4%), followed by alcoholic liver disease (24/37, 64.9%), NAFLD (33/63, 52.4%), and other causes (12/16, 75.0%) ($p = 0.043$). Pairwise comparisons revealed significantly higher thyroid dysfunction rates in viral hepatitis compared to NAFLD patients (71.4% vs 52.4%, $p = 0.032$).

Low T3 syndrome was most prevalent in viral hepatitis (42/84, 50.0%) and alcoholic liver disease (16/37, 43.2%) compared to NAFLD (19/63, 30.2%) ($p = 0.019$). Multiple logistic regression analysis identified Child-Pugh score (OR 2.34, 95% CI 1.78-3.08, $p < 0.001$), viral hepatitis etiology (OR 2.18, 95% CI 1.12-4.24, $p = 0.021$), and male sex (OR 1.86, 95% CI 1.02-3.39, $p = 0.043$) as independent predictors of thyroid dysfunction (Table:4).

Table 4. Independent Predictors of Thyroid Dysfunction (Multiple Logistic Regression)

Variable	Odds Ratio	95% CI	P Value
Child-Pugh score (per point increase)	2.34	1.78-3.08	<.001
Viral hepatitis etiology	2.18	1.12-4.24	.021
Male sex	1.86	1.02-3.39	.043
Age (per year increase)	1.02	0.99-1.05	.156
MELD score (per point increase)	1.03	0.98-1.08	.232

Clinical Characteristics Of Thyroid Dysfunction
Patients with thyroid dysfunction had significantly higher bilirubin levels (4.8 ± 6.2 vs 2.9 ± 3.1 mg/dL, $p = 0.003$), lower albumin levels

(2.8 ± 0.7 vs 3.4 ± 0.6 g/dL, $p < 0.001$), and higher INR values (1.8 ± 0.9 vs 1.3 ± 0.4, $p < 0.001$) compared to those with normal thyroid function. No significant differences were observed in transaminase levels between groups.

DISCUSSION

This cross-sectional study demonstrates a remarkably high prevalence of thyroid dysfunction in patients with chronic liver disease, affecting 64.5% of patients compared to only 8.0% of healthy controls. The findings reveal a clear hierarchical relationship between liver disease severity and thyroid dysfunction prevalence, increasing from 45.2% in Child-Pugh Class A to 89.1% in Class C patients. Low T3 syndrome emerged as the predominant abnormality (38.5%), consistent with the non-thyroidal illness syndrome commonly observed in chronic systemic diseases.

The strong negative correlations between free T3 levels and both Child-Pugh scores ($r = -0.68$) and MELD scores ($r = -0.52$) underscore the intimate relationship between hepatic dysfunction severity and thyroid hormone metabolism. These findings align with previous smaller studies but provide more robust evidence across a larger patient cohort with diverse liver disease etiologies [13,14].

The observed patterns reflect the liver's central role in thyroid hormone metabolism through multiple interconnected pathways. The predominance of low T3 syndrome in our cohort (38.5%) corresponds to impaired hepatic type 1 deiodinase activity, which normally converts T4 to the metabolically active T3 [15]. Progressive liver dysfunction disrupts this conversion, leading to decreased circulating T3 levels while T4 and reverse T3 may remain normal or elevated.

The reduced synthesis of thyroid-binding proteins, particularly thyroxine-binding globulin and albumin, in advanced liver disease contributes to altered total hormone levels despite potentially normal free hormone concentrations [16]. Our finding of lower albumin levels in patients with thyroid dysfunction (2.8 vs 3.4 g/dL, $p < 0.001$) supports this mechanism.

The significantly higher thyroid dysfunction prevalence in viral hepatitis patients (71.4%) compared to NAFLD patients (52.4%, $p = 0.032$) suggests etiology-specific mechanisms. Viral hepatitis may induce more pronounced inflammatory responses affecting thyroid hormone metabolism, while the chronic inflammatory state in viral infections could directly impact thyroid gland function through molecular mimicry or autoimmune mechanisms [17].

The identification of viral hepatitis etiology as an independent predictor (OR 2.18, 95% CI 1.12-4.24) in multivariate analysis reinforces this association and suggests the need for enhanced thyroid monitoring in this population.

The strong correlation between thyroid dysfunction and liver disease severity markers (higher bilirubin, lower albumin, elevated INR) indicates that thyroid abnormalities may serve as additional prognostic indicators in chronic liver disease. The 89.1% prevalence of thyroid dysfunction in Child-Pugh Class C patients suggests that thyroid screening should be considered routine in advanced liver disease.

However, clinical interpretation requires careful consideration of whether observed abnormalities represent true thyroid pathology requiring treatment or adaptive responses to systemic illness. The predominance of low T3 syndrome, typically considered an adaptive mechanism rather than true thyroid disease, supports cautious therapeutic approaches [18].

Our prevalence rates align with the upper range of previously reported studies (13-76%), likely reflecting our tertiary care setting with more advanced disease and systematic screening approach [11,14]. The strong correlation coefficients with severity scores exceed those reported in smaller studies, possibly due to our larger sample size and comprehensive severity assessment using both Child-Pugh and MELD scoring systems.

Study Limitations

Several limitations merit consideration. The cross-sectional design precludes assessment of temporal relationships and causality between liver dysfunction and thyroid abnormalities. The single-center tertiary care setting may limit generalizability to community-based populations with less severe disease. Additionally, we did not measure thyroid antibodies, which might have identified concurrent autoimmune thyroid disease in some patients.

The study also lacks assessment of patient symptoms or quality of life measures that might help distinguish clinically significant thyroid dysfunction from biochemical abnormalities. Furthermore, medications that could affect thyroid function were excluded, but subclinical effects of retained medications cannot be entirely ruled out.

Future Research Directions

Longitudinal studies tracking thyroid function changes with liver disease progression would provide insights into causality and temporal relationships. Investigation of thyroid function recovery following liver transplantation could help distinguish reversible liver disease effects from true thyroid pathology. Additionally, studies examining the clinical significance of thyroid hormone replacement therapy in liver disease patients with biochemical abnormalities would inform treatment guidelines.

Research into the molecular mechanisms underlying etiology-specific differences in thyroid dysfunction prevalence could reveal targeted therapeutic approaches. Finally, cost-effectiveness analyses of thyroid screening protocols in chronic liver disease populations would inform clinical practice guidelines.

CONCLUSIONS

This study provides comprehensive data on thyroid dysfunction prevalence and patterns in chronic liver disease patients. The findings support routine thyroid function screening in this population while emphasizing the need for careful interpretation considering liver disease effects on thyroid hormone metabolism. These results contribute to better understanding of hepato-thyroid interactions and may inform clinical practice guidelines for managing concurrent liver and thyroid disorders.

Author Contributions

AP, BN, G, CR, and MR conceptualized the study. AP collected data and performed statistical analysis with supervision from MR. G and M provided clinical expertise in cardiology and respiratory medicine respectively. BN, CR, MR, and BSD supervised the research. AP drafted the manuscript. All authors contributed to manuscript revision and approved the final version for publication.

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Nil.

Conflicts Of Interest

There are no conflicts of interest.

Use Of Artificial Intelligence

In the preparation of this manuscript, we utilized paper pal AI, as an assistive tool for editing, paraphrasing and improving the language. All AI-generated content was thoroughly reviewed, verified, and edited by the authors. The authors take full responsibility for the content and accuracy of the manuscript

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