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Thyroid Hormone Variability in Liver Cirrhosis: Its Impact on Disease Severity and Clinical Management—A Cross-sectional Study

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ABSTRACT

Introduction

Liver diseases are increasingly recognized as significant public health concerns in India, prompting investigations into novel approaches for assessing disease severity and prognosis. Recognizing the potential utility of thyroid hormone levels in these assessments, we conducted an observational cross-sectional study at our tertiary care hospital. Our study included 89 patients aged 12 years and above, admitted to medicine wards with ultrasound-diagnosed liver cirrhosis, excluding pregnant women and those on thyroid-altering medications.

Results

Our findings revealed a male-to-female ratio of 4.23:1, with the majority of patients falling within the 40–60 age-group, averaging 46.93 years. Notably, 87.6% of patients exhibited thyroid abnormalities, primarily low free T3 (FT3) syndrome and subclinical hypothyroidism. Classifying patients according to Child–Pugh (CP) score, 2.2% were CP class A, 22.5% were CP class B, and the remaining 75.3% were CP class C. Across all CP classes, low FT3 syndrome was prevalent, particularly in CP class C. Correlations

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between thyroid hormone levels and liver disease severity, assessed via CP and model for end-stage liver disease (MELD) scoring systems, were observed. Specifically, FT3 levels demonstrated a negative correlation with liver disease severity (p = 0.001), while no significant correlations were found for free T4 (FT4) and thyroid-stimulating hormone (TSH) levels. Based on our findings, we recommend routine thyroid function testing for all liver cirrhosis patients, irrespective of disease severity, to facilitate early detection and intervention. However, our study had limitations, including a small sample size and a precision error of 10% due to resource constraints for thyroid function testing. Moreover, reliance solely on ultrasound for liver cirrhosis diagnosis may lead to missed diagnoses, highlighting the need for complementary noninvasive tests such as FibroScan and aspartate aminotransferase to platelet ratio index (APRI) scores.

Conclusion

Our study underscores the importance of considering thyroid function in the management of liver cirrhosis patients and provides valuable insights for enhancing clinical practice in this context.

Keywords: Thyroid, Liver cirrhosis, FibroScan, APRI.

Introduction

Cirrhosis, characterized by diffuse hepatic fibrosis and the restructuring of liver architecture into nodules, represents the final stage of various chronic liver diseases (CLD). With liver diseases increasingly recognized as significant public health concerns in India, etiologies such as alcohol abuse, hepatitis B and C, and nonalcoholic steatohepatitis (NASH) commonly lead to cirrhosis in adults.1 Clinically, cirrhosis is categorized as either ”compensated” or ”decompensated,” with the latter exhibiting complications such as jaundice, ascites, hepatic encephalopathy (HE), or bleeding varices.2

The thyroid gland’s crucial role in metabolic regulation and growth is wellestablished. Importantly, the liver plays a pivotal role in thyroid hormone metabolism, including the conversion of thyroxine (T4) to triiodothyronine (T3) by type 1 deiodinase. This enzymatic activity, predominantly found in the liver, contributes significantly to extrathyroidal T3 production.

Furthermore, the liver is involved in the conjugation, excretion, and systemic regulation of thyroid hormones, exerting influences on overall metabolic rate and hepatic function.3 Recent studies have underscored a significant prevalence of thyroid dysfunction among patients with liver cirrhosis. Moreover, correlations between thyroid

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hormone levels, particularly free T3 (FT3) and thyroid-stimulating hormone (TSH), and the severity of liver disease have been well-documented. Consequently, several studies advocate for the routine use of thyroid hormone levels as prognostic markers in liver cirrhosis to mitigate morbidity and mortality.4 Despite the growing recognition of thyroid-liver interactions in the context of cirrhosis, there remains limited data from the Indian subcontinent.

To address this gap, we conducted a study at our tertiary care hospital to investigate the prevalence of thyroid dysfunction and assess the correlation between thyroid hormone levels and the severity of liver disease among cirrhosis patients in our region. Through this research, we aim to contribute valuable insights into the clinical management of liver cirrhosis, advocating for the routine evaluation of thyroid function to enhance prognostication and optimize patient outcomes.

Materials And Methods

Study Design

This observational cross-sectional study was conducted at a tertiary care hospital in Utta Pradesh, following approval from the Institutional Ethics Committee. Participants Patients of both genders aged 12 years and above, diagnosed with liver cirrhosis via ultrasound, were considered eligible for inclusion. Written informed consent was obtained from each participant, with consent from a first-degree relative sought when the patient was unable to provide it. Pregnant women and individuals with thyroid disease unrelated to liver cirrhosis or using thyroid-altering medications were excluded.

Sample Size Calculation

The sample size was calculated based on the prevalence of hypothyroidism among liver cirrhosis patients from a previous study, yielding a sample size of 89 participants.

Data Collection

A comprehensive history and clinical examination were conducted for each enrolled patient, with investigations noted as per the treating physician’s advice. Laboratory investigations, including complete blood count, random blood sugar, renal and liver function tests, prothrombin time, international normalized ratio (INR), and serological tests for human immunodeficiency virus (HIV), hepatitis B, and C, were performed. Abdominal ultrasound findings and additional investigations, such as ascitic fluid analysis and upper gastrointestinal endoscopy, were noted when applicable. Thyroid Function Testing Thyroid function tests (TFTs) were conducted using a fully automated hormone assay analyzer, with normal reference ranges established for FT3, free T4 (FT4), and TSH levels. All eligible patients underwent TFTs free of charge. The cost of

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TFTs was borne by the investigators. Normal reference range of TFTs are as follows: Free T3 = 2.3–6.6 pmol/L, FT4 = 0.8–1.8 pmol/L, and TSH = 0.4–4.0 μIU/mL.

Statistical Analysis Data were entered into an Excel spreadsheet and analyzed using Statistical Package for the Social Sciences (SPSS) version 22. Descriptive statistics such as means, medians, standard deviations, percentiles, and ranges were employed. Correlations between laboratory parameters and liver disease severity, assessed by Child–Pugh (CP), model for endstage liver disease (MELD), and MELD-Na scores, were explored using Spearman rank correlation analysis. Statistical significance was determined by a p-value of <0.05.

Additional Analyses Patients were categorized based on hematological indices and the presence of cytopenias, with correlations established between cytopenia severity and liver disease severity. Associations between liver disease severity and clinical parameters such as ascites, encephalopathy grades, and spleen size were also examined.

Results

Demographic Characteristics

The study included 89 participants with a gender distribution of 72 males (81.0%) and 17 females (19.0%). The mean age of the participants was 46.93 ± 10.94 years, with the majority falling in the age-group of 40–60 years (60.7%), while 39.3% were under 40 years of age. No participants were over 60 years old.

Chief Complaints

The most common chief complaints among the enrolled patients were abdominal distension (89.9%), followed by yellowish discoloration of the sclera (67.4%) and urine (66.3%). Other prevalent complaints included pain in the abdomen (58.4%), nausea (56.2%), and fever (56.2%).

Comorbidities

Among the comorbidities observed in the study population, diabetes mellitus (12.4%) and hypertension (11.2%) were the most common. Other comorbidities included tuberculosis (10.1%) and ischemic heart disease (4.5%).

Clinical Examination Findings

Pallor (94.4%) and pedal edema (93.3%) were the most prevalent clinical signs observed in the patients. Icterus (68.5%) and jaundice (39.3%) were also frequently

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noted, while signs such as gynecomastia (7.9%) and dilated veins (5.6%) were less common.

Investigation Findings

Laboratory investigations revealed a median hemoglobin level of 8.1 gm/dL (range: 2.2–16.3 gm/dL), total leukocyte count (TLC) of 9,600/µL (range: 620–38,700/µL), and platelet count of 91,000/µL (range: 10,100640,000/µL). Abnormalities in liver function tests included elevated levels of total bilirubin, serum glutamic oxaloacetic transaminase/ alanine aminotransferase (SGOT/AST), and serum glutamic pyruvic transaminase/ alanine aminotransferase (SGPT/ALT), as well as prolonged prothrombin time and INR.

Correlation analysis revealed significant associations between various laboratory parameters and the severity of liver disease as assessed by CP, MELD, and MELD-Na scores. Parameters such as total bilirubin, direct bilirubin, prothrombin time, and INR showed strong positive correlations with liver disease severity. Liver Disease Severity Patients were classified according to the severity of CLD based on assessments derived from the CP and MELD scoring systems.

Causes of Liver Cirrhosis Among the cases analyzed, alcohol consumption emerges as the primary culprit, accounting for a significant majority at 78.7%. Notably, this trend is more pronounced in males, with 91.7% of alcohol-related cirrhosis cases reported. Unspecified causes constitute a notable proportion at 10.1%, indicating a lack of clarity or documentation regarding the specific triggers in these instances. Hepatitis B infection stands out as another significant cause, contributing to 4.5% of cirrhosis cases. Interestingly, a smaller proportion of cases (2.2%) are attributed to both alcohol consumption and hepatitis B infection, suggesting a synergistic effect of these factors. Autoimmune hepatitis, cryptogenic causes, and Wilson's disease each contribute to a smaller but still notable percentage of cirrhosis cases at 2.2, 1.1, and 1.1%, respectively. Gender disparities are evident in some categories, such as autoimmune hepatitis and cryptogenic cirrhosis, where females represent a higher proportion of cases compared to males. These findings underscore the multifactorial nature of liver cirrhosis, highlighting the importance of targeted interventions and comprehensive management strategies tailored to the specific etiological factors involved.

The prevalence of various thyroid dysfunctions among patients with liver cirrhosis, stratified by gender, CP classification, MELD scores, and MELD-Na scores, provides insights into the complexity of thyroid involvement in this population. Among males and females, low FT3 syndrome was the most common thyroid dysfunction, affecting 58.4% of patients overall, with a slightly higher prevalence among males (59.7%) compared to females (52.9%). Subclinical hypothyroidism and hypothyroidism were also observed, along with rare cases of hyperthyroidism and transient thyroiditis. Examining thyroid

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dysfunction across CP classes reveals that low FT3 syndrome was prevalent across all classes, particularly in class C, affecting 64.2% of patients in this category. Subclinical hypothyroidism and hypothyroidism showed significant prevalence, particularly in class B.

When categorized by MELD and MELD-Na scores, low FT3 syndrome remained prevalent across all score categories, with the highest prevalence observed in patients with MELD scores between 20 and 29 and MELD-Na scores between 20 and 29. Hypothyroidism was notably prevalent in specific score categories, such as MELD scores between 10 and 19 and MELD-Na scores ≤9.

Overall, these findings underscore the importance of monitoring thyroid function in patients with liver cirrhosis, as thyroid dysfunction appears to be common across various disease severities and scoring systems. The correlation analysis between thyroid hormone levels and CP classes, as well as MELD and MELD-Na scores, revealed significant associations. In terms of CP classes, serum levels of FT3 showed a strong negative correlation, with a test statistic of 14.399 and a p-value of 0.001. This indicates that as CP classes increase, there is a notable decrease in FT3 levels. However, FT4 and TSH levels did not show significant correlations with CTP classes, as indicated by their test statistics and p-values.

Moving on to the correlation with MELD and MELD-Na scores, FT3 levels exhibited negative correlations with both MELD and MELD-Na scores, with correlation coefficients of −0.369 and −0.590, respectively, both statistically significant with p-values < 0.001. Similarly, FT4 and TSH showed negative correlations with MELD scores, but only FT4 had a marginal correlation ($p = 0.057$). However, neither FT4 nor TSH showed significant correlations with MELD-Na scores. Overall, these findings suggest that lower serum levels of FT3 are associated with higher CP classes and MELD/MELD-Na scores, indicating a potential role of FT3 as a marker of disease severity in patients with liver cirrhosis.

Discussion

Our study aimed to investigate the utility of thyroid hormone levels in assessing the severity of liver cirrhosis and its prognostic value. We observed several notable findings, which contribute to the understanding of this relationship. Firstly, we found that liver cirrhosis predominantly affects males, consistent with previous studies. This male predominance underscores the need for targeted interventions and awareness campaigns focused on liver health among men.

Secondly, the majority of patients in our study presented at advanced stages of cirrhosis, as evidenced by the high proportion classified as CP class C. This late

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presentation highlights the importance of early detection and management strategies to prevent disease progression and improve outcomes. Laboratory Parameters and Liver Disease Severity Hemoglobin levels and other laboratory parameters, such as total proteins, alkaline phosphatase (ALP), serum potassium, calcium, and uric acid levels, did not show statistically significant differences concerning the severity of liver disease. Certain parameters, including white blood cell count (WBC) count, blood urea nitrogen (BUN), creatinine, SGPT/ALT, and phosphorus levels, were positively correlated with liver disease severity, as measured by MELD and MELD-Na scores, but not with CP scores. Platelet Count and Albumin Levels Platelet count exhibited a negative correlation with liver disease severity based on MELD scores but not with CP and MELD-Na scores.

Albumin levels were negatively correlated with liver disease severity according to CP and MELD scores but not with MELD-Na scores. Prothrombin Time, International Normalized Ratio, Bilirubin Levels, and Serum Glutamic Oxaloacetic Transaminase/Alanine Aminotransferase These parameters showed a positive correlation with liver disease severity across all scoring systems (CTP, MELD, and MELD-Na). Serum Sodium and Chloride Levels Serum sodium and chloride levels were negatively correlated with liver disease severity based on MELD-Na scores but not with CTP and MELD scores. These observations underscore the complex interplay between laboratory parameters and the severity of liver disease, highlighting the importance of considering multiple factors when assessing disease severity and prognosis.

Our study investigated thyroid hormone levels in liver cirrhosis patients, finding a high prevalence of low serum FT3 levels, normal FT4 levels, and normal TSH levels. We observed no significant differences in thyroid hormone levels based on gender or age-groups. These findings align with prior research by Samarthana et al.,4 which similarly reported low FT3 levels in cirrhosis patients. The prevalence of thyroid abnormalities in our study was 87.6%, with low FT3 syndrome being the most common abnormality. This finding is in line with studies by Mobin et al.5 and Punekar et al.,6 which reported high percentages of cirrhotic patients with low FT3 levels. There were no significant differences in thyroid dysfunction among genders, age-groups, or severity of liver disease as assessed by CP, MELD, and MELD-Na scores.

Our study mirrored findings from Kharb et al., where the prevalent types of thyroid dysfunction observed included sick euthyroid syndrome affecting six individuals (7%), followed by three cases (3.5%) of subclinical hypothyroidism, two cases each (2.3%) of subclinical hyperthyroidism and thyrotoxicosis, and one case of overt hypothyroidism.7 Importantly, we found a significant negative correlation between FT3 levels and the severity of liver disease, as assessed by both CP and MELD scores. This indicates that as liver disease progresses, FT3 levels decrease. This supports the notion proposed by previous studies that thyroid hormones may serve as valuable prognostic markers in cirrhotic patients. However, there was no significant correlation between FT4 or TSH

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levels and the severity of liver disease.8 Our study, akin to Verma et al.,9 revealed a significant inverse correlation between FT3 levels and severe ascites, who noted lower FT3 levels in decompensated liver cirrhosis compared to compensated cases. Furthermore, we found a notable association between low FT3 levels and HE, consistent with Arafa et al.,10 who demonstrated lower T3 levels in patients with varying degrees of HE.

Our study diverged from the findings of Buden concerning FT4 and TSH levels in liver cirrhosis. While Buden observed significantly decreased mean levels of FT3 and FT4, along with significantly increased mean TSH levels in cirrhotic cases compared to healthy controls, our study did not find any correlation between FT4 or TSH levels and disease severity.

Our study revealed a correlation between the severity of cirrhosis and FT3 levels, while no significant correlation was found with FT4 and TSH levels. However, despite this, we emphasize the importance of evaluating thyroid abnormalities comprehensively with complete TFTs, including TSH, FT3, and FT4, to ensure a thorough assessment. Our results support the hypothesis of an adaptive hypothyroid state in cirrhosis patients, potentially influenced by factors such as loss of peripheral deiodination, poor nutrition, and alcohol intake. Controlled induction of hypothyroidism may have beneficial effects in cirrhotic patients, although further studies are needed to explore this.

Conclusion

Thyroid hormone levels, particularly FT3, may serve as valuable prognostic markers in liver cirrhosis patients, aiding in risk stratification and management. However, variations in findings across studies underscore the need for further research, considering factors such as sample size, age, sex, ethnicity, and regional variations in thyroid disorders.

Clinical Significance

The clinical significance of our study lies in highlighting the prevalence of thyroid abnormalities, particularly low FT3 syndrome, in liver cirrhosis patients. These findings suggest that monitoring thyroid hormone levels, especially FT3, could aid in prognostication and risk assessment for liver cirrhosis patients. Understanding the relationship between thyroid dysfunction and liver disease severity may also inform therapeutic interventions, potentially offering avenues for targeted management strategies in this patient population.

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