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ORIGINAL RESEARCH

Examining the Relationship between Thyroid Hormones and Chronic Liver Disease: A Case-Control Study

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ABSTRACT

Background: Chronic liver disease (CLD) is often associated with alterations in liver function and thyroid profiles. **Aim:** Therefore, the present study aimed to evaluate and compare liver function and thyroid profile parameters in patients with chronic liver disease and healthy controls. **Methods**: A case-control study was conducted at the Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, from 2019 to 2021. The study assessed various liver function and thyroid profile parameters, including Bilirubin, SGPT, SGOT, T3, T4, FT3, FT4, and TSH. Blood samples were collected for biochemical analysis, and statistical significance was determined using t-tests and Pearson's correlation. **Results**: Liver function parameters (Bilirubin, SGPT, SGOT) were significantly higher in cases compared to controls ($p < 0.01$ for all). Bilirubin was 2.45 ± 0.61 in cases vs. 0.96 ± 0.19 in controls, SGPT was 52.05 ± 7.51 vs. 27.35 ± 7.43, and SGOT was 48.31 ± 6.96 vs. 32.45 ± 7.78. Thyroid profile parameters, including T3, T4, FT3, FT4, and TSH, were significantly lower in cases ($p < 0.01$). Correlation analysis revealed a moderate negative correlation between Bilirubin and thyroid function ($r = -0.46$, $p = 0.003$), and a positive correlation between SGOT and thyroid function ($r = 0.38$, $p = 0.014$). SGPT showed a weak non-significant correlation ($r = 0.27$, $p = 0.091$). **Discussion & Conclusion**: This study demonstrates significant alterations in liver function and thyroid profile parameters in patients with chronic liver disease compared to controls. The findings highlight the potential interaction between liver function and thyroid status, suggesting that thyroid dysfunction may be an important consideration in the management of chronic liver disease.

Keywords: Chronic liver disease, liver function parameters, thyroid profile, Bilirubin, correlation analysis.

INTRODUCTION

Chronic liver disease, including cirrhosis, remains a critical global health issue. According to the World Health Organization (WHO), chronic liver disease affected approximately 2.5 million individuals in 2014, leading to 1.3 million deaths. Of these, alcohol-related liver damage accounted for 348,000 deaths, while hepatitis C and hepatitis B contributed to 326,000 and 371,000 deaths, respectively (**Vos et al., 2016**). Liver cirrhosis is a progressive disease characterized by the replacement of healthy liver tissue with scar tissue, impairing liver function. This scarring obstructs blood flow within the liver, slows the metabolism of nutrients, hormones, drugs, and toxins, and reduces the production of essential proteins and other substances (**Prasad & Pandey, 2016**). Given the liver's central role in thyroid hormone metabolism, exploring the interplay between the thyroid and liver is essential for advancing our understanding of these interdependent systems.

In cirrhosis, thyroid hormone profiles often reveal low total and free T3 levels with elevated reverse T3 (rT3), a pattern resembling sick euthyroid syndrome (Israel et al., 1979). These changes result from decreased activity of deiodinase type 1, which reduces the conversion of T4 to T3, coupled with increased conversion of T4 to rT3 by deiodinase type 3. The plasma T3; rT3 ratio negatively correlates with cirrhosis severity and serves as a liver function indicator independent of protein binding (**Bermudez**

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et al., 1975). These alterations may reflect an adaptive hypothyroid state that reduces metabolic demands within hepatocytes, thereby conserving liver function and protein stores. Notably, studies suggest that hypothyroidism in cirrhosis might improve biochemical liver function, highlighting a potential therapeutic avenue that warrants further exploration.

The present study aims to examine the relationship between thyroid hormones—specifically T3, T4, FT3, FT4, and TSH—and chronic liver disease. By evaluating hormone levels in individuals with liver dysfunction and analyzing their correlations, the study seeks to provide insights into thyroid hormone imbalances and their association with the progression of liver disease.

METHODOLOGY

Ethical Permission & Consent to Participate

The study was granted approval by the Institutional Ethics Committee of Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, prior to its commencement [IEC-1772]. Informed written consent was obtained from all participants prior to the collection of data and blood samples. Participation was entirely voluntary, and strict confidentiality of all personal and medical information was upheld throughout the course of the study.

Study Design, Selection of Participants and Inclusion Criteria & Exclusion Criteria

The study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine at the MMIMSR, Mullana, Ambala. It followed a case-control study design and was carried out over a period of three years, from 2019 to 2021. The study population consisted of patients who attended the outpatient department (OPD) of the Department of Medicine at MMIMSR for the management of chronic liver disease. A total of 80 participants were included in the study, comprising 40 cases of chronic liver disease and 40 age- and sex-matched controls. Both male and female participants were selected from the Department of Medicine outpatient clinic at MMIMSR.

The study included patients diagnosed with chronic liver disease, of either sex (male and female), and within the age range of 18 to 80 years. Only those patients who voluntarily agreed to participate in the study after providing written informed consent were included. The control group comprised age- and sex-matched individuals who were healthy, with no history of chronic liver disease or thyroid disorders, and no significant medical conditions.

Patients with known thyroid disorders without liver cirrhosis were excluded from the study. Additionally, individuals with a history of organ failure, cancer, or those who had undergone radiotherapy or chemotherapy were not considered. Patients with active infections, including those affecting the bone, muscle, cardiac system, or those with diabetes, chronic kidney disease, or nephrotic syndrome, were also excluded. Furthermore, participants who were using medications known to interfere with thyroid metabolism, such as levothyroxine, propylthiouracil, carbimazole, iodine, amiodarone, and beta-blockers, were excluded from the study.

Study Tool

A self-designed, pre-tested questionnaire was used to assess the characteristics of chronic liver disease in patients attending the Medicine OPD at M.M. Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala. The questionnaire consists of three sections: Section A covers personal details, Section B addresses risk factor information, and Section C includes laboratory investigations. Clinical diagnosis plays a crucial role in confirming the presence of chronic liver disease, ensuring the accuracy of the findings.

Collection and Processing Of Blood Sample &Biochemical Investigation

A 5 ml venous blood sample was carefully collected from the antecubital vein of each subject using a sterile, disposable syringe under aseptic conditions. The sample was then transferred to a sterile, dry, acid-washed vial for subsequent biochemical analysis. After collection, the blood was allowed to stand for 30 minutes to promote clot formation. Once the clot had formed, the supernatant was carefully separated and centrifuged for further testing. The thyroid-stimulating hormone (TSH) levels were measured using the Advia Centaur® XP, employing advanced direct chemiluminometric technology. Similarly, the levels of thyroxine (T4) and triiodothyronine (T3) were also determined using the same system. Additionally, free T3 (FT3) and free T4 (FT4) levels were quantified using precise direct radioimmunoassay methods.

Statistical Analysis

The data collected were entered into a Microsoft Excel worksheet and statistically analyzed using SPSS (Statistical Package for the Social Sciences) version 20. Proportions were expressed as percentages, and the chi-square test was applied to assess associations between various variables. For quantitative data, the mean, standard mean, standard deviation, and t-test were calculated. A p-value of less than 0.05 (<0.01) was considered statistically significant (highly significant) at a 95% confidence interval.

RESULT

In the present study, 40 cases and 40 controls were analyzed, with both groups consisting of 30 males and 10 females (**Figure 1A**), ensuring an equal gender distribution (**Table 1**). The distribution across different age groups revealed that the highest number

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of cases was observed in the 45–55 age group (**Figure 1B**), marking it as the peak age range for cases. In contrast, the total number of controls was slightly higher than the total number of cases across most age groups, suggesting a marginally greater representation of controls overall (**Table 1**).

The study conducted a comprehensive analysis of liver function and thyroid profile parameters in both cases and controls, providing mean and standard deviation (Mean ± SD) values along with statistical comparisons. It was observed that various liver function parameters in the cases, including Bilirubin (2.45 ± 0.61), SGPT (52.05 ± 7.51), and SGOT (48.31 ± 6.96), were significantly higher than those in controls (**Figure 1C**), which had Mean ± SD values of Bilirubin (0.96 ± 0.19), SGPT (27.35 ± 7.43), and SGOT (32.45 ± 7.78) (**Table 2**). A t-test was performed to evaluate the statistical significance of these differences, and the results showed highly significant variations (**Table 2**).

Moreover, the comparison of thyroid profile parameters between cases and controls revealed statistically significant differences across all variables (**Figure 1D**). T3 levels were significantly lower in cases (84.16 ± 9.6) compared to controls (93.14 ± 7.90) with a t-value of -4.57 and a p- value of < 0.001. Similarly, T4 levels were significantly reduced in cases (6.18 ± 1.3) versus controls (7.04 ± 1.26), with a t-value of -2.97 and a p-value of 0.004. FT3 and FT4 levels were also lower in cases (3.61 ± 0.09 vs. 4.22 ± 0.65, t = -3.45, p = 0.001; and 11.35 ± 2.67 vs. 12.88± 2.35, t = -2.72, p = 0.008, respectively). Additionally, TSH levels were significantly lower in cases (3.15 ± 0.92) compared to controls (3.65 ± 0.95), with a t-value of -2.42 and a p-value of 0.018 (**Table 3**).

In the present study, the correlation analysis of liver function parameters revealed a statistically significant moderate negativecorrelation for Bilirubin& T3 (r = -0.46, P = 0.003) (**Figure 2A**) and a significant moderate positive correlation for SGOT (r = 0.38, P = 0.014) (**Figure 2B**). In contrast, SGPT demonstrated a weak positive correlation (r = 0.27) that was not statistically significant (P = 0.091) (**Figure 2C**). These findings underscore meaningful associations for Bilirubin and SGOT, while SGPT exhibited a weaker and non-significant relationship (**Table 4**).

Table 1: Demographic distribution

Variable	Category	Case		Controls	
		N	%	N	%
Gender	Male	30		30	
	Female	10		10	
Age	25 – 35	5		4	
	35 – 45	7		10	
	45 – 55	20		20	
	55 – 80	8		6	
Male	25 – 35	2		2	
	35 – 45	3		3	
	45 – 55	18		20	
	55 – 80	7		5	
Female	25 – 35	3		2	
	35 – 45	4		7	
	45 – 55	2		0	
	55 – 80	1		1	

Table 2: Distribution of Biochemical parameters of liver function of cases & control

Parameters	Cases			Controls			Statistical Testing	
	N	Min-Max	Mean±SD	N	Min-Max	Mean±SD	t-value	p-value
Bilirubin	40	1.3-3.8	2.45±0.61	40	0.6-1.3	0.96±0.19	14.74	<0.001
SGPT	40	40-72	52.05±7.51	40	15-42	27.35±7.43	14.79	<0.001
SGOT	40	32-65	48.31±6.96	40	13-49	32.45±7.78	9.61	<0.001

Table 3: Distribution of Biochemical parameters of Thyroid Hormones of Cases & Controls.

Parameter	Case			Controls			Statistical Testing	
	N	Min-Max	Mean±SD	N	Min-Max	Mean±SD	t-value	p-value
T3	40	76-114	84.16±9.6	40	82-118	93.14±7.90	-4.57	<0.001
T4	40	3.6-9.7	6.18±1.3	40	4.6-10.2	7.04±1.26	-2.97	0.004
FT3	40	2.55-6.1	3.61±0.09	40	2.8-6.4	4.22±0.65	-3.45	0.001
FT4	40	6.3-16.4	11.35±2.67	40	8.75-16.4	12.88±2.35	-2.72	0.008
TSH	40	1.73-5.4	3.15±0.92	40	2.5.5	3.65±0.95	-2.42	0.018

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Table 4: Showing correlation of T3 with Biochemical parameters of Chronic Liver Disease

Parameter	Pearson's Correlation (r)	P value
T3 & Bilirubin	-0.46	0.003
T3 & SGOT	0.38	0.014
T3 & SGPT	0.27	0.091

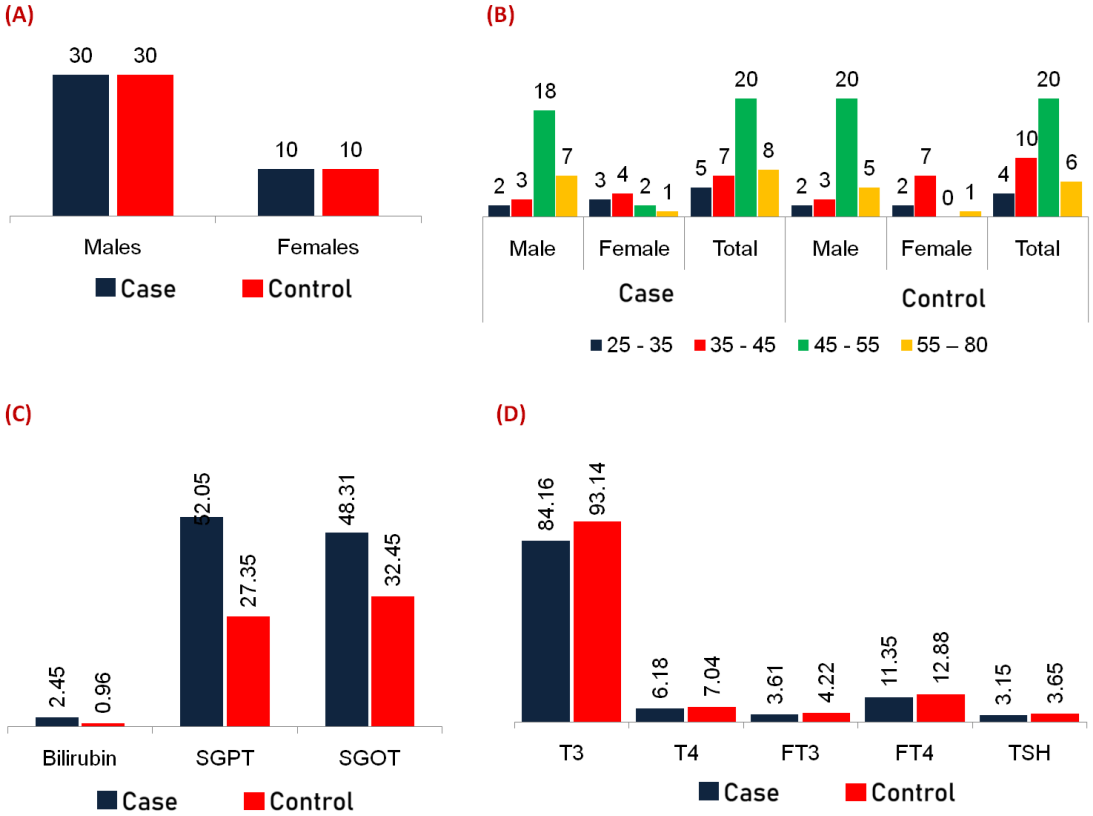

Figure 1: (A) Distribution of study subjects. (B) Age-wise distribution of patients in the study groups. (C) Comparison of liver function parameters between cases and controls. (D) Comparison of thyroid function parameters between cases and controls.

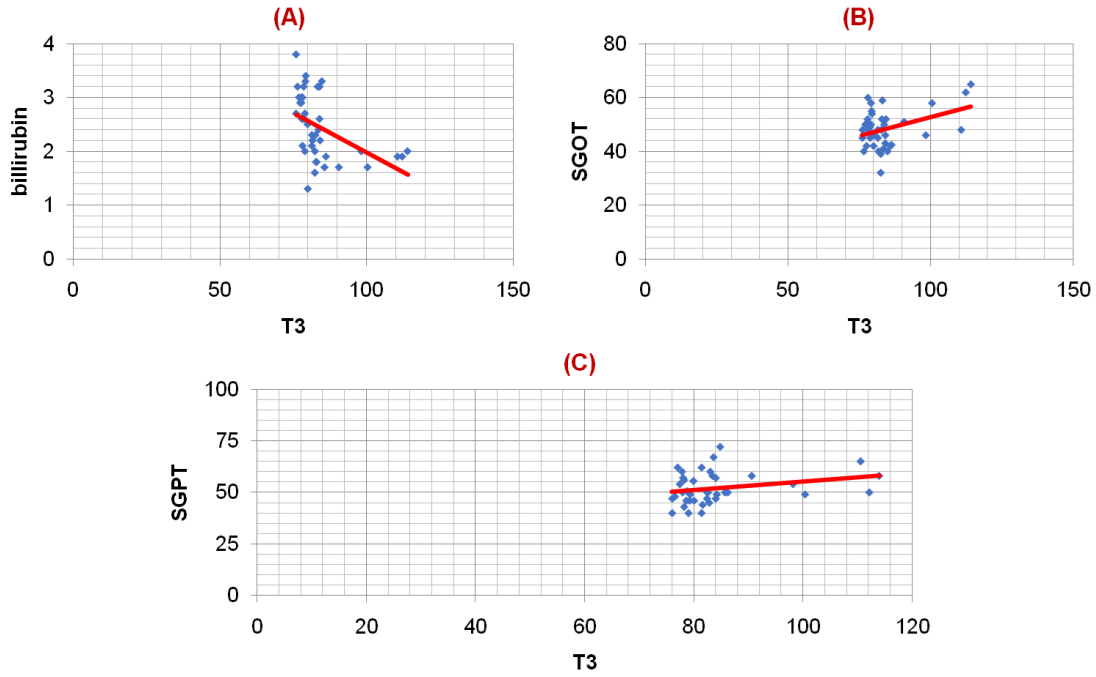

Figure 2: (A) Scatter diagram showing the correlation between T3 and Bilirubin. (B) Scatter plot showing the correlation between T3 and SGOT. (C) Scatter plot showing the correlation between T3 and SGPT.

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DISCUSSION

The liver's critical role in thyroid hormone metabolism, which includes the conjugation, excretion, peripheral deiodination, and synthesis of thyroid binding globulin, underscores its importance in regulating thyroid function. This study reaffirms the presence of significant thyroid hormone disturbances in chronic liver disease (CLD), particularly the marked decrease in serum triiodothyronine (T3) levels, which correlates with the severity of the liver disease. These findings align with the results of Israel et al., who demonstrated a significant association between serum T3 concentrations and the severity of liver dysfunction. Their study further suggested that progressive increases in T3 levels were linked to favorable outcomes, indicating that T3 levels might serve as a useful prognostic indicator in patients with advanced liver disease. Our findings corroborate these observations, particularly the inverse relationship between T3 serum concentration and liver disease severity.

Correlation with Liver Function Markers

Simple correlation analysis in our study also revealed a significant association between serum T3 levels and serum bilirubin, as well as serum glutamic-oxaloacetic transaminase (SGOT). While there was a correlation with serum glutamic-pyruvic transaminase (SGPT), it did not reach statistical significance. These findings suggest that T3 concentration could serve as a sensitive biomarker of hepatic function in liver disease, offering a valuable tool for clinicians in assessing the extent of liver damage. The relationship between low T3 levels and elevated bilirubin and SGOT underscores the potential role of thyroid hormones as markers of liver injury and dysfunction.

Comparison with Existing Literature

Our study is consistent with the work of who observed normal free T3 (FT3) and free T4 (FT4) concentrations in a small group of cirrhotic patients, while a subset of alcoholic fatty liver disease (AFLD) patients exhibited low FT4 and normal FT3 levels. These findings align with our own observations, where we found a pattern of decreased FT3 and either normal or elevated FT4 in patients with chronic liver disease. The discrepancy in FT3 and FT4 levels can likely be attributed to impaired peripheral conversion of T4 to T3 due to liver dysfunction. This is a well-documented phenomenon in liver disease, where altered liver function hinders the deiodination of T4, leading to reduced T3 levels despite normal or elevated T4 levels.

Additionally, the findings of studies involving equilibrium dialysis, which consistently report decreased FT3 and normal or frequently increased FT4 concentrations, are further supported by our results using direct radioimmunoassay of FT3 and FT4. These observations confirm that thyroid hormone abnormalities are common in chronic liver disease, even in asymptomatic cirrhotic patients. As thyroid function tests can be abnormal in liver disease despite normal TSH values, these abnormalities should be considered when assessing the prognosis of liver disease.

Thyroid Hormones as Prognostic Markers

The relationship between thyroid hormone derangements and liver disease severity is not only of academic interest but also has important clinical implications. As seen in the work by Borzio et al., who found significantly reduced T3 levels in patients with cirrhosis and chronic hepatitis, thyroid dysfunction may serve as a valuable marker of liver disease progression. The inverse correlation between T3 levels and liver function parameters, particularly in cirrhosis and chronic hepatitis, suggests that thyroid hormone levels could be utilized to gauge the degree of hepatic injury. Additionally, T3 concentration could potentially serve as a sensitive marker for monitoring the progression of liver disease and predicting patient outcomes.

Furthermore, studies such as those by Nomura et al. (1975), which reported differences in TSH values between liver disease patients and healthy controls, highlight the variability of thyroid function in CLD. The presence of thyroid dysfunction in patients with asymptomatic cirrhosis indicates that thyroid abnormalities should be actively monitored in liver disease patients, particularly in those with advanced stages of liver dysfunction.

Implications for Clinical Practice

Given the relationship between thyroid dysfunction and liver disease severity, clinicians should consider incorporating thyroid function tests into the diagnostic and monitoring protocols for patients with chronic liver disease. Monitoring T3 levels, in particular, could offer valuable insights into liver function and prognosis. It may also provide clinicians with an early indicator of worsening liver function or progression to cirrhosis, potentially guiding therapeutic interventions.

Moreover, given the complex interplay between thyroid hormones and liver function, further research is needed to explore the potential for thyroid hormone replacement or modulation as part of a therapeutic strategy in liver disease. Investigating whether normalization of thyroid hormone levels could have a positive effect on liver function or slow disease progression could open up new avenues for treatment, especially for patients with advanced liver disease or those at risk for liver failure.

Limitations and Future Research

While our study presents important findings regarding the relationship between thyroid hormones and liver disease, there are several limitations that must be considered. First, our study was cross-sectional, and

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thus causality cannot be definitively established. Longitudinal studies that track thyroid hormone levels over time in patients with chronic liver disease would provide more insight into the dynamics of thyroid dysfunction and its role in disease progression. Additionally, our study did not focus on the specific types of liver diseases such as hepatitis B, hepatitis C, or non-alcoholic fatty liver disease, all of which may have distinct effects on thyroid function. Future research should aim to explore these variations across different liver pathologies to better understand how specific liver conditions influence thyroid hormone metabolism.

CONCLUSION

In conclusion, the study underscores the importance of regularly monitoring thyroid function in patients with chronic liver disease, particularly those with cirrhosis. Despite most patients maintaining euthyroidism, thyroid abnormalities were prevalent, with significant correlations observed between thyroid hormone levels (FT3, FT4, TSH) and the severity of liver dysfunction.

Given the increased risk of hypothyroidism in cirrhotic patients, early detection and management of thyroid dysfunction are crucial to optimize patient care and prevent potential complications.

Declaration

Ethical Approval & Informed Consent: The research was reviewed and approved by the Institutional Ethics Committee of Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, with approval number [IEC-1772]. Informed written consent was obtained from all participants after they were fully briefed on the study's nature, objectives, & procedures.

Code Included: NA

Conflict of Interest: The authors declare no conflict of interest.

Data Integrity: No data was manipulated, and the integrity of the data is maintained.

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