Section: General Medicine

Original Research Article

MAGNITUDE OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AMONG PATIENTS WITH HYPOTHYROIDISM

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Abstract

Background: The prevalence of non-alcoholic fatty liver disease (NAFLD) has risen globally, becoming a leading cause of liver disease. NAFLD is closely associated with obesity, insulin resistance, and genetic factors, progressing from simple steatosis to advanced liver conditions. Hypothyroidism, a common endocrine disorder, may be linked to NAFLD. However, the association between hypothyroidism and NAFLD remains unclear, with studies yielding inconsistent results. This study aims to explore the correlation between thyroid dysfunction and NAFLD severity. **Materials and Methods:** A hospital-based cross-sectional analytical study was conducted at Trichy SRM Medical College Hospital from January to April 2024. The study involved 58 patients admitted with thyroid disorders. Patients aged 18 and above were included, excluding those with conditions affecting thyroid function or other metabolic diseases. NAFLD severity was assessed using abdominal ultrasonography, and thyroid function was measured through TSH, T3, and T4 levels. Statistical analysis was performed using SPSS version 22.0. **Result:** The study population had a slightly higher proportion of females (53.4%) with a mean age of 49.6 years. A significant association was observed between thyroid function and NAFLD severity. Patients with subclinical and overt hypothyroidism had higher NAFLD grades, with increased TSH and decreased fT4 levels correlating with worsening liver disease. Specifically, TSH levels rose significantly with NAFLD severity, while fT4 levels decreased, indicating a significant relationship between thyroid dysfunction and NAFLD progression ($p < 0.05$). **Conclusion:** The study demonstrates a significant association between hypothyroidism and the severity of NAFLD. Higher TSH and lower fT4 levels were correlated with more severe NAFLD. These findings emphasize the importance of thyroid function monitoring in NAFLD patients to prevent disease progression. Future research should explore the mechanisms underlying this relationship and potential therapeutic interventions targeting thyroid hormones in NAFLD management.

INTRODUCTION

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased substantially over the past decades, becoming the leading cause of liver disease worldwide. This rise can be partly attributed to the increasing prevalence of obesity. NAFLD is characterized by hepatic fat accumulation without significant alcohol consumption and is influenced by insulin resistance (IR) and genetic predisposition. NAFLD encompasses a spectrum from simple steatosis to steatohepatitis, fibrosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC). NAFLD is associated with various conditions, including cardiovascular disease, type 2 diabetes, chronic kidney disease, and cancer. Identifying risk factors for NAFLD is crucial for developing effective preventive interventions.[1,2]

Hypothyroidism is a common endocrine disorder affecting lifelong health. The thyroid gland plays a critical role in cell metabolism and energy homeostasis. Thyroid dysfunction is linked to numerous diseases, including cardiovascular diseases, chronic kidney disease, dementia, and fractures. Hypothyroidism can be overt, characterized by elevated thyroid-stimulating hormone (TSH) and low free thyroxine (fT4), or subclinical, characterized by elevated TSH and normal fT4 without clinical symptoms. Studies suggest a significant association between hypothyroidism and NAFLD, with hypothyroidism prevalence among NAFLD patients ranging from

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15.2% to 36.3%.[3-5] Although some studies suggest a strong correlation between hypothyroidism and NAFLD, other studies have found no such association, highlighting the need for further research to clarify this relationship.[6-8]

MATERIALS AND METHODS

This hospital-based cross-sectional analytical study was conducted at Trichy SRM Medical College Hospital and Research Centre, Irungalur, Tiruchirappalli, from January 2024 to April 2024. The study population included patients admitted with thyroid disorders in the Department of General Medicine. The sample size was determined to be 58 based on the prevalence of hypothyroidism in NAFLD patients reported by Chung et al.[1] Inclusion criteria were patients aged 18 years and above, admitted with thyroid disorders, and willing to provide informed consent. Exclusion criteria included patients unwilling to provide consent, those on medications affecting thyroid function, those with hypothalamus or pituitary disease, long-term alcohol consumption, viral hepatitis, autoimmune hepatitis, Wilson's disease, total parenteral nutrition, inflammatory bowel disease, Cushing's syndrome, or those taking specific medications like tamoxifen, amiodarone, sodium valproate, methotrexate, or glucocorticoids.

After obtaining Institutional Ethics Committee clearance and written informed consent, detailed histories and clinical examinations were conducted. Blood and urine samples were collected and analyzed. Hypothyroidism was diagnosed based on high TSH, low T3 or T4 levels, and clinical symptoms. The reference ranges for thyroid function tests used in this study were as follows: triiodothyronine (T3) levels were considered normal if they ranged between 100 and 200 nanograms per deciliter (ng/dL), thyroxine (T4) levels were normal between 4.5 and 11.2 micrograms per deciliter (mcg/dL), and thyroid-stimulating hormone (TSH) levels were normal between 0.4 and 5.0 milli-international units per liter (mIU/dL). Abdominal ultrasonography was used to assess NAFLD severity. When the echogenicity is just increased, it is grade I; when the echogenic liver obscures the echogenic walls of portal vein branches, it is grade II, and, when the echogenic liver obscures the diaphragmatic outline, it is grade III fatty infiltration.[9] The correlation between TSH, T3, T4 levels, and NAFLD grading was analyzed using appropriate statistical measures.

Normal distribution variables were expressed as mean ± standard deviation. Comparisons between groups were performed using the independent sample T-test. The chi-squared test compared categorical variables. The association between fatty liver disease in USG and thyroid function was analyzed using linear regression analysis. Statistical analyses were performed with SPSS software package version 22.0.

RESULTS

The study population consisted of a slightly higher proportion of females (53.4%) compared to males (46.6%), with a mean age of 49.6 years (SD ± 12.8), indicating a middle-aged demographic. A significant portion of the participants (43.1%) were classified as overweight or obese, highlighting the relevance of weight management in this group. Nearly 40% of the participants had a family history of coronary artery disease (CAD), suggesting a genetic predisposition and potential interplay between CAD, NAFLD, and thyroid function. About 34.5% of the participants were smokers, and 17.2% were alcohol consumers, both of which are risk factors for NAFLD and other metabolic disorders. Additionally, the prevalence of hypertension (46.6%) and diabetes (36.2%) was notably high among the participants, underscoring the co-occurrence of these metabolic conditions with NAFLD and thyroid dysfunction. These findings emphasize the importance of an integrated approach to managing multiple risk factors in this population to mitigate the progression of metabolic and cardiovascular diseases. [Table 1]

The distribution of NAFLD grades among the study participants shows that the majority were classified as NAFLD Grade 1 (36.21%), followed by Grade 2 (32.76%) and Grade 3 (31.03%). This indicates a relatively balanced distribution of NAFLD severity within the study population. When examining thyroid function, the majority of participants had normal thyroid function (37.93%), followed closely by those with subclinical hypothyroidism (36.21%). A smaller proportion of participants had overt hypothyroidism (25.86%). A significant association between thyroid function and NAFLD severity was observed in [Table 2]. Patients with normal thyroid function predominantly had NAFLD Grade 1 (63.64%), while those with subclinical hypothyroidism showed a higher prevalence of NAFLD Grade 2 (38.1%) and Grade 3 (33.33%). Patients with overt hypothyroidism had the highest prevalence of NAFLD Grade 3 (53.33%). The chi-square test indicated a significant difference ($\chi^2 = 14.21$, $p = 0.006$) among the groups, suggesting that the severity of NAFLD increases with the progression of hypothyroidism. This finding highlights the importance of monitoring and managing thyroid function in patients at risk for or diagnosed with NAFLD to mitigate the progression of liver disease.

A significant relationship between thyroid hormone levels and the severity of non-alcoholic fatty liver disease (NAFLD) was observed in our study [Table 3]. There is a notable increase in thyroid-stimulating hormone (TSH) levels with rising NAFLD severity: mean TSH levels are 4.8 mIU/L for NAFLD Grade 1, 5.5 mIU/L for NAFLD Grade 2, and 6.9 mIU/L for NAFLD Grade 3, with a significant F value of 4.0281 and a p-value of 0.023. Similarly, Free T4 levels decrease as NAFLD severity increases, with mean levels of 1.3 ng/dl, 1.2

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ng/dl, and 1.0 ng/dl for NAFLD Grades 1, 2, and 3 respectively, and a significant F value of 4.7681 and a p-value of 0.012. Although Free T3 levels also decrease with greater NAFLD severity (3.1 ng/dl for Grade 1, 3.0 ng/dl for Grade 2, and 2.7 ng/dl for Grade 3), the differences are not statistically significant (F value of 1.5029 and p-value of 0.2315). These findings indicate that higher TSH levels and lower Free T4 levels are significantly associated with increased NAFLD severity, underscoring the role of thyroid dysfunction, particularly hypothyroidism, in NAFLD progression.

The study presents a significant correlation between thyroid dysfunction and the severity of non-alcoholic fatty liver disease (NAFLD). Higher thyroid-stimulating hormone (TSH) levels and lower Free T4 levels are strongly associated with increased NAFLD severity, indicating the pivotal role of thyroid hormones in liver disease progression. Additionally, as NAFLD severity escalates, there is a noticeable worsening in lipid profiles, with total cholesterol, LDL cholesterol, and triglycerides rising significantly while HDL cholesterol decreases. Liver enzyme levels (SGOT, SGPT, and ALP) also increase markedly with more severe NAFLD, reflecting deteriorating liver function. Fasting blood glucose levels show a similar trend, rising with NAFLD severity and suggesting an association with impaired glucose metabolism. However, urea and creatinine levels remain within normal ranges across all NAFLD grades, indicating stable kidney function. Hemoglobin levels also show no significant variation, suggesting anemia is not a major concern in this cohort. [Table 4] These findings underscore the importance of comprehensive metabolic and thyroid function monitoring in patients with NAFLD to manage and mitigate disease progression effectively.

Table 1: Demographic Characteristics of Study Participants

Characteristic	Frequency (%)
Male	27 (46.6%)
Female	31 (53.4%)
Age (Mean ± SD)	49.6 ± 12.8
Overweight/Obese	25 (43.1%)
Family History of CAD	23 (39.7%)
Smokers	20 (34.5%)
Alcohol Consumers	10 (17.2%)
Hypertension	27 (46.6%)

Table 2: Thyroid Function and NAFLD Severity

Thyroid Function	NAFLD Grade 1 (n, %)		NAFLD Grade 2 (n, %)		NAFLD Grade 3 (n, %)		CSV	χ^2 (p-value)
Normal	14	63.64	5	22.73	3	13.63	14.21	0.006
Subclinical Hypothyroidism	6	28.57	8	38.1	7	33.33		
Overt Hypothyroidism	1	6.67	6	40	8	53.33		

Table 3: Thyroid Hormone Levels and NAFLD Severity

AFLD Severity	N	TSH (mIU/L)		Free T4 (ng/dl)		Free T3 (ng/dl)	
		Mean	SD	Mean	SD	Mean	SD
NAFLD Grade 1	21	4.8	2.1	1.3	0.2	3.1	0.7
NAFLD Grade 2	19	5.5	2.4	1.2	0.3	3	0.6
NAFLD Grade 3	18	6.9	2.5	1	0.4	2.7	0.9
F Value		4.0281		4.7681		1.5029	
P Value		0.023		0.012		0.2315	

Table 4: ?.

Parameter	NAFLD Grade 1 (Mean ± SD)	NAFLD Grade 2 (Mean ± SD)	NAFLD Grade 3 (Mean ± SD)	F value	p-value
Total Cholesterol (mg/dl)	180.45 ± 30.12	200.34 ± 35.28	220.56 ± 40.78	3.1	0.041
LDL Cholesterol (mg/dl)	110.23 ± 25.45	120.89 ± 30.12	130.78 ± 35.45	2.98	0.048
HDL Cholesterol (mg/dl)	45.67 ± 10.34	40.56 ± 8.12	35.45 ± 7.23	3.56	0.032
Triglycerides (mg/dl)	150.89 ± 40.34	180.45 ± 45.56	210.34 ± 50.67	5.1	0.009
SGOT (U/L)	35.12 ± 10.45	45.34 ± 15.67	55.56 ± 20.78	4.54	0.015
SGPT (U/L)	40.34 ± 12.45	50.56 ± 17.78	60.78 ± 22.89	4.89	0.011
ALP (U/L)	70.23 ± 20.34	80.45 ± 25.56	90.67 ± 30.78	4.2	0.021
Fasting Blood Glucose (mg/dl)	100.12 ± 15.34	110.45 ± 20.56	120.78 ± 25.67	3	0.04
Urea (mg/dl)	20.56 ± 5.34	22.45 ± 6.12	24.67 ± 7.34	2.34	0.072
Creatinine (mg/dl)	0.90 ± 0.12	0.95 ± 0.14	1.00 ± 0.16	1.56	0.184
Hemoglobin (g/dl)	13.45 ± 1.23	13.34 ± 1.45	13.23 ± 1.67	0.45	0.637

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DISCUSSION

The significant association found between elevated thyroid-stimulating hormone (TSH) levels and non-alcoholic fatty liver disease (NAFLD) severity in our study aligns with several prior investigations, underscoring the intricate relationship between thyroid dysfunction and hepatic steatosis. Chung et al. reported a higher prevalence of NAFLD among patients with subclinical and overt hypothyroidism, paralleling our findings where patients with overt hypothyroidism exhibited the highest prevalence of NAFLD Grade 3 (53.33%) .1 Similarly, Ludwig et al. established a significant relationship between thyroid dysfunction and hepatic steatosis in a population sample aged 18 to 65 years, reinforcing our observation of increased NAFLD severity with elevated TSH levels and decreased free thyroxine (fT4) levels.[2]

Our results are consistent with the Rotterdam Study, which found a heightened risk of NAFLD associated with lower thyroid function. This study highlighted the importance of monitoring thyroid function to mitigate the progression of liver disease.[3] Moreover, van den Berg et al. identified a higher free triiodothyronine (T3) association with NAFLD in euthyroid subjects, though our study did not find a statistically significant difference in T3 levels across NAFLD grades.[4] The meta-analysis by He et al. also supports our findings, establishing hypothyroidism as a risk factor for NAFLD, further emphasizing the need for integrated thyroid and liver function management.[5]

Interestingly, not all studies agree on the strength of this association. For instance, Puigserver and Spiegelman reported metabolic regulation via the peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1 alpha) pathway, suggesting that the intricate interplay of metabolic pathways may influence the variability observed in different studies.[6] Polyzos et al. also noted that while NAFLD and hypothyroidism share common risk factors like obesity and insulin resistance, the direct causal relationship remains under investigation.[7]

Lonardo et al. discussed the increased risk of diabetes and cardiovascular disease in NAFLD patients, paralleling our findings where a significant portion of the study population exhibited comorbid conditions such as hypertension (46.6%) and diabetes (36.2%).[10] Corey et al. identified obesity and type 2 diabetes as independent risk factors for nonalcoholic steatohepatitis (NASH) and fibrosis, conditions closely related to NAFLD progression.[11] Targher et al. similarly reported an independent association between NAFLD and an increased incidence of cardiovascular events in type 2 diabetic patients, highlighting the systemic nature of NAFLD.[12]

The multifaceted nature of NAFLD as a multisystem disease, as described by Byrne and Targher, emphasizes the need for a holistic approach to management, addressing both liver-specific and systemic risk factors.[13,14] The results of Adams et al and Sanyal et al also demonstrate similar results to our study.[15,16]

The observed worsening of lipid profiles with increasing NAFLD severity is also noteworthy. Total cholesterol, LDL cholesterol, and triglycerides rise while HDL cholesterol decreases, aligning with the known pathophysiology of NAFLD where hepatic steatosis and inflammation contribute to dyslipidemia. This observation is supported by the work of Kartsoli et al,[17] who emphasized the frequent lipid abnormalities in NAFLD patients and the need for targeted lipid-lowering interventions to reduce cardiovascular risk.

Furthermore, the significant elevation of liver enzymes (SGOT, SGPT, and ALP) with greater NAFLD severity reflects worsening liver function and potential liver damage. This finding is critical for clinical practice, as it suggests that regular monitoring of liver enzymes can serve as an indicator of disease progression and the effectiveness of therapeutic interventions. The study by Pagadala et al,[18] also highlighted the high prevalence of liver enzyme abnormalities in NAFLD patients with hypothyroidism, corroborating our findings.

The rise in fasting blood glucose levels with NAFLD severity suggests an association with impaired glucose metabolism. This observation underscores the interplay between liver disease and glucose homeostasis, indicating that patients with NAFLD are at higher risk for developing insulin resistance and type 2 diabetes. The study by Targher and Byrne discussed the systemic implications of NAFLD, including its impact on glucose metabolism, supporting the need for comprehensive metabolic monitoring in these patients.[19]

Additionally, urea and creatinine levels, although not significantly different among the NAFLD grades, were within normal ranges, suggesting that kidney function remained relatively stable across the study population. Hemoglobin levels also showed no significant variation, indicating that anemia is not a major concern.

CONCLUSION

In conclusion, our hospital-based cross-sectional study found a significant association between hypothyroidism and the severity of non-alcoholic fatty liver disease (NAFLD). Elevated TSH levels and decreased fT4 levels were significantly correlated with increased NAFLD severity, highlighting the critical role of thyroid dysfunction, particularly hypothyroidism, in NAFLD progression. These findings underscore the necessity for routine thyroid function monitoring and integrated management approaches in patients at risk for or diagnosed with NAFLD to mitigate the progression of liver disease.Future research should focus on elucidating the underlying mechanisms linking thyroid dysfunction and NAFLD, exploring potential

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therapeutic interventions targeting thyroid hormone pathways, and conducting longitudinal studies to establish causality and assess the impact of thyroid hormone normalization on NAFLD outcomes.

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