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TO STUDY THE PREVALENCE OF HYPOTHYROIDISM IN NON-ALCOHOLIC FATTY LIVER DISEASE IN NORTHERN POPULATION

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ABSTRACT:

Background: Non alcoholic fatty liver disease (NAFLD) is a prevalent condition characterized by the accumulation of fat in the liver, independent of significant alcohol consumption. Emerging evidence suggests a potential association between hypothyroidism and NAFLD, although clinical data and the underlying pathophysiological mechanisms remain unclear, particularly in the Indian population.

Methods: We conducted a hospital-based cross-sectional study involving 50 adult patients diagnosed with NAFLD through abdominal ultrasound at tertiary care hospital in eastern India. Patients were assessed for thyroid status using thyroid function tests (free T3, free T4, and TSH). Exclusion criteria included chronic hepatitis B or C, haemochromatosis, and use of certain medications.

Results: The study revealed a significant association between serum Free T4 levels and the severity of fatty liver, with higher Free T4 levels correlating with lower grades of fatty liver. Serum TSH levels also demonstrated a significant association, with lower TSH levels corresponding to higher grades of fatty liver. Additionally, there was a notable prevalence of hypothyroidism among NAFLD patients, particularly in those with higher grades of fatty liver.

Conclusion: Our findings highlight the importance of thyroid function in NAFLD, suggesting that thyroid status assessment, particularly in patients with moderate to severe fatty liver, may be clinically relevant. The prevalence of hypothyroidism among NAFLD patients underscores the need for further research to elucidate the potential therapeutic implications of thyroid hormone replacement in NAFLD management.

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Keywords- *NAFLD, TSH, T3, T4*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to the accumulation of excess fat in the liver, even in cases where there is no considerable history of alcohol consumption (<20 g per day). Non-alcoholic fatty liver disease (NAFLD) is a frequently encountered condition that affects a significant portion of the global population, with a prevalence ranging from 10% to 30% in different countries [1]. The disease spectrum encompasses a benign condition called steatosis, characterized by the accumulation of fat in liver cells, which has a low likelihood of progressing further. A minority of these patients, approximately 15%, who develop steatohepatitis, are at a significantly elevated risk of rapidly progressing to fibrosis and cirrhosis. Hypothyroidism has been associated with insulin resistance [2, 3], dyslipidemia [4, 5], and obesity [6, 7], all of which are elements of metabolic syndrome.

The association between diabetes and NAFLD is widely recognized, whereas the connection between hypothyroidism and NAFLD has just recently emerged as a risk factor [8]. Nevertheless, there is insufficient clinical data to fully corroborate this connection, and the underlying pathophysiology of this association is still not well understood. Further data is required to verify and more accurately describe the suggested link between NAFLD and hypothyroidism. The research demonstrating the correlation between non-alcoholic fatty liver disease (NAFLD) and hypothyroidism originate from Western countries, where there is a high prevalence of metabolic syndrome [8–12]. The prevalence of non-alcoholic fatty liver disease (NAFLD) in India ranges from 5% to 30% [12], while the prevalence of hypothyroidism is 10% [13]. The adoption of a western lifestyle has led to an increase in the prevalence of metabolic syndrome. However, there is a lack of material on the Indian subcontinent that establishes a connection between NAFLD and hypothyroidism. Therefore, we choose to carry out a case-control study in order to determine the prevalence of hypothyroidism in consecutive NAFLD patients and evaluate relevant factors (such as dyslipidemia, obesity, and diabetes) that may be associated with hypothyroidism.

MATERIAL AND METHODS

The present hospital based cross sectional study was proposed to be undertaken with a total number of 50 patients of NAFLD diagnosed by ultrasonography whole abdomen, attending the department of medicine of a tertiary care hospital from eastern India . Inclusion Criteria All Patients above 18 years of age with NAFLD visiting indoor and outdoor of our institute. Exclusion Criteria Presence of hepatitis B or C infection, Presence of haemochromatosis, Intake of iodine, antithyroid agents or thyroid hormones, Chronic alcoholic liver disease, Diabetes Mellitus., Intake of drugs like Dopamine, Corticosteroids, miodarone and Phenytoin.The present study was a cross-sectional study carried out on 50 adult patients diagnosed as having non-

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alcoholic fatty liver disease by ultrasonography. Patients having age of < 18 years, chronic hepatitis B or C, haemochromatosis, taking iodine, antithyroid drugs or thyroid hormones, chronic alcoholic liver disease, diabetes mellitus and intake of drugs like dopamine, corticosteroids, amiodarone and phenytoin were excluded from the study. Detailed history and clinical examination was conducted on all patients and they underwent routine investigations and thyroid function test (free T3, free T4, and TSH).

RESULT

A significant association was observed between serum Free T4 levels and grades of fatty liver in the study population. Among individuals with normal Free T4 levels, the prevalence of Grade 1 fatty liver was 91%, decreasing to 79% for Grade 2 and further to 36% for Grade 3. Conversely, for those with low Free T4 levels, the prevalence of fatty liver increased from 9% for Grade 1 to 21% for Grade 2 and notably to 64% for Grade 3. These findings suggest a potential correlation between Free T4 levels and the severity of fatty liver, highlighting the importance of thyroid function in the context of liver health.

Table 1. Relationship of Serum Free t4 Levels with Grades of Fatty Liver

Serum Free T4 Levels	Grades of Fatty Liver						Total	Chi- e Squar Value	P-Value
	Grade 1		Grade 2		Grade 3				
	(n 23)	%	(n=21)	%	(n=6)	%			
Normal	21	91 %	17	79 %	2	36 %	**40**	17.022	0.000
Low	2	9 %	4	21 %	4	64 %	**10**		

The analysis revealed a notable relationship between serum TSH levels and the grading of fatty liver among the study participants. Individuals with serum TSH levels below 5 mIU exhibited a higher prevalence of Grade 1 fatty liver (98%), which gradually decreased to 79% for Grade 2 and notably to 27% for Grade 3. Conversely, those with serum TSH levels exceeding 5 mIU demonstrated a contrasting trend, with only 2% prevalence for Grade 1, rising to 21% for Grade 2, and significantly higher at 73% for Grade 3. This indicates a strong association between lower TSH levels and the severity of fatty liver, underscoring the potential role of thyroid function in the progression of liver pathology.

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Table 2. Relationship of Serum TSH Levels with Grades of Fatty Liver									
Serum TSH Levels	**Grades of Fatty Liver**							**Chi-Square Value**	**P-Value**
	Grade 1		**Grade 2**		**Grade 3**		**Total**		
	(n=23)		**(n=21)**		**(n=6)**				
<5 mIU	22	98 %	17	79 %	2	27 %	**41**	30.677	0.001
>5 mIU	1	2 %	4	21 %	4	73 %	**9**		

The analysis of thyroid status in relation to grades of fatty liver revealed a significant association between these variables. Among individuals with normal thyroid function, the prevalence of Grade 1 fatty liver was notably high at 98%, decreasing to 79% for Grade 2 and further to 27% for Grade 3. In contrast, those classified under subclinical hypothyroidism showed a lower prevalence across all grades of fatty liver, with no cases in Grade 1, 7% in Grade 2, and 9% in Grade 3. Notably, individuals with overt hypothyroidism demonstrated a distinct pattern, with only 2% prevalence for Grade 1, rising to 14% for Grade 2, and significantly higher at 64% for Grade 3. This highlights a clear association between different thyroid statuses and the severity of fatty liver, suggesting the potential impact of thyroid dysfunction on liver health.

Table 3. Relationship of Thyroid Status with Grades of Fatty Liver									
	Grades of Fatty Liver							**Chi-Square**	**p-value**
	Grade 1		**Grade 2**		**Grade 3**		**Total**		
Normal Thyroid	**(n 23)**	**%**	**(n=21)**	**%**	**(n=6)**	**%**			0.000
Function	22	98 %	17	79 %	2	27 %	**41**	33.244	
Subclinical	0	0 %	1	7 %	1	9 %	**2**		
Hypothyroidism									
OvertHypdism	1	2 %	3	14 %	3	64 %	**7**		
othyroi									

The distribution of patients according to thyroid status is as follows: 82% of patients had a normal thyroid status, 4% were classified as having subclinical hypothyroidism, and 14% were diagnosed with overt hypothyroidism. This indicates that the majority of patients in the sample had a normal thyroid status, with a smaller proportion exhibiting varying degrees of hypothyroidism. Overall, there were 50 patients included in the analysis.

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Table 4. Distribution of Patients According to Thyroid Status		
Thyroid Status	**No. of Patients**	**Percentage**
Normal Thyroid Status	41	82 %
Subclinical Hypothyroidism	2	4 %
Overt Hypothyroidism	7	14 %
Total	**50**	**100 %**

DISCUSSION

This study was a cross-sectional analysis conducted on a sample of 50 adult patients who were diagnosed with non-alcoholic fatty liver disease using ultrasonography. The patients were visiting Sri Guru Ram Das Institute of Medical Sciences and Research. Patients under the age of 18, with chronic hepatitis B or C, haemochromatosis, taking iodine, antithyroid medications or thyroid hormones, chronic alcoholic liver disease, diabetes mellitus, and using pharmaceuticals such as dopamine, corticosteroids, amiodarone, and phenytoin were not included in the study. A comprehensive medical history and thorough physical examination were performed on all patients, followed by standard diagnostic tests and thyroid function testing (including free T3, free T4, and TSH).

In this study, 45% of the patients were between the ages of 51 and 70. The average age of the patients was 54.81 ± 17.29 years. The study conducted by Eshraghian A et al found that the average age of patients diagnosed with non-alcoholic fatty liver disease (NAFLD) was 48.20 ± 12.82 years.[14] The study conducted by Ludwig U et al found that the average age of patients with non-alcoholic fatty liver disease (NAFLD) was 47.7 ± 11.5 years. The patients in each of these investigations were in a younger age bracket in comparison to the current study.[15]

In this study, 59% of the patients were male and 41% were female, indicating a predominance of males. According to a study conducted by Ulla Ludwig, 70% of those diagnosed with NAFLD were males, whereas the remaining 30% were females, indicating a male predominance.[15] Conversely, a study conducted by Paul Samaresh et colleagues found that the majority (63.3%) of patients with non-alcoholic fatty liver disease (NAFLD) were female.
In this study, 48% of the patients had a body mass index (BMI) ranging from 25 to 29.9 kg/m2, with an average BMI of 25.10 ± 2.34 kg/m2. In a study conducted by Eshraghian A et al., the average BMI was the value is 29.30 with a standard deviation of 5.44.8. In this study, the average BMI was lower because individuals who were classified as obese with a BMI more than 30 kg/m2 were not included. This is important because obesity is known to be a separate risk factor for non-alcoholic fatty liver disease (NAFLD).In the current study, 26% of both males and females had an aberrant waist-hip ratio based on their respective reference values, whereas the remaining 74% had a normal waist-hip ratio. The average waist-to-hip ratio in females was 0.80 ± 0.16, whereas in males it was 0.89 ± 0.07. The average waist-hip ratio of the patients was 0.85.

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The value is approximately 0.12. A study conducted by Ludwig U et al found that the average waist-hip ratio was 0.9 ± 0.1.9. The discrepancy arises from the exclusion of obese participants in the current investigation.

Within the scope of this study, 47% of the patients had aberrant triglyceride levels, with an average value of 150 ± 78 mg/dl. In contrast, only 24% of the patients had abnormal cholesterol levels, with an average value of 172 ± 108 mg/dl. Thirty-eight percent of the patients exhibited elevated serum LDL-C values, with a mean value of 82 ± 37 mg/dL. 63% of females saw a reduction in serum HDL-C levels below 50 mg/dl, with an average of 36 ± 18 mg/dl. 56% of males exhibited reduced serum HDL-C levels below 40 mg/dl, with a mean value of 40 ± 21 mg/dl.

In this study, 18% of the patients had elevated serum ALT levels, 33% had elevated serum AST levels, and 22% had elevated ALP levels. 14% of the patients had elevated ALT levels up to twice the upper limit of normal, whereas 4% had ALT levels above three times the upper limit of normal. The average serum ALT level in our patients was 49 ± 60 U / L. Out of the patients, 67% had serum AST levels within the normal range. In 21% of the patients, serum AST levels were more than double the normal range, and in 12% of the patients, serum AST levels were more than triple the upper limit of the normal range. The average serum AST level was 40 ± 27 U/L. 22% of the patients exhibited elevated blood alkaline phosphatase levels exceeding 116 mg/dl, while 78% had normal serum alkaline phosphatase levels below 116 mg/dl. The average serum alkaline phosphatase level was 102 ± 48 mg / dl.

In this study, 100 individuals with non-alcoholic fatty liver disease were examined. Among them, 47% had grade 1 fatty liver, 42% had grade 2, and 11% had grade 3 fatty liver as determined by ultrasonography. In a study conducted by Paul Samaresh et al, it was shown that 41.7% of patients with non-alcoholic fatty liver disease (NAFLD) were classified as grade 1, 43.3% were classified as grade 2, and 15.0% had grade 3 fatty liver. These findings align with the results of the current study.[16]

A larger proportion of patients with low free T3 levels were found in the higher grades of fatty liver ($p = 0.114$). The study conducted by Chung et al. provided compelling evidence of the link between hypothyroidism and NAFLD. However, the study did not attribute any diagnostic significance to the concentration of FT3.Out of the patients with fatty liver, 11% had grade 1, 21% had grade 2, and 64% had grade 3. Among these patients, it was observed that those with grade 1, grade 2, and grade 3 fatty liver had low levels of free T4. Therefore, as the grades of fatty liver increased, a higher percentage of patients exhibited low levels of free T4, which was found to be statistically significant ($p = 0.000$). An adverse correlation was seen between low levels of free T4 and rising grades of fatty liver. Ittermann et al conducted a study that showed a strong negative relationship between the concentration of free T4 and NAFLD.[18] Research conducted by Xu et al.[19], Chung et al.[17], and Ittermann et al.[18] has also revealed that having lower levels of free T4 is an independent risk factor for non-alcoholic fatty liver disease

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(NAFLD). The findings of these research align with the findings of the present investigation. Out of the patients with fatty liver, 2% had grade 1, 21% had grade 2, and 73% had grade 3. Among these patients, the TSH level was found to be greater than 5 mIU in all cases. Therefore, as the severity of fatty liver increased, a higher proportion of patients exhibited elevated levels of TSH. This correlation was shown to be statistically significant ($p = 0.001$).In addition to the negative correlation with free T4, Chung et al.11 and Xu et al.[19]discovered a positive correlation between NAFLD and TSH. Research conducted by Carulli et al.[20] and Pagadala et al.[21] indicates that there is a correlation between the level of serum TSH and the extent of hepatic steatosis. Ittermann et al.[12] found no reliable link between serum TSH levels and hepatic steatosis. The results of our investigation revealed a strong and statistically significant correlation between serum TSH levels and the progression of fatty liver disease. Bano et al. conducted a prospective study in 2016[22]to examine the relationship between changes in thyroid function and non-alcoholic fatty liver disease (NAFLD). According to their findings, elevated levels of free T4 were linked to a reduced risk of NAFLD. Moreover, elevated blood TSH levels were linked to a heightened likelihood of experiencing clinically significant fibrosis in non-alcoholic fatty liver disease (NAFLD). The study found that there is a correlation between decreased thyroid function and higher grades of non-alcoholic fatty liver disease (NAFLD). The present investigation found a strong connection between free T4, serum TSH, and rising grades of fatty liver, which is consistent with previous findings.

In grade 1 fatty liver, only one patient (2%) had hypothyroidism. In grade 2 fatty liver, 4 patients (21%) had hypothyroidism, with 1 (7%) having subclinical hypothyroidism and 7 (14%) having overt hypothyroidism. In grade 3 fatty liver, 4 patients (73%) had hypothyroidism, with 1 (9%) having subclinical hypothyroidism and 3 (64%) having overt hypothyroidism. Therefore, as the severity of fatty liver increased, there was a higher proportion of individuals with hypothyroidism, and this correlation was found to be statistically significant ($p = 0.000$). Pagadala MR et al demonstrated that 21% of the individuals in their research group had hypothyroidism in patients with non-alcoholic fatty liver disease (NAFLD) ($p = 0.000$).Fifteen Parikh et al conducted a study which revealed that the prevalence of hypothyroidism among patients with non-alcoholic fatty liver disease (NAFLD) was 16.8%.[23] Hypothyroidism shown a substantial association with non-alcoholic fatty liver disease (NAFLD), with a p-value less than 0.001. In this study, 18% of patients with non-alcoholic fatty liver disease (NAFLD) were found to have hypothyroidism. Of these, 4% had subclinical hypothyroidism and 14% had overt hypothyroidism. Additionally, a higher number of patients with grade 2 and 3 fatty liver were found to have hypothyroidism.

CONCLUSIONS

There was no significant correlation between levels of Free T3 and the severity of fatty liver grading. The level of Free T4 exhibited a negative correlation with the escalating severity of fatty liver. There was a direct relationship between serum TSH levels and the severity of fatty liver.

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In this study, 18% of patients with non-alcoholic fatty liver disease (NAFLD) were found to have hypothyroidism. Among these patients, 4% had subclinical hypothyroidism and 14% had overt hypothyroidism. The current study found a hypothyroidism prevalence of 18%, which is approximately twice as high as the prevalence in the general population. A higher proportion of individuals with grade 2 and 3 fatty liver exhibited hypothyroidism.Thyroid function tests should be conducted on patients with non-alcoholic fatty liver disease (NAFLD), particularly those with grade 2 and 3 fatty liver. If necessary, thyroid replacement medication should be initiated.

Thyroid-stimulating hormone (TSH) may have a significant impact on the development and advancement of non-alcoholic fatty liver disease (NAFLD), and replacing thyroid hormones may potentially reverse the accumulation of fat in the liver. Additional research is required on this matter.

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