ORIGINAL ARTICLE CODEN: AAJMBG

Evaluation of non - alcoholic fatty liver disease in hypothyroidism in a tertiary care hospital in southern India

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Received: 30th January 2023; ***Accepted:*** 08th July 2023; ***Published:*** 01st January 2024

Abstract: *Background:* NAFLD ranges from simple fatty liver to non-alcoholic steatohepatitis, which may progress to liver fibrosis, cirrhosis and hepatocellular carcinoma. Subclinical hypothyroidism is associated with metabolic syndrome, cardiovascular mortality and disturbance of lipid metabolism. *Objective:* To study the association between NAFLD and hypothyroidism. *Methods:* A cross-sectional study was conducted at a tertiary hospital on 100 adult non-obese hypothyroid patients. Patients were categorised as per their thyroid profile as: Euthyroidism [(TSH): 0.4-4.0µIU/L with normal FT4], Subclinical hypothyroidism (TSH ≥4.1µIU/L with normal FT4), Overt hypothyroidism (TSH ≥4.1µIU/L and FT4<0.7ng/dL). NAFLD was diagnosed if there was presence of fatty liver by ultrasonography in absence of excess alcohol intake. *Results:* Prevalence of Overt, Subclinical hypothyroidism and NAFLD were 54%, 46% and 70% respectively. All 'Overt Hypothyroidism' patients had NAFLD. Significantly higher proportion of grade III NAFLD was associated with overt hypothyroidism (92.9%). NAFLD was significantly associated with higher levels of TSH (6.8±1.2µU/L) and lower levels of FT4 (0.6±0.2ng/dl). *Conclusion:* In present study, subclinical and overt hypothyroidism patients are at a higher risk for development of NAFLD. Increased TSH levels pose a high risk for NAFLD. This study suggests that management of hypothyroidism plays pivotal role in preventing fatty liver disease and its further progression.

Keywords: Non-alcoholic Fatty Liver Disease, Subclinical Hypothyroidism, Overt Hypothyroidism, Thyroid Stimulating Hormone, FT4.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease with a broad clinical spectrum ranging from benign non-alcoholic fatty liver (NAFL) to more severe non-alcoholic steatohepatitis (NASH) which can progress to liver fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD is defined as the ectopic accumulation of fat in the liver (hepatic steatosis) when no other causes of secondary liver fat accumulation such as alcohol consumption are present [1-3].

It is a major determinant of mortality and morbidity related to liver disorders. NAFLD is associated with endocrinopathies like diabetes mellitus, metabolic syndrome, thyroid dysfunction, insulin resistance, cardiovascular diseases and chronic kidney diseases. Global rise in obesity, diabetes mellitus and metabolic syndrome prevalence have resulted in simultaneous rise in incidence of NAFLD. Hence, the earliest recognition of NAFLD and its risk factors plays a crucial role in preventing further progression of hepatic dysfunction and related complications [1-5].

Hypothyroidism is the most common endocrine disorder. Thyroid hormones play a significant role in energy and cellular metabolism. By regulating lipid metabolism, they contribute to increased metabolic rate, weight loss, lipolysis and lowering serum cholesterol levels [1, 6-8]. Decreased thyroid hormones lead to hypercholesterolemia and

hypertriglyceridemia, which is the main basis for pathogenesis of hypothyroidism induced NAFLD. Hypothyroidism can be manifested either in subclinical or overt forms. Subclinical hypothyroidism is defined as an elevated thyroid stimulating hormone (TSH) level with normal serum free thyroxin (FT4) level and without obvious clinical manifestation. Overt hypothyroidism is defined as a disease with an elevated TSH level and a lower fT4 level, and it may be accompanied by obvious clinical symptoms (NAFLD 2) [1, 7-8].

The prevalence of hypothyroidism ranges from 15.2% to 36.3% among patients with NAFLD/ NASH [8-10]. Subclinical hypothyroidism is found to be associated with metabolic syndrome, cardiovascular mortality and disturbance of lipid metabolism [9, 11]. There is a renewed interest to understand association between NAFLD/NASH and thyroid dysfunction in the recent days [8-10]. This cross-sectional study was conducted at a tertiary care hospital to study the association between NAFLD/ NASH and hypothyroidism.

Material and Methods

After obtaining institutional ethics committee (IEC) clearance, this cross-sectional study was conducted for a duration of one year (from 1st February 2022 to 31st January 2023). Convenience sampling method was applied to select consecutive 100 adult non-obese hypothyroid patients presenting at either out-patient department or treated on in-patient basis at Basaveshwara Medical College &Hospital, Chitradurga. Individuals with obesity, diabetes mellitus, hypertension, chronic kidney disease, underlying liver diseases such as cirrhosis, autoimmune or viral hepatitis and those with >20 g/day alcohol consumption were excluded from the study.

After explaining purpose of the study and obtaining informed consent, 100 adult non-obese hypothyroid patients were included in the study. Information about socio-demographic profile, history of pre-existing comorbid conditions, habits such as alcohol consumption, past history and family history, anthropometric measurements, laboratory tests were collected in a semi-structured pre-designed proforma. All routine investigations were done in each individual after a 12-hour overnight fast.

Euthyroidism was defined as a serum Thyroid Stimulating Hormone (TSH) level between 0.4 and 4.0 µIU/L with normal free T4 (FT4) levels (0.7-1.8 ng/dL). Subclinical hypothyroidism was defined as serum TSH ≥4.1 µIU/L with normal FT4 concentration. Overt hypothyroidism was defined as serum TSH ≥4.1 µIU/L and FT4 level less than 0.7 ng/dL [11].

NAFLD was diagnosed if there was presence of fatty liver by ultrasonography, in the absence of excess alcohol intake (>20 g/day), medications known to cause fatty liver, seropositivity of hepatitis B surface antigen and antibody to hepatitis C virus.

Ultrasound criteria for Non-alcoholic fatty liver disease [12]: Fatty liver is seen as bright liver with echogenicity of liver more than that of right kidney. NAFLD were categorised into *Grade I:* Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity, *Grade II:* Increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm and *Grade III:* Increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm [12].

Statistical Analysis: Data was compiled in Microsoft excel worksheet and analysed using SPSS software v:16 (Statistical Package for the Social Sciences version 16, SPSS Inc., SPSS for Windows, Chicago, USA). All characteristics were summarized descriptively. For continuous variables, summary statistics of N, mean, standard deviation about the arithmetic mean were used and categorical data were represented as frequency and percentages.

To test significance of associations, chi-square tests (for categorical data), independent student t' test (for continuous independent variables with parametric distribution), One way ANOVA test (for continuous variables with parametric distribution) were applied. Those associations with p-value of <0.05 were considered to be statistically significant at 95% confidence interval.

Results

A total of 100 hypothyroid patients who fulfilled the study eligibility criteria were included in the present study. The prevalence of overt hypothyroidism and subclinical hypothyroidism in the present study were 54% and 46% respectively. Prevalence of Non-alcoholic fatty liver disease in the study was 70%. Majority of hypothyroid patients in age group of ≥ 60 years had overt hypothyroidism (71.4%) compared to subclinical hypothyroidism (28.6%). Majority of hypothyroid patients in age group of 18-39 years had subclinical hypothyroidism (61.5%) compared to overt hypothyroidism (38.5%). These associations were found to be statistically significant (Table 1).

Table-1: Characteristics of study participants

Patient characteristics	Types of Hypothyroidism		Total n (%)	p value*
	Overt hypothyroidism n (%)	Subclinical hypothyroidism n (%)		
Age				
18-39 years	10 (38.5%)	16 (61.5%)	26(100.0%)	p=0.04
40-59 years	24 (52.2%)	22 (47.8%)	46(100.0%)	
≥ 60 years	20 (71.4%)	8 (28.6%)	28(100.0%)	
Sex				
Male	24 (54.5%)	20 (46.5%)	44 (100.0%)	p=0.92
Female	30 (53.6%)	26 (46.4%)	56 (100.0%)	
Total	54 (54%)	46 (46%)	100 (100%)	

*Chi Square Test applied.

The grades of NAFLD increased steadily with increasing mean values of TSH and decreasing mean values of FT4. This association was found to be statistically significant. It was found that, the average levels of thyroid stimulating hormone were significantly higher among patients with non-alcoholic fatty liver disease (6.79±1.16µU/L) compared to those without NAFLD (5.99±0.59µ U/L) And significantly lower levels of FT4 were found to be associated with presence of NAFLD (0.59±0.20ng/dl) compared to that among patients without NAFLD (1.280±0.24ng/dl) (Table 2). Similarly, the severe grades of NAFLD are directly proportion to the serum levels of TSH and indirectly proportional to serum levels of FT4 (Table 3).

Table-2: NAFLD Distribution in Relation to TSH levels (N=100)

NAFLD	TSH (µU/L) Mean ± SD	FT4 (ng/dl) Mean ± SD
Present	6.79 ± 1.16	0.59 ± 0.20
Absent	5.99 ± 0.59	1.28 ± 0.24
p-value*	p < 0.01	p < 0.01

*Independent sample t test applied.

Table-3: The association of mean TSH and FT4 values with USG grades of NAFLD

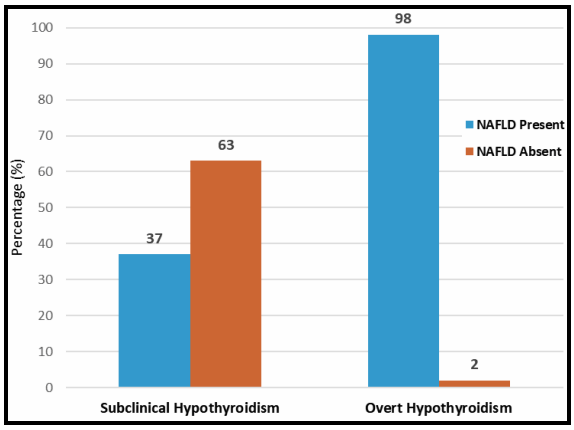
USG grading of NAFLD	TSH (µlU/L) (Mean ± SD)	FT4 (ng/dl) (Mean ± SD)
Grade I	5.97 ± 0.75	0.65 ± 0.17
Grade II	6.73 ± 0.36	0.58 ± 0.15
Grade III	8.52 ± 0.71	0.28 ± 0.07
p value*	p < 0.01	p < 0.01

*One way ANOVA test applied.

Higher proportion of non-alcoholic fatty liver disease was associated with overt hypothyroidism (98%.) compared to subclinical hypothyroidism (37%). This association was found to be statistically significant. (Figure 1) Also, a significantly higher proportion of grade III NAFLD was associated with overt hypothyroidism (86%) compared to Grade I NAFLD (64.3%). Similarly, significantly higher proportion of Grade I NAFLD (35.7%) was found to be associated with subclinical hypothyroidism compared to grade III NAFLD (14%) (Table 4).

Table-4: Association of NAFLD and its grades with types of hypothyroidism					
Hypothyroidism Types	NAFLD Grading				Total
	NAFLD Absent	NAFLD I	NAFLD II	NAFLD III	
Subclinical hypothyroidism n(%)	29 (96.6%)	10 (35.7%)	05 (17.8%)	02 (14.0%)	46 (45%)
Overt hypothyroidism n(%)	01 (4.4%)	18 (64.3%)	23 (82.2%)	12 (86.0%)	54 (55%)
Total n (%)	30(100.0%)	28(100.0%)	28(100.0%)	14 (100.0%)	100 (100.0%)
Chi square test applied. p:<0.05					

Fig-1: Prevalence of NAFLD in subclinical and overt hypothyroidism



Discussion

The results of this study demonstrated significant association of hypothyroidism with NAFLD. Few previous studies have also shown that hypothyroidism might contribute for development of NAFLD [1, 12-14]. These findings indicate that routine screening of all hypothyroid patients for NAFLD should be carried out, since these patients are more prone for developing NAFLD. In other words, it may also be useful for diagnosing hypothyroidism in patients with NAFLD and to prevent further progression [1, 12-14].

There are several possible mechanisms implicated in pathogenesis of NAFLD in hypothyroidism. Firstly, hypothyroidism is associated metabolic changes like Insulin resistance (IR), dyslipidemia and obesity, which can lead to development of NAFLD. Both IR and obesity are important risk factors for NAFLD [1, 14]. Secondly, lipid metabolism is controlled by thyroid hormones binding through specific thyroid hormone receptor β, which helps for influx of free fatty acids into hepatocytes, leading to decrease in triacylglycerol (TG) and cholesterol levels. Thyroid hormones can also increase fatty acid oxidation and promote intrahepatic lipolysis through lipophagy with subsequently decreased TG clearance and increased TG hepatic up-take [13-14]. Hence, deficiency of thyroid hormones leads to increased accumulation of cholesterol, low-density lipoproteins and triglycerides.

Hypothyroidism patients have lower concentration of thyroid hormones and increased TSH levels. This elevated TSH is associated with higher risk for development of metabolic syndrome which can further progress to onset of NAFLD. TSH directly affects the hepatocyte cell membranes, it can promote hepatic lipogenesis, gluconeogenesis, and diminish hepatic bile acid synthesis [13-14].

In the present study, it was found that, the average levels of thyroid stimulating hormone were significantly higher among patients with non-alcoholic fatty liver disease (6.79±1.16µU/L) compared to those without NAFLD (5.99±0.59µU/L) (Table 2 and 3). Various scientific literature has shown that raised TSH levels have correlation with higher hepatic lipoprotein lipase activity and provides sufficient free fatty acids for de-novo synthesis of triacylglycerol and further development of fatty liver. So, the concentration of TSH is directly proportional to the development of fatty liver in hypothyroidism patients.

According to the results of the present study, we found similar phenomenon that the correlation between overt hypothyroidism and NAFLD was more significant than that between subclinical hypothyroidism and

NAFLD. The more significant correlation between overt hypothyroidism and NAFLD may be explained by the synergistic effects of higher TSH level and lower thyroid hormones in the pathogenesis of NAFLD, because TSH itself may induce hepatocyte steatosis via TSH receptor signal [13-14].

Conclusion

In our study we found that both the cases of subclinical hypothyroidism and overt hypothyroidism were at a higher risk for the development of NAFLD compared to patients with normal thyroid function. It also demonstrated that increased level of TSH may be a risk for development of NAFLD. This study suggests that effective management of hypothyroidism plays a pivotal role in preventing the development of fatty liver disease and its further progression.

Acknowledgement

The authors are grateful to the Head of Institution and Management of Basaveshwara Medical College & Hospital for providing valuable support to undertake the study. Authors are also indebted to the patients who willingly participated in the study.

Financial Support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

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Cite this article as: Savadi BV, Patil L, Malipatil P and Patil S. Evaluation of non - alcoholic fatty liver disease in hypothyroidism in a tertiary care hospital in southern India. *Al Ameen J Med Sci* 2024; 17(1): 55-59.

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