PREVALENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE IN HYPOTHYROIDISM IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

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ABSTRACT

BACKGROUND

Thyroid hormones are involved in lipid metabolism, insulin resistance and regulation of bodyweight. There are inconclusive data regarding substantial involvement of hypothyroidism in non-alcoholic fatty liver disease (NAFLD).

The aim of this study is to evaluate the prevalence of NAFLD in hypothyroidism.

MATERIALS AND METHODS

A descriptive study was conducted in the Department of General Medicine of SCB Medical College, Cuttack and consecutively 100 adult non-obese hypothyroid patients (50 treated and 50 untreated) were included in the study, and the patients were evaluated for NAFLD using ultrasonography. The results were compared with 100 age, sex and body mass index (BMI) matched euthyroid controls.

RESULTS

From 100 hypothyroid patients, 30 NAFLD patients were detected and 12 NAFLD patients were detected in controls (p=0.003). There was increased incidence of NAFLD in persons with high serum TSH value (≥4.1 mIU/ L) and low free T_4 value (≤0.7 ng/dL).

CONCLUSION

Prevalence of NAFLD in non-obese hypothyroid patients is higher in comparison to non-obese euthyroid controls, and the incidence is also high in untreated hypothyroid patients in comparison to treated hypothyroid patients.

KEYWORDS

Hypothyroidism, Insulin Resistance, Non-alcoholic Fatty Liver Disease.

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BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) includes diseases of liver ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH), which if untreated may lead to cirrhosis of liver and hepatocellular carcinoma.[1] It is the commonest liver disease worldwide.[2] The increased prevalence of NAFLD is directly related to increased incidence of obesity, metabolic disorders such as insulin resistance, diabetes mellitus, and hypertension and dyslipidaemia.[3] Since thyroid hormones are thoroughly involved in cell metabolism, energy homoeostasis, regulation of body weight, lipid and carbohydrate metabolism, and adipogenesis,[4,5] there is chance of association between thyroid dysfunction and NAFLD/NASH. There is growing data about higher prevalence of thyroid dysfunction in the form of overt or subclinical hypothyroidism among patients with NAFLD/NASH.[6] The prevalence of hypothyroidism was reported to range from 15.2 % to 36.3 % among patients with NAFLD/NASH.[7] Several studies using healthy controls showed a significantly higher prevalence of hypothyroidism in patients with NAFLD/NASH compared to the controls. Several studies also demonstrated that hypothyroidism is an independent risk factor for NAFLD.[6] This indicates that hypothyroidism may directly result in NAFLD irrespective of other metabolic risk factors. Considering the results of these studies, hypothyroidism may be added to risk factors of NAFLD/NASH. Chung et al,[6] in their population based study, evaluated a relatively large number of healthy individuals and showed that prevalence of NAFLD plus elevated alanine aminotransferase (ALT) was higher in patient with hypothyroidism. An increased serum ALT level is a surrogate biomarker for NAFLD in the absence of other causes of liver disease. Therefore, this study confirms the association between the severity of NAFLD and hypothyroidism. Pagadala et al[8] reported that hypothyroidism was more common in patients with NASH compared to patients with NAFLD. This finding remained statistically significant after adjusting for other variables including age, diabetes,

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dyslipidaemia and hypertension but not gender.[9] The prevalence of NAFLD in hypothyroidism has not been well studied in our region. A descriptive study was conducted to highlight the prevalence of NAFLD in non-obese euthyroid patients and its association with both treated and untreated hypothyroid patients.

MATERIALS AND METHODS

This study was a descriptive study. After clearance from institutional ethics committee (IEC), we designed an observational descriptive study as per the following:

Patient Selection Criteria

Consecutively 100 adult non-obese hypothyroid patients those attended the outpatient department (OPD) or admitted to indoor department of SCB Medical College, Cuttack, were included in the study. Sample size was taken conveniently. These patients were divided into two groups, those who were under treatment for hypothyroidism in the form of L-thyroxin replacement therapy were included in treated group (n=50) and those who were not under treatment were included in non-treated group (n=50). The controls were age, sex and BMI matched non-obese euthyroid persons (n=100).

Exclusion Criteria

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.

Case Definition

Euthyroidism was defined as a serum TSH level between 0.4 and 4.1 mIU/L with normal free T_4 (FT_4) levels (0.7-1.8 ng/dL). Subclinical hypothyroidism was defined as serum TSH ≥4.1 mIU/L with normal FT_4 concentration, and overt hypothyroidism was defined as serum TSH ≥4.1 mIU/L and FT_4 level less than 0.7 ng/dL.

Methods

All patients and controls were subjected to detailed history and thorough clinical examination with reference to past medical history, anthropometric assessment and laboratory tests. Height and body weight were measured and body mass index (BMI) was calculated as follows: BMI= body weight (kg)/ height squared (m^2). The normal range of BMI is 19-24.9 kg/m^2, overweight is 25-29.9 kg/m^2, and obesity ≥30 kg/m^2. Waist circumference was measured in millimetre at the midpoint between the lower costal margin and anterior superior iliac crest. Waist circumference more than 1020 mm in case of males and 880 mm in case of females was considered obesity.[10] All routine investigations were done in each individual after a 12-hour overnight fast. Baseline thyroid functions (FT_4 and TSH) were measured using a commercial immunoradiometric assay (Abbot, North Chicago, USA). Other lab tests include liver function tests, lipid profile, fasting & two-hour plasma glucose, serum urea & creatinine, hepatitis B surface (HBsAg) antigen and antibody to hepatitis C virus.

NAFLD was diagnosed as 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[11]**:** Fatty liver is seen as bright liver with echogenicity of liver more than that of right kidney.

Grade I: Increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity.
Grade II: Increased hepatic echogenicity with imperceptible periportal echogenicity, without obscuration of diaphragm.
Grade III: Increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of diaphragm.

Statistical Analysis

The observed data was statistically analysed by using IBM-compatible Statistical Package for the Social Sciences (SPSS) version 20.0. The qualitative data were expressed as numbers (%) and the comparisons of continuous variables between the two groups were performed with the Student's t-test and categorical variables were compared using the Chi-square test. A p-value of <0.05 was considered significant and p-value of <0.001 was considered highly significant, while p-value of >0.05 was considered not significant.

RESULTS

A total 100 hypothyroid cases were included in the study, of which 50 were untreated and 50 were treated. Among untreated hypothyroid cases, 18 (36%) were between 18-39 yrs., 28 (56%) were between 40-59 yrs. and 4 (8%) were above 60 yrs. of age. In treated group, 18 (36%) were between 18-39 yrs., 27 (54%) between 40-59 yrs. and 5 (10%) were above 60 yrs. of age. Majority of hypothyroid cases were between 40-59 yrs. of age. [Table-1].

Age	Hypothyroid Cases				Total
	Untreated, n=50	%	Treated, n=50	%	
18-39 yrs.	18	36	18	36	36
40-59 yrs.	28	56	27	54	55
≥ 60 yrs.	4	8	5	10	9
Total	**50**		**50**		**100**

Table 1. Age Distribution of Study Population

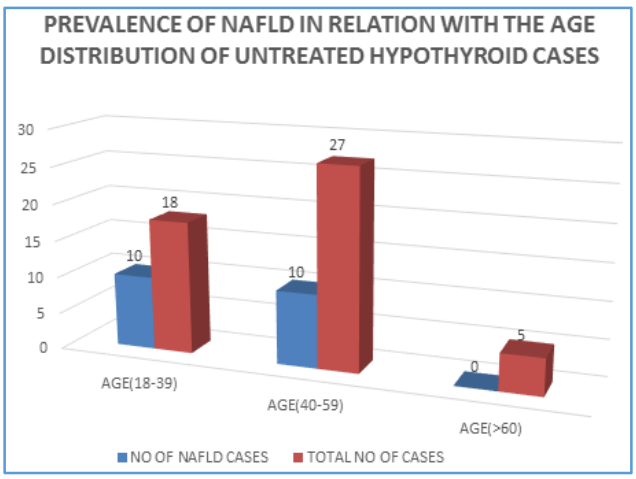
In our study, from 100 hypothyroid cases, 68 (68%) were male and 32 (32%) were female. Among untreated hypothyroid cases, 40 (80%) were male and 10 (20%) were female. Among treated hypothyroid cases, 28 (56%) were male and 22 (44%) were female. [Table-2].

Gender	Hypothyroid Cases				Total
	Untreated, n=50	%	Treated, n=50	%	
Male	40	80	28	56	68
Female	10	20	22	44	32
Total	**50**		**50**		**100**

Table 2. Sex Distribution Study Population

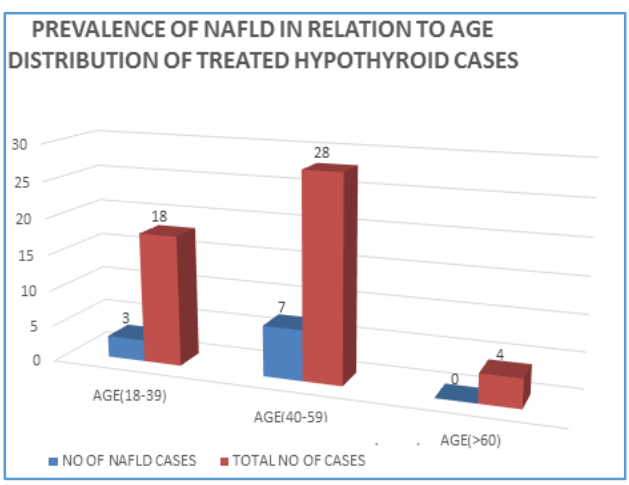
Age	NAFLD Present	Untreated Hypothyroid Cases	%
18-39 yrs.	10	18	55.5
40-59 yrs.	10	27	37
≥ 60 yrs.	0	5	
Total	**20**	**50**	**40**

Table 3. Prevalence of NAFLD in Relation to Age Distribution of Untreated Hypothyroid Cases



Age	NAFLD Present	Treated Hypothyroid Cases	%
18-39 yrs.	3	18	16.6
40-59 yrs.	7	28	25
≥ 60 yrs.	0	4	
Total	**10**	**50**	**20**

Table 4. Prevalence of NAFLD in Relation to Age Distribution of Treated Hypothyroid Cases



Among 50 untreated hypothyroid cases, 20 NAFLD cases were detected of which 10 (50%) were between 18-39 yrs., 10 (50%) were between 40-59 yrs. and no NAFLD cases were detected above 60 yrs. of age. Among 50 treated hypothyroid cases, 10 NAFLD cases were detected of which 3 (30%) were between 18-39 yrs., 7 (70%) were between 40-59 yrs. and no NAFLD cases were detected above 60 yrs. of age. Out of 100 hypothyroid cases, 30 were having NAFLD of which 20 (40%) were in the untreated group in comparison to 10 (20%) in treated group. P=1.563 which is statistically insignificant showing no significant relation between age distribution and presence of NAFLD.

Gender	NAFLD Present	Untreated Hypothyroid Cases	%
Male	12	28	42.8
Female	8	22	36.3
Total	**20**	**50**	**40**

Table 5. Presence of NAFLD in Relation to Gender Distribution of Untreated Hypothyroid Cases

Gender	NAFLD Present	Treated Hypothyroid Cases	%
Male	7	40	17.5
Female	3	10	30
Total	**10**	**50**	**20**

Table 6. Presence of NAFLD in Relation to Gender Distribution of Treated Hypothyroid Cases

Among 50 untreated hypothyroid cases, 20 (40%) NAFLD cases were detected of which 12 (24%) were male and 8 (16%) were female. Among 50 treated hypothyroid cases, 10 (20%) NAFLD cases were detected of which 7 (14%) were male and 3 (6%) were female. In our study, NAFLD cases were more prevalent in female population i.e. 34%. P=0.216 in untreated hypothyroid cases and P=0.781 in treated hypothyroid cases which is statistically insignificant.

Age	USG Grade, n=30			Total	%
	Grade-I	Grade-II	Grade-III		
18-39 yrs.	2 (15.3%)	7 (53.8%)	4 (30.7%)	13	43.3
40-59 yrs.	6 (35.2%)	6 (35.2%)	5 (29.6%)	17	56.7
Total	8 (26.6%)	13 (43.3%)	9 (30.1%)	30	

Table 7. Relation of Age with USG Grading of NAFLD, n=30

Total 30 NAFLD were detected of which 13 (43.3%) were between 18-39 yrs., 17 (56.7%) were between 40-59 yrs. and no NAFLD case was detected above 60 yrs. of age. Out of these 13 NAFLD cases, 2 (15.3%) were of USG grade-I, 7 (53.8%) of USG grade-II and 4 (30.7%) were of USG grade-III. Among 17 NAFLD cases in age group 40-59 yrs., 6 (35.2%) were of USG grade-I, 6 (35.2%) were of USG grade-II and 5 (29.6%) were of NAFLD USG grade-III. From total 30 NAFLD cases, 8 (26.6%) were of USG grade-I, 13 (43.3%) were of USG grade-II and 9 (30.1%) were of USG grade-III NAFLD. Out of total NAFLD cases, majority 13 (43.3%) were of USG grade-II. (P=1.685).

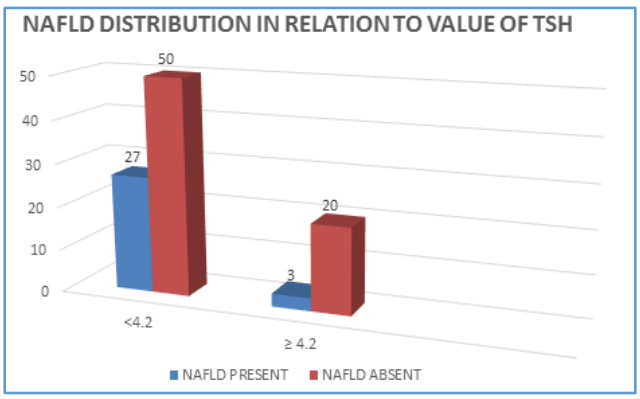
Gender	USG Grade, n=30			Total	%
	Grade-I	Grade-II	Grade-III		
Male	5 (26.3%)	8 (42.1%)	6 (31.6%)	19	63.3
Female	3 (27.2%)	5 (45.4%)	3 (27.2%)	11	36.7
Total	**8**	**13**	**9**	**30**	

Table 8. Relation of Gender with USG Grading of NAFLD, n=30

Among 30 NAFLD cases, 19 (63.3%) were male and 11 (36.7%) were female. Out of 19 male NAFLD cases, 5 (26.3%) were of NAFLD USG grade-I, 8 (42.1%) were of USG grade-II and 6 (31.6%) were of USG grade-III NAFLD. Among 11 female NAFLD cases, 3 (27.2%) were of USG grade-I, 5 (45.4%) were of USG grade-II and 3 (27.2%) were of USG grade-III NAFLD. From total 19 male NAFLD cases, 8 (42%) were of USG grade-II and from 11 female NAFLD cases, 5 (45%) were of USG grade-II. (P=0.063).

TSH (mlU/L)	NAFLD Present	Total	%
≥ 4.1	27	77	35
<4.1	3	23	13
Total	**30**	**100**	**30**

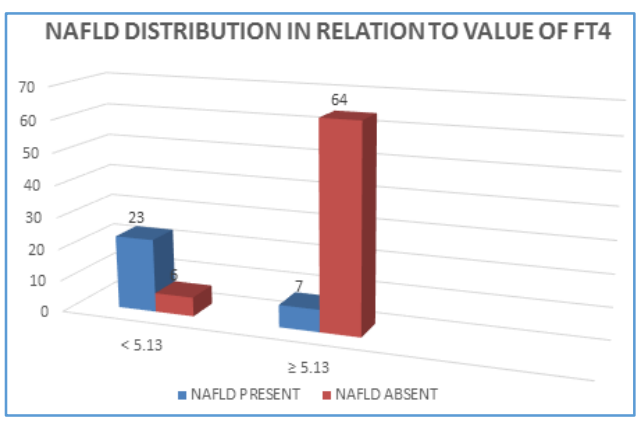
Table 9. NAFLD Distribution in Relation to Value of TSH, n=100



Among 100 hypothyroid cases (treated and untreated), 77 had TSH ≥4.1 mIU/L, of which 27 (35%) had NAFLD, and 23 had TSH <4.1 mIU/L of which 3 (13%) had NAFLD. (p=0.0163).

FT4 (ng/dL)	NAFLD Present	Total	%
< 0.7	23	29	79.3
0.7-1.8	7	71	9.8
Total	**30**	**100**	**30**

Table 10. NAFLD Distribution in Relation to Value OF T4, n=100



Among 100 hypothyroid cases (treated and untreated), 71 had FT_4 between 0.7 to 1.8 ng/dL of which 7 (9.8%) had NAFLD, and 29 had FT_4 < 0.7 ng/dL, of which 23 (79.3%) had NAFLD. (p= 0.0238).

Hypothyroid	NAFLD Present	Total	%
Untreated	20	50	40
Treated	10	50	20
Total	**30**	**100**	**30**

Table 11. Prevalence of NAFLD in Treated and Untreated Hypothyroid Cases

Among 30 cases of NAFLD, 20 were detected in untreated hypothyroid cases and 10 were detected in treated hypothyroid cases. (p= 0.003).

	NAFLD Present	Total	%
Case	30	100	30
Control	12	100	12

Table 12. Prevalence of NAFLD in Hypothyroid Cases and Controls

Total 30 NAFLD were detected in hypothyroid cases and 12 were detected in control population. P= 0.003, which is statistically significant and shows more prevalence of NAFLD in non-obese hypothyroid cases in comparison to age, sex and BMI matched control population.

DISCUSSION

In our study, 100 non-obese hypothyroid patients were included and USG was done on every patient to detect presence of NAFLD and USG grading of NAFLD was done. These hypothyroid patients were divided in two groups, basing on their treatment status, of which 50 were in treated group and 50 were in untreated group. The results were compared with 100 age, sex and BMI matched non-obese euthyroid control population.

In treated group, maximum number of patients 27 (54%) belonged to age group of 40-59 years and in untreated group also maximum number of patients 28 (56%) belonged to age group of 40-59 years. Among all hypothyroid cases, 68 (68%) were male and 32 (32%) were female. In treated group, 28 (56%) were male and 22 (44%) were female, whereas in the untreated group 40 (80%) were male and 10 (20%) were female. In a study by Liangpunsakul and Chalasani (2003), the association between thyroid dysfunction and NAFLD have been characterised by relatively small sample and gender imbalance showing female preponderance.[12] Mean age of male patients was 45.58 yrs. and female was 45.09 yrs. which was fairly correlated.

Out of 100 hypothyroid patients, 30 patients had NAFLD of which 20 were in untreated group and 10 in treated group. Study by Marco Bertolotti, Amedeo Lonardo et al demonstrated that prevalence of NAFLD increases with age,[13] but in our study majority of NAFLD cases i.e. 56.6% were found in the age group 40-59 yrs., P=1.563 which is statistically insignificant. In our study, out of 30 NAFLD cases, 19 (63.3%) were male and 11 (36.7%) were female. From 19 male NAFLD cases, majority cases i.e. 8 cases (42.1%) were having NAFLD USG grade-II and out of 11 female NAFLD cases, 5 (45.4%) were having NAFLD USG grade-II. P= 0.063, which was statistically insignificant showing no significant relationship between gender & USG grading of NAFLD. So far as age is concerned, majority NAFLD cases i.e. 17 (56.7%) were of age group 40-59 yrs. and no NAFLD case was detected above 60 yrs. of age.

In the study group, 77 cases were having TSH ≥ 4.1 mIU/L, from which 27 (35%) had NAFLD and rest 23 cases were having TSH < 4.1 mIU/L, of which 3 (13%) had NAFLD. P= 0.0163, which is statistically significant, shows increased value of TSH is associated with increased prevalence of NAFLD. In a study by Loria Paola et al regarding endocrine and liver interaction, the role of endocrine pathway in NASH showed that increase in TSH value increases the risk of developing NAFLD.[14]

Among 100 hypothyroid cases, 71 had FT_4 between 0.7 to 1.8 ng/dL, of which 7 (9.8%) had NAFLD and rest 29 had FT4 < 0.7 ng/dL, of which 23 (79.3%) had NAFLD. P=0.0238, which is statistically significant and shows decreased value of FT_4 is associated with more prevalence of NAFLD. Study by Loria Paola et al demonstrated decrease in FT_4 increases the risk of developing NAFLD.[14]

Among total 30 cases of NAFLD, 20 were detected in untreated hypothyroid cases and 10 were detected in treated hypothyroid cases. P=0.0034, which was statistically significant, showing more prevalence of NAFLD in untreated hypothyroid patients than treated hypothyroid patients.

Total 30 NAFLD cases were detected in the study population which is 30% of total study population and 12 NAFLD cases were detected in control population which is 12% of total control population. P=0.003, which is statistically significant shows that there is increased prevalence of NAFLD in non-obese hypothyroid patients than age, sex and BMI matched non-obese euthyroid controls.

CONCLUSION

Our study suggests that prevalence of NAFLD is more in untreated hypothyroid patients. Hypothyroidism is closely associated with NAFLD as an independent risk factor thereby confirming a relevant clinical relationship between these two diseases.

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