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ORIGINAL RESEARCH

A **Study to Determine the Incidence of Non-Alcoholic Fatty Liver Disease In Patients With Thyroid Dysfunction**

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ABSTRACT

Aim: To determine the incidence of non-alcoholic fatty liver disease in patients with thyroid dysfunction.

Materials & method: A cross-sectional study was conducted on 100 patients attending the out-patient and in-patient department of general medicine. Ethical committee clearance was obtained.A detailed history was taken with reference to the onset, duration, and progression of the symptoms, anorexia, malaise, fatigue, weight loss, constipation, reflux, nausea, hematemesis, vomiting, pain in abdomen, itching, melena, fullness of abdomen, alcohol intake and amount, long-term diseases like diabetes mellitus, hypertension, iron storage disorders, celiac disease, TPN, history of jejuno-ileal bypass, abetalipoproteinemia, disorders of copper metabolism, personal history and habits, family history, drug history, and such other relevant history.CBC, thyroid profile, liver function test, kidney function test, RBS, PPBS, FBS, lipid profile, blood urea, creatinine, HbA1c, total protein, albumin, globulin, A:G ratio and ultrasonography.

Results: In our study, elevated ALT and AST was reported among 40% and 37% of study subjects respectively. The incidence of non-alcoholic fatty liver disease (NAFLD) among the subjects having thyroid dysfunction was 36%.Univariate and multivariate analysis revealed that thyroid dysfunction and age > 50 years were independent risk factor of NAFLD.

Conclusion: Overall, our study suggests that thyroid function is associated with NAFLD.This is an important finding because it opens a discussionif the adequacy of the TSH level to a lower reference couldprevent the emergence of NAFLD.

Keywords: NAFLD, Thyroid, T4, TSH

INTRODUCTION

NAFLD (Non-Alcoholic Fatty Liver Disease) is a chronic liver disease with a histological spectrum ranging from steatosis alone to non-alcoholic steatohepatitis (NASH), the latter having an increased risk for progression to cirrhosis[1]. The frequency of non-alcoholic fatty liver disease (NAFLD) has increased significantly throughout the past periods, and it has become the prominent reason of liver disease worldwide with a global prevalence of 25%, which can be moderately recognized to the rising prevalence of obesity[2,3]. NAFLD has been recognized as the most common cause of abnormal liver function worldwide. The global

prevalence of NAFLD is 24%, with the highest rates are reported from South America, the Middle East, and Asia[4].NAFLD can be categorized into two main histological categories, to be exact nonalcoholic fatty liver and nonalcoholic steatohepatitis, which is the progressive subtype of NAFLD and can further induce liver cirrhosis and hepatocellular carcinoma[5,6].

A 'two-hit' theory was posited for several years to explain NASH pathogenesis. This theory suggests that in the setting of steatosis alone (i.e., NAFL), a second 'hit' from other factors (for example, oxidant stress) was required for the development of NASH; however, this view is now considered outdated. There are many molecular pathways that contribute to the development of NASH, and it is not even certain whether NASH is always preceded by NAFL. Moreover, pathogenic drivers are not likely to be identical among all patients. Thus, both the mechanisms leading to disease and their clinical manifestations are highly heterogeneous[7].

Presence of metabolic syndrome (MetS) in an individual is the strongest risk factor for NAFLD and NASH. MetS is variably defined, but typically includes increased waist circumference (i.e., obesity), hyperglycemia, dyslipidemia and systemic hypertension (HTN). The association between NAFLD and features of MetS may be bidirectional, particularly with respect to diabetes and HTN, meaning that not only does MetS increase the risk of NAFLD, but also NAFLD may enhance several features and comorbidities of MetS[8-10].NAFLD is strongly associated with metabolic syndrome, which is also linked to subclinical hypothyroidism. Considering the important role of thyroid hormone in lipid metabolism, hypothyroidism may cause hyperlipidemia which plays a crucial role in the pathogenesis of NAFLD[11-13].

Thyroid hormones control all metabolic paths, acting on carbohydrates, protein and lipid metabolism. Low thyroid hormone levels are related with hypometabolism categorized by decreased weight gain, resting energy expenditure, reduced lipolysis, increased cholesterol levels, and reduced gluconeogenesis. Thyroid hormones similarly have a role in hepatic lipid metabolism and hepatic insulin resistance[14]. It is well known that hypothyroidism is associated with high levels of LDL-cholesterol and triglycerides secondary to a decrease in LDL receptor's activity and clearance of triglyceride-rich lipoproteins[15].

Previous studies propose that hypothyroidism might play a crucial role in the pathogenesis of NAFLD. Some studies report that the prevalence of hypothyroidism is from 15.2 to 36.3% among patients with NAFLD, indicating that hypothyroidism is a common concomitant disease of NAFLD and may be related to the development of NAFLD. At present, there are a number of observational studies which have explored the relationship between hypothyroidism and NAFLD. Some studies suggested a strong correlation between hypothyroidism and NAFLD, but there were also studies pointing out that there was no correlation[16,17]. Therefore, the association between hypothyroidism and NAFLD risk remains in dispute up to now. Hence the present study was planned to determine the incidence of non-alcoholic fatty liver disease in patients with thyroid dysfunction.

MATERIALS & METHOD

A cross-sectional study was conducted on 100 patients attending the out-patient and in-patient department of general medicine. Ethical committee clearance was obtained.

INCLUSION CRITERIA

1. Patient age more than and equal to 18 years with thyroid dysfunction
2. Patients who give consent for the study.

EXCLUSION CRITERIA

1. Patients diagnosed with viral hepatitis.(hep B,hep C)

2. Known cases of autoimmune hepatic diseases.
3. Patients with alcohol intake
4. Pt age <18 years.
5. Patients with Chronic liver disease.
6. Patients diagnosed with Chronic Kidney disease
7. Patients consuming long-term drugs which affect thyroid functions (steroids, β-blockers).
8. Patients not giving consent.

METHODS

After the purpose and the contents of the study have been fully explained, written informed consent was obtained from all patients fulfilling the inclusion criteria.A detailed history was taken with reference to the onset, duration, and progression of the symptoms, anorexia, malaise, fatigue, weight loss, constipation, reflux, nausea, hematemesis, vomiting, pain in abdomen, itching, melena, fullness of abdomen, alcohol intake and amount, long-term diseases like diabetes mellitus, hypertension, iron storage disorders, celiac disease, TPN, history of jejuno-ileal bypass, abetalipoproteinemia, disorders of copper metabolism, personal history and habits, family history, drug history, and such other relevant history.

GENERAL PHYSICAL EXAMINATION

VITAL SIGNS

- Blood pressure
- Pulse rate
- Cyanosis
- Clubbing
- Respiratory rate.
- Pallor
- Icterus
- Clubbing
- Lymphadenopathy
- Cyanosis
- Edema

Anthropometry includes height, weight, BMI, Waist-hip ratio.

Systemic examination includes Central nervous system examination, Cardiovascular examination, Per abdomen examination, and Respiratory system examination and local examination.

INVESTIGATIONS

CBC, thyroid profile, liver function test, kidney function test, RBS, PPBS, FBS, lipid profile, blood urea, creatinine, HbA1c, total protein, albumin, globulin, A:G ratio and ultrasonography.

DATA RECORDING

Data was collected in structured data collection forms

All the findings and observations were coded and entered in Excel master sheet.

STATISTICAL ANALYSIS

Data so collected was tabulated in an excelsheet, under the guidance of statistician.The means and standard deviations of the measurementsper group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA).Univariate and multivariate analysis

was conducted. Univariate involves the analysis of a single variable while multivariate analysis examines two or more variables. Multivariate analysis involves a dependent variable and multiple independent variables. Thelevelof significance was set at $p < 0.05$.

RESULTS

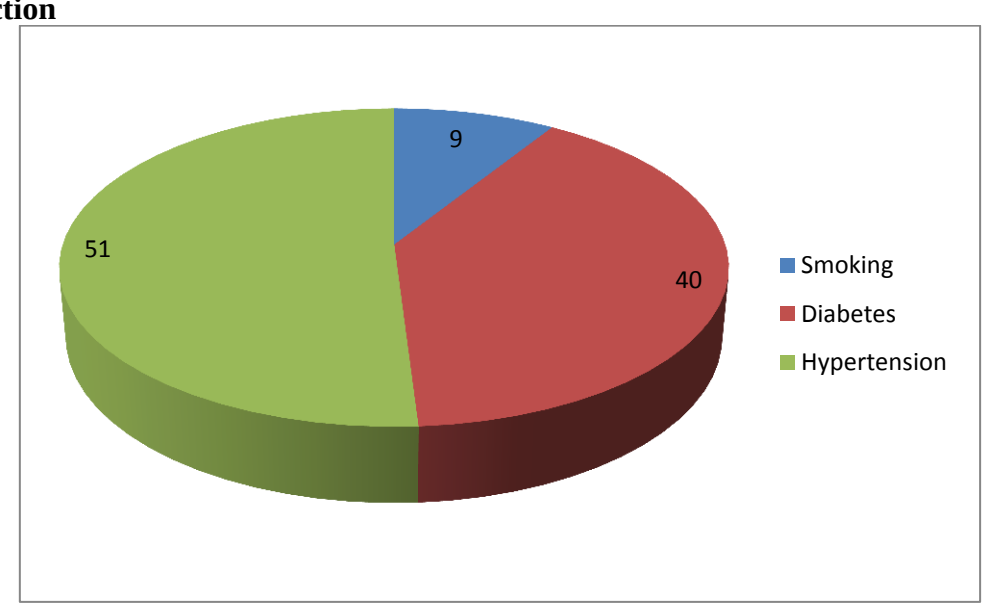
The present cross sectional study was conducted among 100 patients with thyroid dysfunction to evaluate the relationship and incidence ofNon-Alcoholic Fatty Liver Disease (NAFLD). Out of 100 subjects, 53% were males and 47% were females. The age distribution among the study patients showed that majority of the patients are in a late age group with 58% patients belonged to >50 years of age (table 1).

Table 1: Gender distribution among the subjects having thyroid dysfunction

Gender	N	%
Male	53	53
Female	47	47
Age Group (in years)		
<30	5	5
31-40	13	13
41-50	24	24
51-60	27	27
>60	31	31
Total	100	100

As per graph 1, smoking, diabetes and hypertension was present in 9%, 40% and 51% patients respectively among the subjects having thyroid dysfunction.

Graph 1: Smoking, Diabetes and hypertension among the subjects having thyroid dysfunction



Mean BMI (kg/m^2) among the study group was 20.17 kg/m^2. Mean HbA1c (%) was 6.3. ALT (IU/L), AST (IU/L) and Gamma-glutamyltransferase (IU/L) were 45.8 IU/L, 45.5 IU/L, 105.39 IU/L among the subjects having thyroid dysfunction (Table 2).

Table 2: Mean BMI (kg/m^2), HbA1c (%), ALT (IU/L), AST (IU/L),Gamma-glutamyltransferase (IU/L), FT4 (ng/dL) and TSH (µU/L)among the subjects having thyroid dysfunction

Parameters	Mean	SD
BMI (kg/m^2)	20.17	2.94
HbA1c (%)	6.3	1.7
ALT (IU/L)	45.8	69.82
AST (IU/L)	45.5	60.31
Gamma-glutamyltransferase (IU/L)	105.39	238.72
FT4 (ng/dL)	1.19	0.94
TSH (μU/L)	6.3	1.7

Mean total cholesterol, triglyceride and HDL- cholesterol among the study population was 1.19 mg/dl, 134.92 mg/dl and 57.18 mg/dl (Table 3).

Table 3: Lipid profile among the study subjects

Lipid Profile	Mean	SD
Total cholesterol(mg/dL)	1.19	0.94
Triglyceride (mg/dL)	134.92	81.38
HDL-cholesterol (mg/dL)	57.18	17.70

In our study, elevated ALT and AST was reported among 40% and 37% of study subjects respectively (Graph 2).

Graph 2: ALT and AST elevation among the study subjects

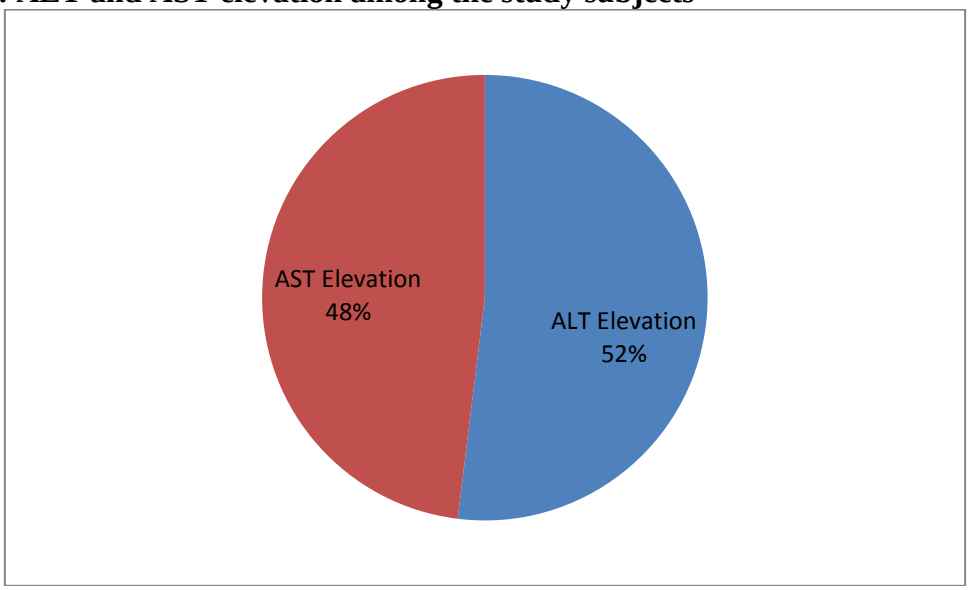


Table 4 showed that incidence of non-alcoholic fatty liver disease (NAFLD) among the subjects having thyroid dysfunction was 36%.

Table 4: Incidence of non-alcoholic fatty liver disease (NAFLD) among the subjects having thyroid dysfunction

Variables	N	%
Present	36	36
Absent	64	64
Total	100	100

Risk factors of non-alcoholic fatty liver disease were assessed by univariate and multivariate analysis in study subjects. Thyroid dysfunction and age > 50 yrs were statistically significant

on both univariate analysis (p value 0.004 and 0.03 respectively) and multivariate analysis (p value <0.01 and 0.04 respectively). Gender, BMI, triglyceride, HDL- cholesterol, hypertension and diabetes were not statistically significant(Table 5).

Table 5: Risk factors of non-alcoholic fatty liver disease assessed by univariate and multivariate analyses

Variables	Univariate Model			Multivariate Model		
	Odds Ratio	95%CI	p value	Odds Ratio	95%CI	p value
Thyroid Dysfunction	3.38	1.43-8.12	0.004*	4.83	2.79-11.81	<0.01*
Age>50 Years	2.86	1.11-5.74	0.03*	2.71	1.02-5.16	0.04*
Gender (Male)	1.04	0.87-1.29	0.45			
BMI	1.17	1.08-1.39	0.16			
Triglyceride	0.99	0.95-1.02	0.19			
HDL-Cholesterol	0.97	0.96-1.01	0.16			
Hypertension	1.42	0.69-2.97	0.11			
Diabetes	1.32	0.81-2.18	0.24			

*: statistically significant

DISCUSSION

There is dispute in the literature regarding the relation between hypothyroidism and NAFLD as some studies suggested astrong correlation between hypothyroidism and NAFLD,but there were also studies pointing out that there was no correlation[2]. Therefore, the association between hypothyroidismand NAFLD risk remains in dispute up to now. Hence this study was conducted to determine the incidence of non-alcoholic fatty liver disease in patients with thyroid dysfunction.

The present cross sectional study was conducted among 100 patients with thyroid dysfunction to evaluate the relationship and incidence ofNon-Alcoholic Fatty Liver Disease (NAFLD). Out of 100 subjects, 53% were males and 47% were females. Similar gender distribution was reported by Kazuki Tahara et al[18] in their study.

The age distribution among the study patients showed that majority of the patients are in a late age group with 58% patients belonged to >50 years of age (mean age: 67.89 years) in our study. Kazuki Tahara et al in their study[18] revealed mean age of 69.1±8.1 which is approximately similar to our study.

In our study smoking, diabetes and hypertension was present in 9%, 40% and 51% of the patients respectively having thyroid dysfunction. In a study by Kazuki Tahara et al[18], the prevalenceof diabetes or hypertension was not significantly differentbetween patients with subclinical hypothyroidism and those witheuthyroidism.

In this study, mean FT4 and TSH was 1.19 ng/dl and 6.3 μU/Lamong the study subjects. In our study, elevated ALT and AST was reported among 40% and 37% of study subjects respectively. These findings were in accordance with study done by Tahara et al[18].Chung et al[19] reported that the prevalence ofNAFLD and abnormal liver enzyme levels (ALT)progressively increases as the grade of hypothyroidismincreases. Eshraghian et al found that higher serumALT and AST levels were associated with NAFLD.According to Eshraghian and Jahromi[16], an increasedserum ALT level is a surrogate biomarker for NAFLDin the absence of other causes of liver disease and anindicator for the development of diabetes, cardiovascular disease and long term adverse complications frommetabolic syndrome.

In the present study, the incidence of non-alcoholic fatty liver disease (NAFLD) among the subjects having thyroid dysfunction was 36%. Thyroid hormones act as potent regulators of metabolicand energy homeostasis and have been implicated in variousmetabolic diseases. Hypothyroidism reduces resting energyexpenditure, lipolysis, and gluconeogenesis; increases

weight;and increases cholesterol levels. Therefore, hypothyroidism leads to hyperlipidemia, obesity, and insulin resistance, which are riskfactors of the metabolic syndrome associated with NAFLD. In our study, risk factors of non-alcoholic fatty liver disease were assessed by univariate and multivariate analysis in study subjects. Thyroid dysfunction and age > 50 yrs were statistically significant on both univariate analysis (p value 0.004 and 0.03 respectively) and multivariate analysis (p value <0.01 and 0.04 respectively). Gender, BMI, triglyceride, HDL-cholesterol, hypertension and diabetes were not statistically significant. Therefore thyroid dysfunction and age > 50 years were found to be independent risk factors of NAFLD in our study. Although the mechanism cannot be explainedby our study, our findings indicate that TSH might directly contributeto the development of NAFLD. Recently, multiple studiesreported extra-thyroid tissues expressing the TSH receptor. Ithas been reported that functional TSH receptors were expressedin hepatocytes and that the cAMP/PKA/CREB pathway of theliver was involved in the induction of cholesterol synthesis byTSH. Similarly Kazuki Tahara et al in their study found that TSH levels were independently associated withNAFLD, adjusted by metabolic-related factors such as BMI, triglyceride,HDL-cholesterol, hypertension, and diabetes, asassessed by multivariate analysis[18].

However, recent meta-analyses investigating the association ofhypothyroidism with NAFLD showed inconsistent results. Jaruvongvanich et al[20] have reported that NAFLD is not associatedwith thyroid hormone levels and hypothyroidism. Conversely,results of other meta-analyses have indicated that thereis an association between NAFLD and hypothyroidism. Based on the results of those meta-analyses, the relationshipbetween NAFLD and thyroid function parameters is controversial. Guo et al[21] have reported that the association betweenNAFLD and FT3 and FT4 levels was heterogeneous among thepopulation, and the TSH level may be an important risk factorfor the development and progression of NAFLD, independent ofthyroid hormones. He et al[22] have reported that the correlation between overt hypothyroidism and NAFLD was more significantthan that between subclinical hypothyroidism and NAFLD. Mantovani et al[23] reported that subclinical hypothyroidism was notindependently associated with the risk of incident NAFLD. However, Chung et al. reported a positive association betweenNAFLD and TSH. They showed that subclinical hypothyroidismwas closely related to NAFLD in a TSH dose-dependentmanner, even within the normal upper TSH level range. In addition, Kim et al[24] reported that an increase in the TSH level, evenwithin the normal clinical range of T4, was associated withbiopsy-proven non-alcoholic steatohepatitis (NASH) andadvanced fibrosis.

The present study has some limitations. First, this was across-sectional study. Second, as NAFLD was diagnosed byultrasonography, there was limited accuracy for the detection ofmild steatosis.

CONCLUSION

Overall, our study suggests that thyroid function is associated with NAFLD.This is an important finding because it opens a discussionif the adequacy of the TSH level to a lower reference couldprevent the emergence of NAFLD.Our findings highlight the need for future investigationson preventive measures (eg, screening of thyroidfunction in NAFLD patients) and possible therapeutic interventions(eg, decision of treatment in subclinical thyroiddysfunction).

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