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INCIDENCE OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IN HYPOTHYROIDISM

A.K. Koushik*, Panchapakesan Ganesh, Shanmugnathan Subramanyam, Chunduri Venkata Viswa Vikranth

ABSTRACT

Thyroid hormones are involved in the regulation of body weight, lipid metabolism, and insulin resistance. Therefore, it is expected that thyroid hormones may have a role in the pathogenesis of Non-Alcoholic Steatohepatitis (NASH) and **Non-alcoholic fatty liver disease (NAFLD)**. This study aimed to characterize the relationship between hypothyroidism and NASH. Possible explanations for this association are the recognized links between hypothyroidism and various elements of the metabolic syndrome, which is often present in NASH. In this study, we reviewed the association between thyroid dysfunction and NAFLD. Thyroid dysfunction in the form of overt or subclinical hypothyroidism is prevalent among patients with NAFLD/ NASH. The study population consisted of 70 adult patients ≥18 years of age with laboratory, ultrasound proven non-alcoholic steatohepatitis (NASH). Descriptive statistics were computed for all factors. Hypothyroidism was more frequent among patients with NASH (27%) but statistically not significant. Mean TSH is 3.04. The prevalence of NASH and abnormal liver enzyme levels increased steadily with increasing grades of hypothyroidism The prevalence of NASH/NAFLD and abnormal liver enzyme levels increased steadily with increasing grades of hypothyroidism

Hypothyroidism appears to be an independent risk factor for NAFLD/NASH in some studies; however, other newly published studies failed to find such an association. The results of the studies on the role of thyroid abnormalities in NASH are inconsistent, and further research is recommended to determine the relationship between hypothyroidism and NASH and the underlying mechanisms.

Authors Affiliations:

Department of Medical Gastroenterology, *Sri Ramachandra Institute of Higher Education and Research* (SRIHER), No.1, Ramachandra Nagar, Porur, Chennai, Tamil Nadu 600116

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***Corresponding Author:**

Dr A.K. Koushik, Assistant professor, Department of Medical Gastroenterology,
Sri Ramachandra Institute of Higher Education and Research (SRIHER)
No.1, Ramachandra Nagar, Porur, Chennai, Tamil Nadu 600116
Email: drakkoushik@gmail.com
Mobile- 9551556666

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has huge spectrum ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH), and if pathological insult it may progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma. NASH is a rapidly growing cause of liver disease, and it is the most common cause of abnormal liver function tests worldwide [(1)]. The growing pattern of NASH prevalence is generally attributed to a global increase in the prevalence of obesity and other metabolic risk factors. Advanced age and metabolic disorders, such as diabetes type 2, impaired glucose tolerance, and central obesity, are among the risk factors for NASH [(2)]. Non-alcoholic fatty liver disease and thyroid dysfunction: A systematic review. Patients with liver cirrhosis who lack any identifiable viral, alcoholic, autoimmune, or drug-related cause of the condition are labelled as having cryptogenic cirrhosis. NASH is believed to be responsible for the majority of the cases of cryptogenic cirrhosis [(3)] considering the increasing incidence of NAFLD/NASH, especially in developed and developing countries; it is expected to surpass other causes of cirrhosis in near future. Thus understanding the pathophysiology and newer treatment modalities of NAFLD/NASH is of paramount importance in the foreseeable future. Endocrine hormones play a central role in cell metabolism, energy balance, and fat distribution and their alterations result in profound multisystemic abnormalities. The thyroid hormone in conjunction with other hormones plays a central role in body energy regulation; lipid and carbohydrate metabolism. In a clinical setting, subclinical hypothyroidism has been associated with metabolic syndrome, abdominal obesity, cardiovascular mortality, and dyslipidemia. Growing evidence over the years has showed an association between NAFLD/NASH and hypothyroidism[(4,5,6,7)]. Herein, we investigated the association between NAFLD/ NASH and

thyroid dysfunction, and on the proposed underlying mechanisms.

METHODS AND DESIGN

The study population consisted of 70 adult patients ≥18 years of age with laboratory, ultrasound proven non-alcoholic steatohepatitis (NASH) attending the department of gastroenterology, Sri Ramachandra Medical University. Exclusion criteria included subjects with significant alcohol use, pediatric patients, or those with any laboratory or clinical evidence to suggest probable underlying chronic liver disease including viral hepatitis, hemochromatosis, autoimmune hepatitis, Wilson's disease, or chronic cholestatic liver disease. NASH patients were categorized as having hypothyroid based on thyroid function test. Patients with a clinical diagnosis of hypothyroidism who were on thyroid replacement therapy were considered to be hypothyroid.

Age, gender, weight, height, thyroid function test, HbA1c, cholesterol levels, triglycerides, serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), Ultrasound grading, were assessed in all subjects. The height was measured using stadiometer. Weight measured with mechanical weighing machine. Thyroid function tests were done by chemiluminescence method, HbA1C was done using High-performance liquid chromatography (HPLC). Lipid profile was done after at least 8 hours of fasting Triglycerides by enzymatic endpoint method, High density lipoprotein (HDL) and Low density lipoprotein (LDL by direct measure method. Ultrasound was done to establish steatosis and elastography was done to grade hepatic steatosis.

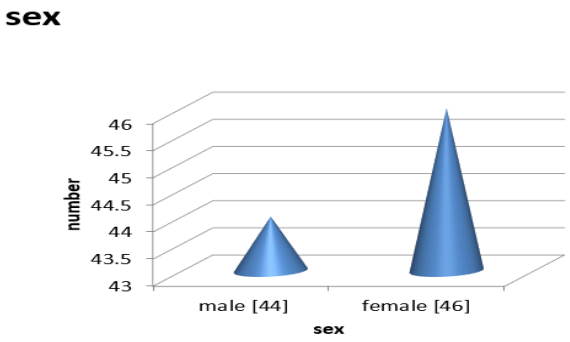
Statistical analysis

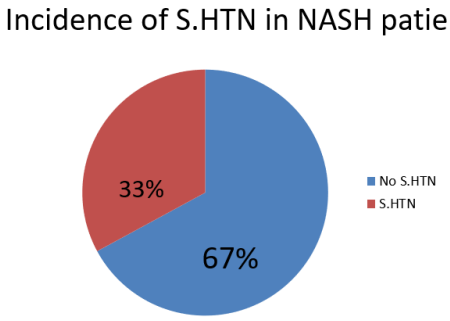
Descriptive statistics were computed for all factors. Mean and standard deviations were calculated for continuous variables and frequencies and percentages for categorical variables. Pearson Correlation, Sig. (2-tailed) Correlations calculated. P <0.05 was considered statistically significant.

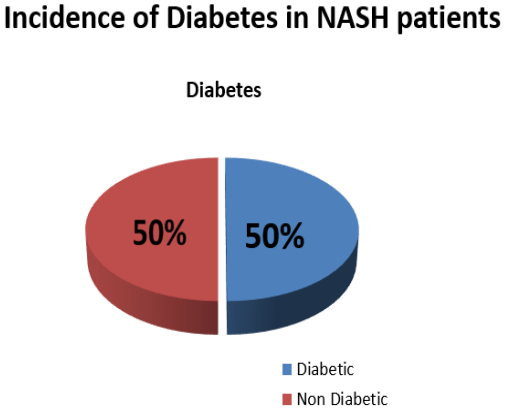
RESULT

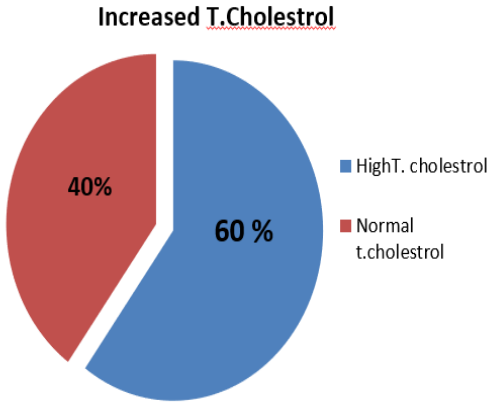
Hypothyroidism was more frequent among patients with NASH (27%) but statistically not significant. Mean TSH is 3.04 (table1). The prevalence of NASH and abnormal liver enzyme levels increased steadily with increasing grades of hypothyroidism. The mean age of patients in our study is 45yrs (table1). Most of the patients are overweight,

mean being 27.34, which is statistically significant (table1). Female predominance (46; 54%) was noted in study population (44; 46% males) (Figure 1). 33% of patients had systemic hypertension (figure2), and 50% patient had type 2 Diabetes mellitus DM (Figure3); among them, 60% had uncontrolled diabetes. Majority of the patients are dyslipidemia. 60% of the patients had high cholesterol and the mean is 230 mg/dl (Figure4); 62.8 % of patients had hypertriglyceridemia with a mean of 176 mg/dl (Figure5).









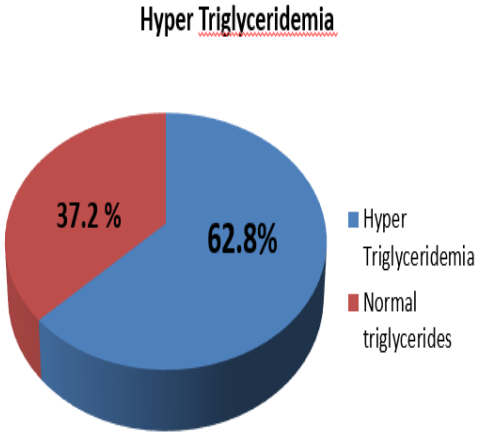


Fig 1-5: Distribution of Gender, Hypertension, Diabetes Mellitus, Total Cholesterol and Hyper triglyceridemia among hypothyroidism patients

General variables	Mean	Median	Standard deviation
Age	**45.06**	**44.5**	**8.98**
BMI	**27.34**	**27.0**	**2.26**
SGPT	**96.4**	**74.0**	**56.3**
SGOT	**63.7**	**56.5**	**20.5**
TSH	**3.04**	**2.11**	**2.46**
HbA1c	**6.5**	**6.4**	**1.20**
Cholesterol	**230**	**217**	**55.7**
Triglycerides	**176**	**172**	**59.16**

Table1: Mean, Median and Standard deviation of various parameters among hypothyroidism patients

DISCUSSION

There is growing data about the higher prevalence of thyroid dysfunction in the form of overt or subclinical hypothyroidism among patients with NAFLD/NASH [8] [3] [4]. The prevalence of hypothyroidism was reported to range from 15.2% to 36.3 % among patients with NAFLD/NASH [2]. Studies showed higher prevalence of hypothyroidism in patients of NASH/NAFLD when the healthy people were used as controls. Thus studies labelled hypothyroidism as an independent risk factor for NASH/NAFLD [9]. Indicating that hypothyroidism may directly result in NASH irrespective of other metabolic risk factors.

Pagadala *et al. reported that hypothyroidism was* more common in patients with NASH compared to patients with NAFLD (9). Contrary to these two studies, the results of the study by Mazo and co-workers did not show a statistically significant association between hypothyroidism, simple steatosis, and NASH (10). Furthermore, two other recently published studies of healthy participants also confirmed the Mazo *et al.* findings [7] [11]. A fat regulatory hormone Leptin was found to be elevated in hypothyroid patients, and it may be responsible for the development of NAFLD/NASH. Leptin is an adipocytokine involved in the regulation of appetite, with an increased level seen in cases of obesity, can induce collagen synthesis in the liver and promotes hepatic insulin resistance. Patients with NAFLD/NASH have abnormal lipid profiles notable for elevated cholesterol, low-density lipoprotein, and triglyceride levels. Thyroid hormones induce their effects on lipid metabolism via thyroid hormone receptor β, expressed on the hepatocytes. Hypothyroidism and elevated TSH result in decreased hepatic lipoprotein lipase activity and cause elevated serum triglyceride levels. The role of

Fibroblast growth factor-21 (FGF-21), which increases in hypothyroid subjects, has been recently proposed in NAFLD/NASH. FGF-21 is a member of the endocrine FGF family that has several hormone-like activities [(12) (13)]. The other theory is based on hepatic damage through mitochondrial dysfunction, oxidative stress, and reactive oxygen species (ROS) production [(13)]. With the excessive accumulation of FFA in the hepatocytes, there is excessive oxidation of FFA in mitochondria, microsomes, and peroxisomes, leading to overproduction of ROS.

CONCLUSION

The prevalence of hypothyroidism in patients with NASH in our study is not statistically significant. The results of the current study are conflicting about the association between thyroid abnormalities and NASH. The results of the reviewed studies showed conflicting results; some studies showed a statistically significant association between NASH and hypothyroidism, while other studies did not support the significant association. The high prevalence of thyroid dysfunction among NASH patients, suggests that hypothyroidism may identify a subgroup of patients in the general population who may benefit from screening for the presence of fatty liver disease. As hypothyroidism is a modifiable risk factor and can easily be treated with thyroid replacement therapy, the interesting issue for future studies will be to evaluate whether hypothyroid patients with NASH/NAFLD would benefit from treatment of hypothyroidism. None of the present studies are interventional trials. Placebo-controlled clinical trials should be conducted to elucidate the issue further.

Conflict of Interest Statement-

There is no conflict of interest.

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