Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Thyroid Profile of Patients with Non-alcoholic Fatty Liver Disease

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is associated with various metabolic abnormalities such as obesity, insulin resistance, and dyslipidemia. The prevalence of NAFLD is increasing gradually, which may progress to non-alcoholic steatohepatitis (NASH), cirrhosis of liver, and hepatocellular carcinoma. The important association of NAFLD and metabolic disease can lead to endocrinopathy, including thyroid diseases.

Methodology: Serologically diagnosed NAFLD patient was evaluated biochemically for liver function and thyroid function to evaluate any association between these two.

Results: The study shows female preponderance (63.3%) NAFLD. It was observed that 77.50% were having normal transaminase level and 22.50% had raised transaminase levels (NASH). Subclinical hypothyroidism was present among 18.30%, overt hypothyroidism was 7.50%, and hyperthyroidism was 0.80%. Among the individuals with normal transaminase level, 20.50% were hypothyroid (15.10% subclinical and 5.40% overt), and persons with raised transaminase levels (NASH), 44.44% were hypothyroid (29.63% subclinical and 14.81% overt).

Conclusion: This study shows that though there was a female preponderance of NAFLD, raised transaminase was more common among male and so is the hypothyroidism. This may form a matrix to the future study for cause and effect relationship of NAFLD and thyroid disease.

Key words: Hypothyroid, Non-alcoholic fatty liver disease, Subclinical hypothyroid, Transaminase

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of fat in the liver (hepatic steatosis) either on imaging or on liver histology after the exclusion of secondary causes of fat accumulation in the liver, for example, significant alcohol consumption (defined as greater than 40 g/day)[1] or certain medications such as estrogen, antitubercular therapy (ATT), tamoxifen, methotrexate, and amiodarone.[2]

NAFLD represents one of the most common chronic disorders of the liver in the Western industrialized nations.[3-6] Its prevalence worldwide is estimated at 20–30%.[7-9] Recently, a gradual increase in NAFLD being observed in developing countries. It is presumed to be due to the adaptation of Western culture, sedentary lifestyle, and an increase in diagnostic modalities in developing countries.

The mechanism underlying the pathogenesis and progression of NAFLD is not entirely clear. The best-understood mechanisms pertain to hepatic steatosis. This is proven to result when hepatocyte mechanisms for triglyceride synthesis (e.g., degradative metabolism and lipoprotein export), leading to the accumulation of fat (i.e., triglyceride) within hepatocytes. Obesity stimulates hepatocyte triglyceride accumulation by altering the intestinal microbiota to enhance both energy harvest from dietary sources and intestinal permeability. Reduced intestinal barrier function increases hepatic exposure to gut-derived products, which stimulates liver cells to generate inflammatory mediators that inhibit insulin

Access this article online

www.ijss-sn.com

Month of Submission : 11-2019
Month of Peer Review : 12-2019
Month of Acceptance : 12-2019
Month of Publishing : 01-2020

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actions. Obese adipose depots also produce excessive soluble factors (adipokines) that inhibit tissue insulin sensitivity. Insulin resistance promotes hyperglycemia. This drives the pancreas to produce more insulin to maintain glucose homeostasis. However, hyperinsulinemia also promotes lipid uptake, fat synthesis, and fat storage. The net result is hepatic triglyceride accumulation (i.e., steatosis).[10]

NAFLD includes a variety of entities ranging from simple fatty liver or hepatic steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis of the liver[11-13] and is associated with the risk of malignant degeneration to hepatocellular carcinoma and the increased necessity of liver transplantation.[14,15] A central role in the development of NAFLD has been ascribed to the metabolic syndrome, whose main characteristics, such as obesity, insulin resistance, and/or type-2 diabetes mellitus and dyslipidemia, are closely associated with NAFLD.[11] Not surprisingly, there is also an association between NAFLD and cardiovascular disorders.[3,4]

Thyroid hormones are secreted from thyroid gland and regulated by hypothalamo–pituitary–adrenal axis. The hypothalamic–pituitary–thyroid axis (HPT axis for short, also known as thyroid homeostasis or thyrotropic feedback control) is part of the neuroendocrine system responsible for the regulation of metabolism. As its name suggests, it depends on the hypothalamus, the pituitary gland, and the thyroid gland. The hypothalamus senses low circulating levels of thyroid hormone (triiodothyronine [T3] and thyroxine [T4]) and responds by releasing thyrotropin-releasing hormone (TRH). The TRH stimulates the pituitary to produce thyroid-stimulating hormone.

The TSH, in turn, stimulates the thyroid to produce thyroid hormone until levels in the blood return to normal. Thyroid hormone exerts negative feedback control over the hypothalamus as well as anterior pituitary, thus controlling the release of both TRH from hypothalamus and TSH from anterior pituitary gland.[16]

Recently, a correlation between thyroid dysfunction, especially clinical or subclinical hypothyroidism, and NAFLD has been detected.[8,17-20] Hormones synthesized in the thyroid gland play an important role in the regulation of diverse metabolic processes. Disturbances in thyroid hormone concentrations may promote hyperlipidemia and obesity, thus contributing to NAFLD.[17,21] Early identification of at-risk patients is important since the treatment of the hypothyroidism may reduce the risk of NAFLD and potential complications.[22] Hence, this present study was planned to assess the thyroid dysfunction among the patients of NAFLD attending a tertiary care center of the Northeastern region of India.

Aim of the Study

The aim of the study was as follows:

1. To study the frequency of subclinical and overt hypothyroidism and hyperthyroidism among the patients with NAFLD
2. To study the association between transaminase level with thyroid hormone level.

METHODOLOGY

Study Population

Patients who were diagnosed to have NAFLD during the study duration of the year were included in the study.

Sample Size

Patients, who have undergone ultrasonography (USG) of whole abdomen examination in the radiology department for some or other reason and incidentally diagnosed to have fatty liver, have been screened by inclusion and exclusion criteria to diagnose NAFLD. All of such NAFLD patients, thyroid profile has been estimated. From the previous records, it is found that approximately 80 patients are diagnosed to have NAFLD in 1 year. Hence, in 1½ years, approximately the sample was considered to be 120.

Operational Definition

NAFLD

NAFLD is defined as the presence of fat in the liver (hepatic steatosis) either on imaging or on liver histology after the exclusion of secondary causes of fat accumulation in the liver, for example, significant alcohol consumption (defined as greater than 40 g/day)[1] or certain medications such as estrogen, ATT, tamoxifen, methotrexate, and amiodarone.[2]

NASH

When NAFLD is associated with raised transaminase levels, the diagnosis of NASH is made[10] (normal aspartate aminotransferase 12–38 U/L and alanine aminotransferase 7–41 U/L).[23]

Hypothyroidism

The diagnosis of subclinical hypothyroidism was made in subjects with TSH concentration > 4.5 μ IU/ml (normal value 0.34–4.25 μ IU/ml) and <10 μ IU/ml and normal thyroid hormone concentrations (total T4: 70–151 nmol/l; total T3: 1.2–2.1 nmol/l). The diagnosis of clinically manifest or overt hypothyroidism will require reduced total T4 concentrations (< 70 nmol/) and elevated TSH levels (TSH > 10 μIU/ml).[24,25]

Inclusion and Exclusion Criteria

Inclusion criteria

Adult patients with fatty liver and no significant alcohol consumption (defined as greater than 40 g/day) were included in the study.[1]

Exclusion criteria

The following criteria were excluded from the study:

- Patients with hepatitis B virus and hepatitis C virus positivity
- Liver diseases of other known causes
- Patients consuming a significant amount of alcohol or drugs such as estrogen, ATT, tamoxifen, methotrexate, and amiodarone[2]
- Intake of iodine, antithyroid agents, or thyroid hormone
- Pregnant women
- Unwilling or incapacity to provide informed consent.

Method of Data Collection

Patients, who have undergone USG of whole abdomen examination in the radiology department for some or other reason and incidentally diagnosed to have fatty liver, are considered. After excluding relevant patients study group, patients were evaluated for liver function and thyroid profile.

RESULTS AND ANALYSIS

Among all the patients of NAFLD (n: 120) 36.70% were male and 63.30% were female. Commonest age group was 31–50 years (45.80%), whereas 37.50% was >50 years & 15% was in 18–30 years of age group [Figure 1].

It was found that 34.20% of NAFLD patients were diabetic and 31.70% were hypertensive.

Among all NAFLD patients, 77.50% were having normal transaminase level and only 22.50% had raised transaminase levels (NASH). However, male NAFLD patients had more transaminasemia (36.4%) than female (14.4%).

Hypothyroidism was found among 25.8% of total patients (subclinical hypothyroidism 18.30% and overt hypothyroidism 7.50%) and hyperthyroidism was 0.80%. Among the patients with normal transaminase, 20.50% were hypothyroid (15.10% subclinical and 5.40% overt), and among patients with raised transaminase level, 44.44% were hypothyroid (29.63% subclinical and 14.81% overt) [Figure 2].

Pearson Chi-square test was applied to find out the association between transaminase level and hypothyroidism, which shows that they have a strong association with $P = 0.013$ (<0.05), that is, patients with raised transaminase level (NASH) than with normal transaminase are more prone to develop hypothyroidism.

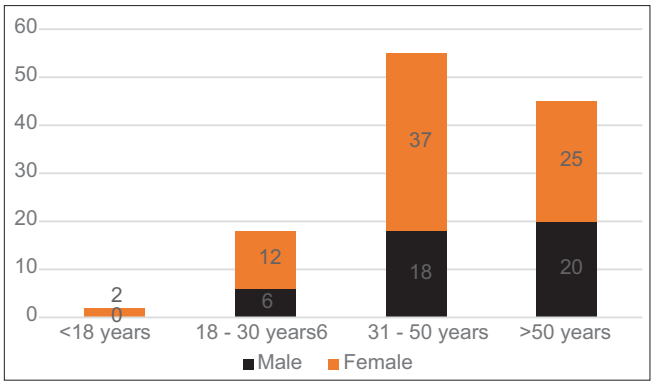

Figure 1: Age and sex distribution of non-alcoholic fatty liver disease

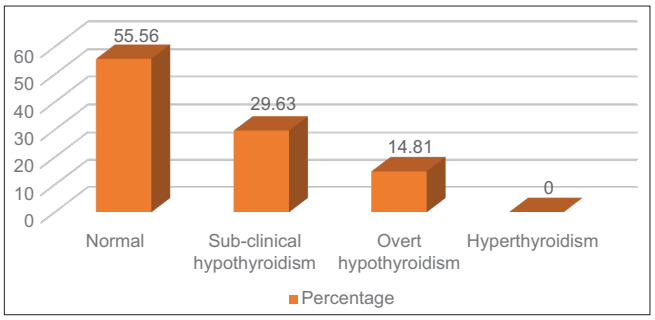

Figure 2: Thyroid status in patients with raised transaminase level

DISSCUSSION

NAFLD is gradually becoming the most common cause of liver disease worldwide, similarly in developing counties. This study was conducted in a tertiary care center of the Northeastern region of India to see the thyroid profile of patients with NAFLD and to see the association between transaminase level and thyroid disorder. The study showed that there is a female preponderance (63.3%) among NAFLD patients, and common age group was 31–50 years (mean age of all NAFLD patients was 46.07 years), that is, most productive age. Pagadala *et al.* conducted a cross-sectional study with 233 patients, which also showed female preponderance (56.2%). Raised transaminase (NASH) was found in 22.5% of NAFLD patients, but there was a male preponderance (36.4% male vs. 14.4% female).

The study shows that though NAFLD had female preponderance (63.3% vs. 36.7%), developing NASH had male preponderance (36.4% vs. 14.4%). Harrison's Principles of Internal Medicine has stated that the prevalence of NASH in NAFLD, at any given point, is about 25%. Almost similar result was obtained in this study. Almost one-fourth patients of NAFLD were having hypothyroidism and hyperthyroidism was insignificant (0.8%). The study conducted by Pagadala *et al.* showed that the frequency of hypothyroidism in NAFLD patients was 21%. Raised transaminase was closely associated

with thyroid dysfunction (subclinical and overt hypothyroid), which was statistically highly significant. A higher frequency of hypothyroidism was demonstrated in patients with NASH than to NAFLD (44.44% vs. 20.5%).

The study conducted by Pagadala *et al.* showed that hypothyroidism was more frequent among patients of NAFLD with NASH than to NAFLD without NASH (25% vs. 12.8%). Pearson Chi-square test is applied to find out the association between transaminase level and hypothyroidism, which shows that they have a strong association with $P = 0.013$ (<0.05), that is, patients with raised transaminase level (NASH) than with normal transaminase are more prone to develop hypothyroidism.

The study showed that among total patients of NFLD, 41.7% was found to be in Grade 1, 43.3% was found to be in Grade 2, and 15.0% was found to be in Grade 3. The study also showed that 34.2% of NAFLD patients were diabetic and 31.7% were found to be hypertensive.

CONCLUSION

This study shows that though female was more prone to develop NAFLD, male was more prone to develop raised transaminase level.

Most of the patients were among the age group of 31–50 years. Hypothyroidism (subclinical + overt) was present in about 25.8% of all study subjects of NAFLD, and it was more frequent in patients with raised transaminase level.

It is concluded that all diagnosed patients of NAFLD should be evaluated for thyroid function at the time of diagnosis and subsequently at a regular interval, particularly where there is a raised transaminase.

Hypothyroidism may accelerate the progress of NAFLD and simultaneously progress of NAFLD may be associated with more number of subclinical and overt hypothyroid diseases.

This study may form a matrix to the future study for cause and effect relationship of NAFLD and thyroid disease.

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How to cite this article: Samaresh P, Pradip B, Swatilekha B. Thyroid Profile of Patients with Non-Alcoholic Fatty Liver Disease. Int J Sci Stud 2020;8(1):72-75.

Source of Support: Nil, **Conflicts of Interest:** None declared.