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ORIGINAL ARTICLE

Study of Prevalence of Non-Alcoholic Fatty Liver Disease in Hypothyroidism and Possible Association of Hypothyroidism with NAFLD Fibrosis Score in Odisha

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Abstract

Introduction: Hypothyroidism is being increasingly recognized as a risk factor for developing non-alcoholic fatty liver disease (NAFLD). This study was planned to study the prevalence and evaluate any possible association between hypothyroidism and severity of NAFLD. **Materials and Methods:** This case control study was conducted in the department of Medicine, IMS and SUM Hospital, Bhubaneswar among 50 hypothyroid patients and 50 age and sex matched control group. USG abdomen, and various biochemical parameters including TSH levels were done and NAFLD fibrosis score was calculated. **Results:** Out of the 50 hypothyroid cases, 42 (84%) showed fatty liver changes, whereas only 6 (12%) of controls demonstrated fatty liver changes on ultrasonography. A positive correlation was found among the various grades of NAFLD and TSH, triglyceride, and cholesterol levels ($p<0.05$) and slight positive correlation found between serum TSH and fibrosis score of the cases ($p=0.044$, $r=0.167$). however, a higher TSH value was not associated with raised ALT levels in cases ($p>0.05$, $r=0.064$). **Conclusion:** The prevalence of NAFLD in hypothyroid patients excluding all other confounding risk factors in our study was 84%. A positive correlation was found between hypothyroidism and the NAFLD fibrosis score but not with ALT levels. A larger group of NAFLD subjects secondary to hypothyroidism is required to validate such association.

Keywords:
NAFLD Fibrosis score, Hypothyroidism, NAFLD

Introduction

The clinical spectrum of non-alcoholic fatty liver disease (NAFLD) ranges from a simple fatty liver to non-alcoholic steatohepatitis, which may advance to liver fibrosis, cirrhosis, and hepatocellular cancer[1]. NAFLD has emerged as an enormous public health problem in India. Patients with NAFLD often lack specific signs and symptoms. Therefore, the prevalence is underappreciated. The prevalence of NAFLD in Asia-pacific region is between 6-30 %[2]. NAFLD has also been linked to global increases in childhood obesity rates. Nonalcoholic steatohepatitis (NASH) has become the third most common indication for liver transplantation in the United States and is expected to become the leading indication in the near future[3]. The escalating trend of NAFLD is largely related to the widespread increase in obesity and other metabolic risk factors such as advanced age, type 2 diabetes, and central obesity.

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Clinicians are of the view that, patients initially thought to have cryptogenic cirrhosis without any identifiable viral, autoimmune, alcoholic, or drug-related aetiology might actually be a consequence of NASH.

Hypothyroidism is an emerging risk factor for NAFLD[4]. Hormone like thyroid is significantly engaged in cellular metabolism, fat distribution, regulation of body weight and basal metabolic rate, thereby serving a crucial role in the development of metabolic abnormalities. Subclinical hypothyroidism have been linked to metabolic syndrome, dyslipidemia, and cardiovascular mortality in multiple studies[5]. Over past few years, mounting evidence has led to skepticism regarding the relationship between NAFLD/NASH and hypothyroidism. According to various studies, the prevalence of hypothyroidism in India is 10.95% [6]. Early diagnosis of at-risk patients is crucial, as treatment of hypothyroidism may lower the likelihood of developing NAFLD and related consequences. This study is a step forward in understanding the association between hypothyroidism and NASH.

Materials and Methods

This was a hospital based prospective observational study carried out from February 2021 to April 2022 in IMS and SUM hospital, Bhubaneswar after approval from the institution ethical committee (DR/IMS.SH/SOA/2021/043).A total of 100 patients were included in our study, out of which 50 cases were hypothyroid, and 50 were controls. A universal sample technique was used to estimate a sample size by considering the prevalence of hypothyroid in previous studies. The study was conducted in IMS and SUM medical college and hospital, Bhubaneswar, in the department of general medicine. Cases with hypertension, impaired fasting glucose (IFG), diabetes, body mass index (BMI) of more than 30 kg/m^2, consuming alcohol of more than 20 gm per day, pregnancy, having other liver diseases including hepatitis, currently on drugs causing steatohepatitis, patients on total parenteral nutrition (TPN) and who have undergone previous gastric bypass surgeries were excluded from our study. Controls included in the study were euthyroid and satisfied the exclusion criteria.Both verbal and written consent were obtained from each participant. All patients underwent a full physical examination. Blood parameters such as TSH, T3, T4, complete blood count (CBC) including haemoglobin and total platelet counts (TPC), serum bilirubin, SGOT, SGPT, ALP, total serum protein, albumin, lipid profile, fasting blood sugar (FBS), viral markers such as HbsAg, Anti HCV, HIV, and radiological parameters such as USG abdomen were done. NAFLD fibrosis score was calculated.

Data was analysed by SPSS version 20. Pearson correlation was applied to detect positive and negative co-relation between various parameters.

The presence of fatty infiltration of the liver in the absence of excessive alcohol intake and other chronic liver diseases was essential for the diagnosis of NAFLD. The patients underwent ultrasonography of the whole abdomen by a single radiologist, where a positive case of NAFLD was diagnosed with a "generalized enhancement of hepatic echogenicity (bright liver), greater than in the renal cortex and splenic parenchyma, attributable to intracellular lipid accumulation, as well as hepatomegaly and vascular blurring of the portal or hepatic vein"[7].

Grades of fatty liver on USG: **grade I-** increased hepatic echogenicity with visible periportal and diaphragmatic echogenicity; **grade II-** increased hepatic echogenicity with visible periportal echogenicity, without obscuration of the diaphragm; **grade III-** increased hepatic echogenicity with imperceptible periportal echogenicity and obscuration of the diaphragm; **grade IV-** cirrhosis[8].

Diagnosis of NAFLD was based on a careful history to determine the amount of alcohol consumed, less than 20 gm/day and radiological imaging, as explained earlier.

NAFLD fibrosis score was calculated using the formula: NAFLD fibrosis score = -1.675 + 0.037 × age (year) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count (×109/L) - 0.66 × albumin (g/dL). The score was calculated and the percentage of subjects having Chronic liver disease was recorded.[9]

Results

In this study, 50 hypothyroid patients (cases) and 50 controls were enrolled. Females out-numbered males both in cases and control groups in the ratio of 5.6:1. The mean and standard deviation of various parameters of cases and controls are described in [*Table 1*].

Out of 50 cases, 86% had complains of dry skin, 88% gave history of experiencing cold intolerance, 84% had hair loss, 80% had constipation, 90% gave history of menstrual abnormalities, 88% had weight gain and 82% complained of tiredness.

Out of the 50 hypothyroid cases, 42 (84%) showed fatty liver changes on ultrasonography, among which 23 (46%) had Grade I Fatty liver, 12 (24%) had Grade II Fatty liver, 6 (12%) had Grade III Fatty liver, and 1 case (2%) had Grade IV Fatty liver Disease. Whereas, out of the 50 controls, 6 (12%) demonstrated fatty liver changes on ultrasonography [*Table 2*].

Table 1. Mean and Standard Deviation of Baseline Parameters

	Cases (n=50) Mean ± SD	Control (n=50) Mean ± SD
Age (years)	38.08 ± 10.505	32.28 ± 9.89
BMI (Kg/m^2)	25.06 ± 2.0	23.97 ± 2.03
TSH	18.45 ± 15.0	3.12 ± 0.95
Hb (mg/dl)	11.32 ± 0.767	11.76 ± 1.39
Platelets (in lakhs)	1.45 ± 0.61	2.45 ± 0.81
Bilirubin total (mg/dl)	1.05 ± 0.28	0.67 ± 0.28
AST (IU/L)	96.02 ± 79.74	23.10 ± 8.55
ALT (IU/L)	76.32 ± 63.70	30.10 ± 10.07
ALP (IU/L)	111.84 ± 47.90	107.18 ± 24.52
Total protein (g/dl)	6.71 ± 0.59	6.62 ± 0.59
Albumin (g/dl)	4.09 ± 0.37	4.07 ± 0.40
Cholesterol (mg/dl)	173.58 ± 29.09	135.34 ± 22.66
Triglyceride (mg/dl)	143.32 ± 33.95	103.46 ± 21.66
Fibrosis score	-0.7934 ± 1.36	-3.3454 ± 1.110

Table 3: Serum Cholesterol, Triglyceride, ALT, TSH levels, BMI and Fibrosis Score in Various Grades of Fatty Liver among cases

	USG ABDOMEN					
Fatty liver	**Grade I**	**Grade II**	**Grade III**	**Grade IV**	**Normal**	**P value**
FREQUENCY	23	12	6	1	8	<0.05
BMI (Mean ± SD)	24.85 ± 1.81	24.8 ± 2.15	25.28 ± 1.60	30.0 ± 0	25.31 ± 2.17	<0.001
NAFLD FIBROSIS SCORE (Mean ± SD)	-0.7926 ± 1.135	-0.7683 ± 2.0	-1.766 ± 0.878	0.76 ± 0	-	<0.001
TSH (Mean ± SD)	22.63 ± 19.98	19.6 ± 18.21	11.02 ± 26.78	10.5 ± 0	15.76 ± 8.89	<0.001
ALT (Mean ± SD)	59.74 ± 32.05	83.91 ±75.324	111.83 ± 69.06	340 ± 0	53.00 ± 14.85	<0.001
CHOLESTEROL (Mean ± SD)	171.35 ± 24.94	183.58 ± 19.29	186.33 ±31.16	221 ± 0	149.5 ± 37.14	<0.001
TRIGLYCERIDE (Mean ± SD)	143.78 ± 28.50	160.50 ± 27.70	166.17 ± 38.36	178 ± 0	102.25 ± 22.64	<0.001

Table 2: USG finding among cases and controls

USG Findings	Cases (n=50)	Controls (n=50)
Grade I Fatty liver	23 (46%)	4 (8%)
Grade II Fatty liver	12 (24%)	2 (4%)
Grade III Fatty liver	6 (12%)	0 (0%)
Grade IV Fatty liver	1 (2%)	0 (0%)
Normal USG	8 (16%)	44 (88%)

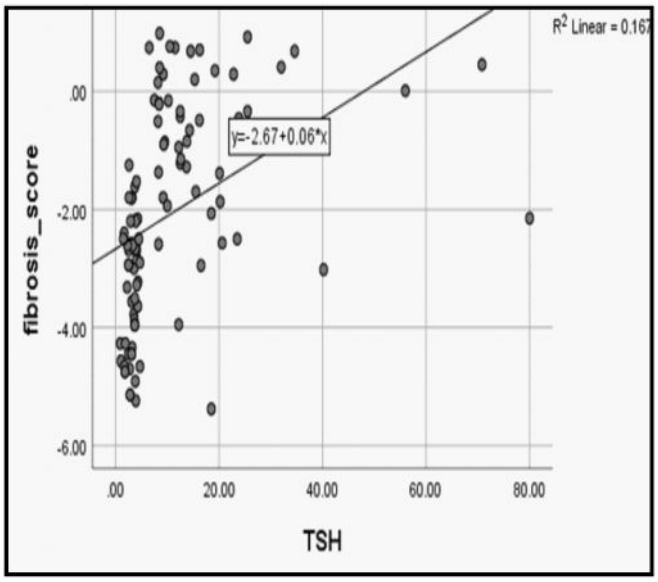

Fig 1: Correlation between serum TSH and fibrosis score in cases (p=0.044, r=0.167).

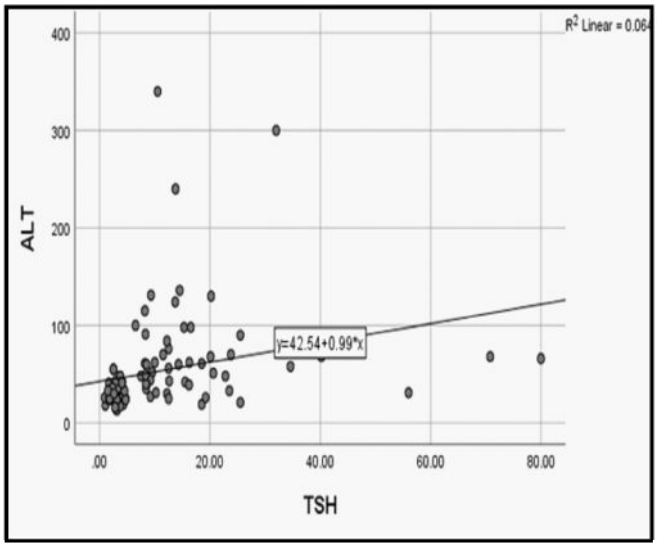

Fig 2: Correlation between serum TSH and ALT in cases (p=0.05, r=0.064).

Out of the 42 cases who had NAFLD changes in USG, 23 patients (54.76%) had Grade I, 12 patients (28.57%) had Grade II, 6 patients (14.28%) had Grade III and 1 patient (2.3%) had Grade IV fatty liver disease. As the grade of fatty liver disease increased, the triglyceride, cholesterol, and ALT levels also increased [*Table 3*].

A significant positive correlation was found among the various grades of NAFLD and TSH, triglyceride, and cholesterol levels ($p<0.05$).

There was slight positive correlation found between the serum TSH and fibrosis score of the cases (p=0.044, r=0.167) [*Fig 1*].

A higher TSH value was not found to be associated with raised ALT levels in cases (p=0.05, r=0.064) [*Fig 2*].

Discussion

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease across the world. It ranges from simple steatosis to non-alcoholic steatohepatitis with fibrosis, which can eventually progress to cirrhosis and hepatocellular carcinoma. Non-alcoholic steatohepatitis-related cirrhosis is anticipated to become the leading indication for liver transplantation by 2030.[10] Thyroid dysfunction is a common metabolic disorder that affects lifelong health. Because thyroid hormones play a fundamental role inlipid metabolism, hypothyroidism may cause hypercholeste rolemia and play an essential role in the pathogenesis of NAFLD.[11] Thyroid also plays an important role in regulating energy homeostasis, insulin sensitivity, lipid/carbohydrate metabolism and reproduction functions. The thyroid hormones (T4) and triiodothyronine (T3) also exert several important metabolic actions similar to adiponectin.[12] Although hypothyroidism has been implicated in the aetiologyof NAFLD, previous studies regarding the association between thyroid function and NAFLD risk have yielded controversial results varying from strong to no correlation. This study was planned to evaluate any possible association between hypothyroidism and NAFLD. Hypothyroidism being a treatable condition, if found to be significant independent risk factor for NAFLD, can be of clinical significance in preventing progression to NASH and cirrhosis.

Our study was conducted on 100 subjects, 50 hypothyroid patients (cases) and 50 age and sex matched controls. There were 42 females (84%) and 8 males (16%) among the cases; while 43 females (86%) and 7(14%) males among the controls. Hypothyroidism is a hormonal disorder more common in females compared to males. Study conducted by Hamid Bashir *et al* in Government

medical college, Srinagar showed that prevalence of subclinical hypothyroidism was more in females (81.8%) than in males (18.2%) and most of the patient was in the group of 20-65 years.[13]

USG proven NAFLD i.e., fatty liver was found in 42 (84%) cases and in 6 (12%) controls which is similar with study by Goh Sun Chung *et al* having NAFLD in 66% cases (29.9% subclinical and 36.3% overtly hypothyroid subjects).[14]

Parikh P *et al*, found that the prevalence of hypothyroidism in patients with NASH was 16.8%.[15] Pagadala *et al*, also showed high prevalence of hypothyroidism in NAFLD.[16] Xu *et al* study showed that patients with lower FT4 or higher TSH are more likely to develop NAFLD.[17]

In our study, the mean levels of aspartate aminotransferase (AST) in cases and controls were 96.02 ± 79.74, and 23.10 ± 8.55 and the mean levels of alanine aminotransferase (ALT) in cases and controls were 76.32 ± 63.70 and 30.10 ± 10.07 respectively. Ahad et al study showed that elevated ALT was independently predictors of NAFLD hypothyroid patients.[18]

Our study revealed 46 % hypothyroid patients with NASH had grade I fatty liver, 24% had grade II fatty liver, 12 % had grade III fatty liver and 2% had grade IV fatty liver disease. The diagnostic performance of USG in detecting patients without coexisting liver disease offers a fairly accurate diagnosis of moderate to severe hepatic steatosis, with reported sensitivity ranging from 81.8% to 100% and specificity as high as 98%. Therefore, abdominal ultrasound is widely used for screening fatty liver disease in asymptomatic disease with an incidental elevation of liver enzymes. Ultrasound is very sensitive, but it cannot detect small amounts of hepatic steatosis and it is not quantitative. Study conducted by Karlas T *et al*'s it was found that USG based acoustic structure quantification parameters correlate with steatosis, but not with fibrosis in fatty liver disease.[19]

It was found in our study that grading of NAFLD was positively associated with dyslipidaemia and increasing serum TSH levels in the cases.Chung et al in his study revealed the presence of USG diagnosed NAFLD and abnormal ALT levels increased progressively with increasing grades of hypothyroidism.[20] Subclinical hypothyroidism even in the range of upper normal TSH levels, was found to be related to NAFLD in a dose dependent manner.[20]

In a study including subjects with biopsy- proven non-alcoholic steatohepatitis (biopsy proven NASH), subjects with hypothyroidism were found to have higher chances of NAFLD than without hypothyroidism, even after eliminating the impact of other metabolic disorder combined with obesity such as diabetes , hypertension, hyperlipidaemia.[21] In another study, Carulli *et al* found that euthyroid patients with biopsy proven NASH had higher TSH levels compared with those with simple steatosis.[22] TSH concentrations were significantly associated with an increased prevalence of hepatic steatosis and elevated ALT concentrations. The results obtained in our study are in consensus with studies mentioned above.

In our study it was found that there is increased total cholesterol, triglyceride levels which correlated well with the USG findings suggestive of NAFLD. Similarly study by Pagadala MR *et al*, showed that hypothyroidism causes elevation in cholesterol and low-density lipoproteins and increased triglyceride levels and low HDL levels. Hypothyroidism contributes to the dyslipidaemia in NAFLD.

Our cross-sectional study found a positive correlation between TSH and NAFLD (p=0.044, r=0.167). The prevalence of NAFLD among hypothyroids was found to be 84 % compared to 12% in age and sex matched controls. However, our study did not find any positive correlation between TSH and ALT levels.

Conclusion

Hypothyroidism is commonly encountered in women than in men. The mean age affected is 20-40 years. The most common symptomspatient presented to the clinics in our study was the feeling of tiredness and constipation.

Hypothyroidism leads to deranged lipid profile by its action on lipid metabolism, as seen in our study that the triglyceride, cholesterol levels were increased in hypothyroid compared to the euthyroid subjects. Dyslipidaemia leads to steatosis manifesting as fatty liver i.e., NAFLD which might lead to deranged LFT's causing NASH.

The prevalence of NAFLD in hypothyroid in our study population was 80% and a positive correlation was found between the severity of hypothyroidism and ALT values. The NAFLD score did not show a significant correlation, a larger group of NAFLD subject secondary to hypothyroidism is required to validate such association. It remains to be seen if correction of hypothyroidism causes any improvement in fibrosis score.

Limitations

Limitations of our study is very low sample size. Demographic, ethnical and regional variations need to be

considered in a larger randomized population for better conclusions.

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Conflicts of Interest
There are no conflicts of interest.

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