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Metabolic dysfunction associated steatotic liver disease in Patients with Hypothyroidism: a single centre study

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Abstract

Background: Hypothyroidism is a potential modifiable factor for metabolic dysfunction associated steatotic liver disease (MASLD). MASLD is associated with diminished thyroid action. Hypothyroidism causes reduction in uptake of free fatty acid and decreased lipolysis in the adipose tissue resulting in hepatic accumulation of triglycerides and increased low-density lipoprotein uptake. Hypothyroidism also increases triglyceride which contributes to hepatic insulin resistance, a factor for MASLD. **Methods**: A hospital based cross-sectional study was conducted at National Academy of Medical Sciences, Bir hospital on 28 newly diagnosed overt or subclinical hypothyroidism patients as hypothyroid group and matched 28 euthyroid patients visiting wellness clinic as comparison group who qualified for the eligibility criteria. The prevalence of MASLD in both groups was determined by ultrasonography (USG) which was done by a single radiologist. **Results**: The mean ages in hypothyroid and euthyroid groups were 41.07 years and 39.71 years respectively. The female to male ratio in hypothyroid was 3.6:1 and 1.5:1 in euthyroid group. MASLD was present in 15 (53.6%) hypothyroid and 7 (25%) of euthyroid group which was statistically significant (p value 0.029). Severity of MASLD was seen more in hypothyroid patients. There was no statistically significant correlation between thyroxine (T4), thyroid stimulating hormone (TSH) and severity of MASLD. **Conclusion**: Hypothyroidism is associated with MASLD and severity of MASLD is more with hypothyroid patients as compared to euthyroid group.

Key words: hypothyroidism, thyroid hormones, MASLD, lipid, triglyceride

Introduction

Thyroid hormones play important roles in energy expenditure. They maintain basal metabolic rate, maintain thermogenesis, modulate appetite and food intake thereby regulating body weight.[1] Thyroid hormones regulate cholesterol synthesis mainly by stimulation of the transcription of low-density lipoprotein receptor (LDL-R) gene resulting in increased uptake and enhanced cholesterol synthesis.[2] The mobilization of lipid droplets into hepatocytes is regulated by tri-idothyronine (T3).[3] The impairment of this process is associated with hepatic steatosis and insulin resistance.[4] MASLD is associated with diminished thyroid action.[5] Hypothyroidism is a potential modifiable factor for MASLD. There is association of hypothyroidism with hyperlipidemia through modifications in lipid synthesis, absorption, circulation, and metabolism. Increased triglyceride accumulation in the liver contributes to hepatic insulin resistance; a factor for MASLD.[6]

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MASLD is one of the commonest causes of chronic liver disease with global prevalence of 25%. MASLD can range from simple steatosis to metabolic dysfunction associated steatohepatitis which can be progressive leading to hepatic cirrhosis and hepatocellular carcinoma.[7] Since thyroid dysfunction might potentially play a role directly or indirectly in the pathogenesis of MASLD[8] and untreated MASLD could be progressive with detrimental consequences, this study was aimed to look for association between hypothyroidism and MASLD in our population as such study from our population is very scarce.

Material and method

This is a single centre cross-sectional observational study conducted at National Academy of Medical Sciences, Bir hospital among 28 newly diagnosed hypothyroidism cases and 28 healthy euthyroid group visiting wellness clinic for general health check-up. Ethical clearance was obtained from Institutional Review Board of National Academy of Medical Sciences (NAMS). Subclinical hypothyroidism was defined as normal fT3 and fT4 with elevated TSH[9] and overt hypothyroidism was defined as decreased fT3 and/ or fT4 with elevated TSH.[10] Patients taking thyroxine supplementation, people with diabetic mellitus, patients on lipid lowering therapies, patients with history of alcohol consumption of more than 20 gm per day, patients with hepatitis B or hepatitis C or patients with any underlying liver disease were excluded from the study. Anthropometric measurements such as weight (kg) and height (meters) were taken and body mass index (BMI) was calculated and classified according to World Health Organization (WHO) classification criteria of 2004 for Asian population. Biochemical profiles like fT3, fT4 and TSH, lipid profile and liver enzymes-alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were done. USG of the abdomen was done in both groups to diagnose the MASLD with Siui curvilinear probe of 3.5 megahertz by a single radiologist. The hepatic steatosis was classified using B-mode images as none, grade 1, grade 2, or grade 3. The presence of fatty liver was graded as: a) absent: when the the echotexture of liver was normal, b) grade 1: when there was slight and diffuse increase of liver echogenicity with normal visualization of the diaphragm and of the portal vein wall, c) grade 2: when there was moderate increase of liver echogenicity with slightly impaired appearance of the portal vein wall and the diaphragm, d) grade 3: when there was marked increase of liver echogenicity with poor or no visualization of portal vein wall, diaphragm, and posterior part of the right liver lobe.[11,12] The collected data were checked and reviewed, entered and analyzed in IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Data were analyzed by using descriptive statistics.

Results

Among the hypothyroidism group, 16 (57.14%) were subclinical hypothyroidism and 12 (42.85%) were overt hypothyroidism. The female to male ratio in hypothyroid and euthyroid groups were 3.6:1 and 1.5:1 respectively. The mean ages in hypothyroid and euthyroid groups were 41.93 and 39.79 years respectively. As obesity itself could lead to fatty liver disease, care was taken during randomization to include population with comparable BMI in both groups. Obesity was classified according to WHO classificaton of obesity for Asian population.[13] All baseline characteristics are highlighted in table 1.

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1. Baseline characteristics of study population

Parameter	Hypothyroid		S.D.	Range	Euthyroid		S.D.	Range
Mean Age(years)	41.07		14.86	20 - 72	39.71		12.48	20 - 79
Sex	Female N (%)	Male N(%)	----	----	Female N (%)	Male N (%)	----	----
	22(78.57)	6(21.43)			17(60.71)	11(39.29)		
Mean TSH (mIU/L)	25.31		33.40	4.203-150	2.34		0.87	0.72–3.98
Mean FT3 (pg/mL)	3.45		0.84	1.19–4.96	3.85		0.86	0.6 – 5.11
Mean FT4 (ng/dL)	1.02		0.81	0.08–4.44	1.19		0.24	0.87 – 1.98
Mean ALT (IU/L)	31.04		20.77	8 – 92	32.86		24.21	11 - 113
Mean LDL (mg/dL)	88.45		23.46	51.2 – 138	91.34		19.28	50.6 - 132
Mean TG (mg/dL)	162.86		62.50	61 - 310	135.71		59.32	45 - 279

BMI category (kg/m^2) [13]	Hypothyroid	Euthyroid	P-value
Normal (18.5-22.9)	8	4	0.83
Overweight(23-24.9)	2	6	
Obese 1(25-29.9)	14	17	
Obese 2(≥30)	4	1	

MASLD as determined by USG was present in 15 cases (53.6%) as compared to 7 controls (25%) and this was statistically significant (p-value 0.029). On comparing subclinical and overt hypothyroidism MASLD was seen in 10 cases (62.5%) of subclinical hypothyroidism compared to 5 cases in overt hypothyroidism (41.66%).

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Table 2: Chi-Square Test for MASLD Prevalence

Group	MASLD Present	MASLD Absent	Total Cases	P value
Hypothyroid group	15	13	28	0.029
Euthyroid group	7	21	28	

The grades of MASLD was compared among hypothyroid and euthyroid groups. Among the hypothyroid group grade 1 MASLD was seen among 11 (39.28%) patients as compared to 6 (21.43%) among euthyroid group. Grade 2 MASLD among hypothyroid group was seen in 4 patients (14.29%) as compared to 1 among euthyroid group (3.57%) which showed higher grade of MASLD was prevalent among hypothyroid patients as shown in figure 1.

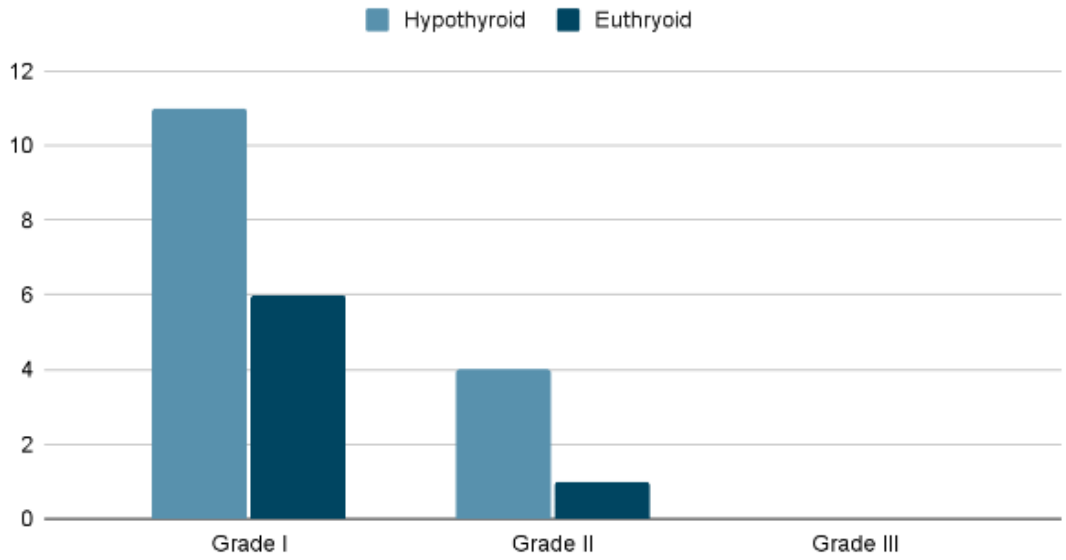

Figure 1: Bar diagram showing grades of MASLD among hypothyroid and euthyroid groups

TSH level was compared with presence or absence of MASLD in the hypothyroid group and no correlation was seen between increasing TSH and prevalence of MASLD. Similarly, comparison between fT4 levels and presence of MASLD was done among the hypothyroid groups and no correlation was seen between decreasing fT4 and prevalence of MASLD.

Discussion

Hypothyroidism is one of the common endocrine conditions and thyroid hormones play critical roles in cell metabolism and energy homeostasis.[14] MASLD is a chronic condition where there is accumulation of fat in the absence of excess alcohol consumption and there is insulin resistance and the genetic factors play key roles in the pathogenesis.[15] There were prior studies stating prevalence of hypothyroidism in MASLD to be ranging from 15.2% to 36.3% and hypothyroidism

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might be related to MASLD.[16] There have been a number of studies to find association between hypothyroidism and MASLD. Some studies suggested strong correlation between hypothyroidism and MASLD whereas others suggested no correlations so that the association remains in dispute.[17] The result of this cross-sectional study conducted at a tertiary care hospital showed MASLD was present in 53.6% of hypothyroid patient as compared to 25% in euthyroid patients. Among hypothyroid group 62.5% of subclinical hypothyroidism and 41.66% of overt hypothyroidism had MASLD. This is similar to the findings in the study conducted by Patel et al [18] where 59.15% of the untreated hypothyroid patients had USG proven fatty liver. Our study demonstrated that grade 2 MASLD was more common in hypothyroidism as compared to euthyroidism (14.29% vs 3.57%). This was in accordance with study conducted by Elshinshawy et al which was a cross-sectional study that included 60 patients with hypothyroidism and 30 controls where it was shown that patients with overt and subclinical hypothyroidism had significantly higher values of controlled attenuation parameter as compared to controls.[19] In a study conducted by Dalai et al [20] among 50 hypothyroid patients and 50 euthyroid patients where MASLD was evaluated using USG as imaging methodology it was seen that grade 1 MASLD was seen in 46% hypothyroid and 8% euthyroid samples (39.28% and 21.43.7% respectively in our study) and grade 2 MASLD was seen in 24% hypothyroid and 4% of euthyroid samples (14.29% and 3.57% respectively in our study). Our study was in agreement with the study of Dalai et al where higher grades of MASLD were associated with hypothyroidism. In a study done by Chung et al, it was seen that hypothyroidism was statistically significantly associated with MASLD and metabolic syndrome (30.2% vs. 19.5% and 23.1% vs. 14.6%, $p<0.001$). It also showed MASLD was statistically significantly associated with hypothyroidism and the grade of hypothyroidism.[21] In our study MASLD did not correlate according to the severity of hypothyroidism in terms of decreasing fT4 or rising TSH likely due to the fact that our study was not sufficiently powered due to small sample size as compared to the study by Chung et al (56 vs 4648). The study conducted by Tahara et al showed that TSH elevation was an independent risk factor for MASLD. There was significantly higher prevalence of MASLD in patients with subclinical hypothyroidism than in those with euthyroidism[22]. A systemic review and meta-analysis was conducted by Zeng et al in order to evaluate relationship between MASLD and hypothyroidism. The major take away from the study was hypothyroidism was positively associated with the risk of developing MASLD and fT4 was significantly associated with the risk of MASLD.[23]

For more clarity regarding the topic larger studies are required to see association between fT4 TSH and MASLD. The strength of our study is it is first of its kind in our population and has hypothyroid group and normal euthyroid group as comparator group. The limitations of this study are it is a single center study and has a relatively small sample size.

Conclusion:

Hypothyroidism is associated with MASLD and MASLD is more severe in patients with hypothyroidim. Further larger studies are required to assess relation fT4 and TSH.

Conflicts of interest: None

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