The Relation between Thyroid Dysfunction and Metabolic Dysfunction-Associated Fatty Liver Disease in Egyptian Patients

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Background and study aim: Metabolic-dysfunction Associated Fatty Liver Disease (MAFLD) is caused by multiple risk factors like obesity, hepatitis C virus infection, and diabetes mellitus. One of the most important risk factors that may be implicated in MAFLD is thyroid dysfunction due to its important effects on hepatic fatty acid and the synthesis of cholesterol. So, in this study, we aimed to assess the association between thyroid dysfunction and MAFLD in Egyptian patients.

Patients and Methods: This study was carried out on 100 patients who attended to Tanta Tropical Medicine outpatient clinic. They were older than 18 years fulfilling the criteria of MAFLD and thyroid functions were done for them .

Results: There were 67% cases of euthyroidism, 29% cases of subclinical hypothyroidism(SCH), and 4% cases of overt hypothyroidism. The number of females with subclinical hypothyroidism was 22(40%) but males were 7 (15.6%). Overt hypothyroidism was present in 4(7.3%) females, but in males was 0.

Conclusion: One of the most common endocrine abnormalities that may be present in MAFLD patients is thyroid dysfunction particularly subclinical hypothyroidism especially in females .

INTRODUCTION

One of the most common causes of chronic liver diseases worldwide is Metabolic dysfunction-associated fatty liver disease (MAFLD), which affects about 30% of adults **[1,2].** MAFLD means fatty infiltration of the liver (FLD) associated with metabolic dysfunctions.

Some studies reported that the complications of MAFLD made it one of the most common causes of liver transplantation **[3].**

MAFLD has complex risk factors such as obesity, hypertension, atherogenic dyslipidemia, Prothrombotic disorders, Pro-inflammatory conditions, and diabetes **[4].**

Dysfunctions of the thyroid gland have been implicated as one of the most important risk factors of MAFLD due to its important role in the hepatic synthesis of fatty acid and cholesterol **[5, 6].**

Maintaining liver metabolism needs thyroid function to be normal; while thyroid disorders may lead to liver disease progression **[7].**

All thyroid hormones give an image for the decrease of thyroid function, while a high TSH level more than the normal range usually means hypoactivity of the thyroid gland, as in subclinical hypothyroidism (SCH) **[8]**.

SCH means elevated plasma level of TSH while FT4 level is normal, with a prevalence of about 4–20% **[9].** A previous study reported that the patients suffering from SCH with fatty liver diseases (FLD) had metabolic abnormalities than those with SCH and a normal liver **[10].**

The studies that investigate the prevalence of thyroid dysfunction among patients with MAFLD are not sufficient **[9, 11, 12].**

So In this study, we tried to study the thyroid function in MAFLD patients and to assess the prevalence of thyroid dysfunction in patients with MAFLD in Egyptian patients.

PATIENTS AND METHODS

This cross-sectional study was carried out on 100 patients who attended to Tanta Tropical Medicine outpatient clinic, faculty of medicine. From October 2021 until October 2022.

This study included male or female patients more than 18 years old with MAFLD which is diagnosed when hepatic steatosis was present in addition to the presence of three or more of the following risk determinants: 1) increased waist circumference (>102 cm [>40 in] for men, >88 cm [>35 in] for women); 2) elevated triglycerides (≥150 mg/dl); 3) low HDL cholesterol (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (≥130/≥85 mmHg) or taking antihypertensive drug; and 5) impaired fasting glucose (≥110 mg/dl) or taking antidiabetic drug **[8]**.

We excluded patients who were aged < 18 years, taking medication that may affect thyroid functions or lipid levels, had alcoholic liver disease taking more than 40g of alcohol (or four units) per day, had viral hepatitis, Pregnant women, and who unwilling to participate in our study.

All the patients were subjected to; Personal history (name, age, sex, occupation, residence, and marital state) and anthropometric measures: weight, length, BMI, waist circumference, and complaint.

In addition to FreeT3, Free T4, TSH, Lipid profile (triglycerides, HDL, LDH, cholesterol level), Fasting Blood glucose level and or HBA1C, PCR for HCV for exclusion of viral hepatitis, liver enzymes, ultrasound on abdomen and pelvis for evaluation of liver condition and Fibroscan were done for all patients.

Fibroscan was used to assess the stages of fibrosis and steatosis using Dimensional ultrasound TE (transient elastography). Dimensional ultrasound TE (transient elastography) was used for staging liver fibrosis and steatosis by measuring the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver. This velocity has a direct relation to the stiffness of the tissue, called the elastic modules (expressed as E=3qv2, where v is the shear velocity and q is the density of the tissue, assumed to be constant). When the tissue is stiffer, the shear wave propagates faster.

The results are expressed in Kilopascals (KPa) and range from 1.5 to 75 KPa with 5 KPa as a normal value higher in men and in patients with low or high body mass index (BMI) (U-shaped distribution).

The CAP score (Controlled attenuation parameter) is measured in decibels per meter (dB/m) and ranges from 100-400 as follows, S0:<237.7, S1: 237.7- 259.4, S3(severe steatosis) :>292.3.

The liver stiffness is measured by the fibrosis score which is an indication of scarring. A fibrosis score F0 to F1 (2 to 7 kPa) means there is little or no scarring on the liver, while F2 (7.5 to 10 kPa) means moderate scarring that has spread outside the liver, while F3 (10 to 14 kPa) indicates severe scarring which has spread and disrupts normal blood flow, finally, F4 (14 kPa or higher) means late-stage scarring or cirrhosis, where the scarring is permanent and the damage is irreversible.

Statistical analysis:

The organization, tabulation, presentation, and analysis of data were performed by using SPSS IBM Chicago, version 23. Qualitative data was divided into categories and presented as frequency number and percentage, with the chi-square test used to determine the relationship between groups. Quantitative data was presented as mean ± SD and the relationship between groups was done by using an independent student t-test. The level of significance adopted was $p < 0.05$.

RESULTS

The study population consisted of 100 subjects including 45 men and 55 women. There were 50 patients with diabetes mellitus and 64 patients were hypertension, as demonstrated in table (1).

There were 67% cases of euthyroidism, 29% cases of subclinical hypothyroidism, and 4% cases of overt hypothyroidism. as demonstrated in table (2).

Subclinical hypothyroidism is defined as elevated TSH with free T4 concentrations at the lower end of the euthyroid range. In overt primary hypothyroidism, TSH levels are high and T4 and T3 levels are low.

The number of females with subclinical hypothyroidism was 22(40%) but the number of

males with subclinical hypothyroidism was 7 (15.6%). Overt hypothyroidism was present in 4(7.3%) female cases, with female predominance (p= 0.002), as demonstrated in Table (3).

Regarding steatosis grades, there were 62 patients in grade 1, 29 patients in grade 2, and 9 patients in grade 3. Regarding fibrosis stages, there were 5 patients in stage 0, 67 patients in stage 1, 26 patients in stage 3, and 2 patients in stage 4.

Mean and standard deviation of THS among studied group (4.4±1.9 uIU/mL) with normal reference range (0.3-6 uIU/mL), Mean and standard deviation of T3 among studied group (5.1±1.3 pg/ml) with normal reference range (3-7.8 pg/ml) Mean and standard deviation of T4 among studied group (16.5±3.2 ng/dl) with normal reference range (12-22 ng/dl), as demonstrated in table (4).

There was a significant difference in waist circumference, HDL, and triglyceride among different thyroid dysfunction groups. There was a difference in LDL and FBS, but not statistically significant, as demonstrated in table (5).

There was a significant positive correlation between TSH (waist circumference and TG), but there was a significant negative correlation between TSH and HDL. There was a significant negative correlation between T3 (waist circumference, TG, and HDL), There was a significant negative correlation between T4 (waist circumference, TG, and HDL), and regarding steatosis grade, there was a significant positive correlation between the grade of steatosis and the level of TSH, as demonstrated in table (6). However, there was no significant difference between the grade of steatosis and T3 and T4 levels.

Table (1): General characteristics of the studied patients.

Sociodemographic data	N%, mean±SD
Age	46±5.4
Sex:	
Male	45%
Female	55%
Hypertension:	
Yes	64%
No	36%
DM:	
Yes	50%
No	50%
Waist circumference(Cm)	108.9±13

DM: diabetes mellitus, **SD:** standard deviation

Table (2): Thyroid Status of the Study Population.

Group	Percentage (%)
Euthyroidism	67%
Subclinical hypothyroidism	29%
Overt hypothyroidism	4%

Table (3): Relation between gender and thyroid function groups.

Thyroid function	Female	Male	P =
Euthyroid	29(52.7%)	38(84.4%)	0.002*
Subclinical hypothyroidism	22(40%)	7(15.6%)	
Overt hypothyroidism	4(7.3%)	0(0%)	

p: p-value for comparing between the two studied groups
*: Statistically significant at $p \leq 0.05$, chi-square test

Table (4): Clinical data among the studied group.

Clinical Data	N (%), mean±SD
FBS (mg/dL)	125.4±22.1
HbA1C	5.9±0.8
TG(mg/dL)	192±19.8
LDL(mg/dL)	129.1±23.4
HDL(mg/dL)	37.6±5.7
Cholesterol(mg/dL)	201±24.8
ALT(IU/L)	40.9±14.7
AST(IU/L)	40.9±14.2
Steatosis grade:	
S1	62%
S2	29%
S3	9%
Fibrosis stage:	
F0	5%
F1	67%
F3	26%
F4	2%
TSH (uIU/mL)	4.4±1.9
Free T3 (pg/ml)	5.1±1.3
Free T4 (ng/dl)	16.5±3.2

ALT: alanine aminotransferase **AST**: aspartate transaminase**, HDL**: high-density lipoproteins**, LDL:** low-density Lipoproteins, **TG**: triglyceride, **FBS**: fasting blood sugar, **HbA1C**: hemoglobin A1C, **S**: steatosis, **TSH**: thyroid stimulating hormone, **Free T3**:Free triiodothyronine, **Free T4**: Free thyroxine
SD: standard deviation

Table (5): Components of metabolic syndrome among different thyroid dysfunction groups.

	Euthyroidism 67%	Subclinical hypothyroidism 29%	Overt hypothyroidism 4%	P=
Waist circumference(Cm)	104.5±11.4	117.3±11.7	122.3±10	0.0001*
Hypertension:				0.1
Yes	38(56.7%)	23(97.3%)	3(75%)	
No	29(43.3%)	6(20.7%)	1(25%)	
DM:				0.9
Yes	34(50.7%)	14(48.3%)	2(50%)	
No	33(49.3%)	15(51.7%)	2(50%)	
Triglyceride	188.2±21.7	199.2±13.3	202.6±6.7	0.02*
HDL	37.5±6.2	33.4±2.3	39.2±3.1	0.002*
LDL	131.6±25.2	123.9±19.8	125.5±10.4	0.3
FBS	125.1±22.4	125.5±22.6	130.3±16.9	0.9

DM: diabetes mellitus ***** Statistically significant at $p \leq 0.05$, chi-square test, F test

Table (6): Correlation between metabolic data and thyroid function tests.

Thyroid function	Waist circumference	TG	HDL	Steatosis grade
TSH	p=0.000*	p=0.009*	p=0.0001*	P=0.0001*
T3	p=0.000*	p=0.003*	p=0.03*	P=0.6
T4	p=0.000*	p=0.006*	p=0.04*	P=0.9

TSH: thyroid stimulating hormone , **Free T3** :Free triiodothyronine , **Free T4** : Free thyroxine
* Statistically significant at $p \leq 0.05$, **R test**

DISCUSSION

In 2020 the MAFLD is prepared to replace NAFLD definition. So, many studies have been made to find the associations between thyroid dysfunction and NAFLD, reporting that NAFLD patients are always characterized by low T4, FT4 levels, and high TSH levels **[13].**

The prevalence of thyroid dysfunction and hypothyroidism in metabolic syndrome patients is higher than the prevalence in the normal population, which is 5.9% for thyroid dysfunction and 4.6% for hypothyroidism (0.3% overt and 4.3% subclinical hypothyroidism) **[14,15]**.

Low-normal thyroid function was much more prevalent than SCH (21.70% vs. 4.16% in the general population and 21.97% vs. 4.22% in patients with MAFLD) **[16].**

Several possible mechanisms can explain the relationship between hypothyroidism and MAFLD such as insulin resistance, dyslipidemia, and obesity and they have important roles in the development of MAFLD, both insulin resistance and obesity are vital factors in the development of MAFLD, which are also common in hypothyroidism patients comparing with the general population, in our study thyroid dysfunction prevalence was 33% among MAFLD patients **[17].**

Metabolism has a sex dimorphism, which results in different disease risks for men and women, there are several studies including the general population reported that females had thyroid dysfunction more than males **[18]** this is in agreement with our result as the percentage of females with subclinical hypothyroidism were (40%) but males with subclinical hypothyroidism were (15.6%).

Thyroid hormones are recognized as catabolic hormones and they regulate various processes of metabolism, including the synthesis, mobilization, and breakdown of lipids. Hypothyroidism had been reported to be associated with an increased risk for dyslipidemia and atherosclerotic cardiovascular disease, in our study there was a significant negative correlation between T4 and TG and this was in agreement with Jang J, et al. that found a negative association between triglycerides and FT4 **[19]**.

Waist circumference was significantly different between patients with and without thyroid dysfunction this was in agreement with Khatiwada S, et al **[20].**

The positive association of TSH with TC and LDL-c may be due to autoimmune activation involving lipoprotein(a). In our study, HDL cholesterol had a significant negative association with TSH level and this was reported also by Khatiwada S, et al and Rajendra Kc et al **[20,21].**

The study done in India found that subclinical hypothyroidism had a significant association between the levels of TSH and cholesterol levels, triglycerides, LDL, and HDL across the metabolic syndrome group **[22]**.

In our study, there was a significant positive correlation between TSH and waist circumference, a significant positive correlation between TSH and TG, and a significant negative correlation between TSH and HDL. However, a study done in Turkey showed that TSH was not correlated with any metabolic syndrome parameters **[23].** However, the study done by Fan et al reported that patients suffering from thyroid hypofunction were more likely to be old age, females, and total cholesterol, low-density lipoprotein (LDL), and triglycerides were high in them **[16].**

Higher TSH levels can induce steatosis via TSH receptor (TSHR) signaling. TSH not only contributes to the negative feedback regulation of T4 secretion via TSHR in the thyroid gland but may also increase hepatic gluconeogenesis, decrease hepatic bile acid synthesis, and cause hypercholesterolemia by decreasing 3-hydroxy-3-methylglutaryl-CoAreductase phosphorylation,

In this study, we reported that the grades of steatosis in MAFLD patients were positively correlated with the level of TSH and this was the same results found by Chung et al and Xu et al, who reported that grades of fatty liver increased more in patients who had high TSH and this relationship was statistically significant ($p = 0.001$), this was reported by other studies that identified a positive association between NAFLD and TSH **[24,25].**

The studies done by Carulli et al. and Pagadala et al, suggested that the serum TSH concentration is correlated with the severity of hepatic steatosis **[26,27].**

On the other hand, Ittermann et al detected no consistent association between serum TSH concentrations and hepatic steatosis**[28].**

Other studies showed a highly significant relationship between serum TSH levels and increasing the grades of fatty liver **[29].**

This study had some limitations: firstly, fatty liver disease was diagnosed by ultrasound and fibroscan, secondly, the sample size in our study is relatively small and finally, the study population was from one hospital and cannot represent the general population. Therefore, findings need to be validated using more sophisticated techniques as liver biopsies and a more representative population.

CONCLUSION

In conclusion, keeping in mind that thyroid dysfunction particularly subclinical hypothyroidism is one of the most common endocrine abnormalities that may occur in MAFLD, especially in females .hence, thyroid function tests may be included as a routine investigation in all MAFLD patients, especially females.

Abbreviation
MAFLD: Metabolic-associated fatty liver diseases.
SCH: subclinical hypothyroidism.
NAFLD: non-alcoholic fatty liver disease.
DM : diabetes mellitus
ALT: alanine aminotransferase
AST :aspartate transaminase
HDL: high-density lipoproteins
LDL: low-density Lipoproteins
TG: triglyceride
FBS: fasting blood sugar
HbA1C: hemoglobin A1C,
S: steatosis
CAP: Controlled attenuation parameter
TSH: thyroid stimulating hormone
Free T3 :Free triiodothyronine
Free T4 : Free thyroxine
SD: standard deviation
Funding: None .

Conflict of interest: None.

Ethical consideration:

A written informed consent was signed by all patients and a code number for each patient was used, The study was approved by the Ethical Committee of the Faculty of Medicine Tanta University (approval code 34913/9/21)

HIGHLIGHTS

1- Dysfunction of the thyroid gland has been implicated as one of the most important risk factors of MAFLD due to its prominent role in hepatic fatty acid and cholesterol synthesis.

2- Normal thyroid function is needed for maintaining liver metabolism; while thyroid disorders may lead to liver disease progression.

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