

Association between the Thyroid Hormone Levels and Metabolic Associated Fatty Liver Disease in Type 2 Diabetes Mellitus Egyptian Patients

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Abbreviations:

MAFLD: Metabolic associated fatty liver disease;
T2DM: Type 2 Diabetes Mellitus;
MAS: Metabolic associated steatosis;
MASH: Metabolic associated steato-hepatitis;
DM: Diabetes Mellitus;
FT3: free triiodothyronine;
CP: C-peptide;
FLI: Fatty Liver-index;
CRP: C-reactive protein;
USCD: Transabdominal ultrasonography with color Doppler.

ABSTRACT

Background: Metabolic associated fatty liver disease (MAFLD) can significantly increase the prevalence of chronic complications in patients with T2DM.

Objectives: to analyse the association between the thyroid hormones and MAFLD in T2DM Egyptian patients.

Methods: This case control study was conducted on 180 T2DM patients with and without MAFLD who admitted to Department of Internal Medicine, and Endocrinology Unit, Faculty of Medicine, Menoufia University from December 2022 to October 2023. Patients were categorized into three groups to abdominal colour ultrasonography: Group I: Includes 60 patients T2DM patients without MAFLD. Group II: Includes 60 patients T2DM patients with MAFLD, according to MAFLD fibrosis score they further divided to: 30 patients as a group without progressive liver fibrosis, and 30 patients as a group with progressive liver fibrosis. Group III: Includes (60 healthy subjects) as a control group.

Results: FT3 and FT4 were significantly different among three groups ($p < 0.001$). FT3 and FT4 were significantly lower in group I and group II than group III ($p < 0.001$) and insignificantly different between group I and group II. TSH was significantly different among three groups ($p < 0.001$). TSH was significantly higher in group II than group I and group III ($p < 0.001$) and lower in Group I than group II ($p = 0.023$). Thyroid profile (FT3 and FT4) was significantly lower in group IIb than group IIa ($p < 0.001$) while TSH was significantly higher in group IIb than group IIa ($p < 0.001$).

Conclusions: The present study indicated that there is closely association between the abnormal thyroid hormone levels and liver fibrosis in T2DM patients, i.e., the prevalence of MAFLD increased following the decrease of FT3 and FT4 ratio and increase of TSH.

Key words: thyroid hormone levels, metabolic associated fatty liver disease, type 2 diabetes mellitus.

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INTRODUCTION

Metabolic associated fatty liver disease (MAFLD) is a clinical syndrome

characterized by hepatic steatosis resulting from excessive fat accumulation in the liver. Diagnosis relies on evidence of hepatic steatosis along with criteria such as overweight/obesity, type 2 diabetes mellitus, or metabolic disorders. The disease spectrum encompasses Metabolic associated steatosis (MAS), Metabolic associated steatohepatitis (MASH), liver fibrosis, and liver cancer (1).

A meta-analysis involving 35,599 patients with type 2 diabetes mellitus (T2DM) from six countries revealed a 59.67% prevalence of MAFLD (2). MAFLD substantially increases the risk of chronic complications in T2DM patients. Conversely, T2DM can promote the progression from MAFLD to MASH and facilitate the development of liver fibrosis (3).

Currently, liver biopsy serves as the "gold standard" for diagnosing MAFLD and progressive liver disease. However, due to its invasive nature, Angulo et al. (4) recommended using the MAFLD liver fibrosis score as an initial assessment, with an MFS > 0.676 indicative of progressive liver fibrosis. Nevertheless, MFS is seldom explored in T2DM patients, and existing studies often rely on color ultrasound, limited to identifying AFLD with liver fat content exceeding 30% (5).

Therefore, an alternative strategy is essential for the effective assessment of MAFLD in T2DM patients. Given the liver's pivotal role in cholesterol and triglyceride metabolism, thyroid hormones influence hepatic lipid homeostasis. Lower thyroid hormone levels can elevate blood lipids, increasing MAFLD prevalence (6).

Byrne et al. (7) emphasized hypothyroidism as a key factor in MAFLD occurrence, while Lee et al. (8) contradicted this correlation. Van den Berg et al. (9) found that MAFLD patients with normal thyroid function exhibited elevated free triiodothyronine (FT3) levels and low free thyroxine (FT4) levels.

The association between the thyroid hormones and metabolic associated fatty liver disease (MAFLD) in type 2 diabetes mellitus (T2DM) Egyptian patients is not clear yet.

The objective of this study is to analyze the association between the thyroid hormones and Metabolic associated fatty liver disease (MAFLD) in type 2 diabetes mellitus (T2DM) Egyptian patients.

PATIENTS AND METHODS

This case-control study involved 180 participants with type 2 diabetes mellitus (T2DM), both with and without metabolic associated fatty liver disease (MAFLD), admitted to the Department of Internal Medicine and Endocrinology Unit at the Faculty of

Medicine, Menoufia University, between December 2022 and October 2023. Approval from the Local Ethical Committee of Menoufia University was obtained, and written informed consent was acquired from all participants before their inclusion in the study.

Exclusion criteria encompassed excessive drinking, malignant tumors, pregnancy, acute complications of diabetes mellitus (DM), acute cardiovascular events, severe liver and kidney dysfunction, thyroid dysfunction, other acute or chronic liver diseases, and a history of receiving immune-modulating drugs. The eligible participants, meeting inclusion criteria, were categorized into three groups based on abdominal color ultrasonography:

- Group I: Comprising 60 T2DM patients without MAFLD.
- Group II: Encompassing 60 T2DM patients with MAFLD, further divided into:
 - Group IIa: 30 patients without progressive liver fibrosis.
 - Group IIb: 30 patients with progressive liver fibrosis.
- Group III: Consisting of 60 healthy subjects, serving as the control group.

All participants underwent comprehensive assessments, including detailed history-taking (Body Mass Index, DM duration, family history, and medication type), clinical examinations (Systolic Blood Pressure, Diastolic Blood Pressure, waistline, hipline, and waist-hip ratio), and laboratory investigations (Liver Function Test, HbA1C, Fasting Blood Glucose, Homeostatic Model Assessment of Insulin Resistance, lipid profile, and thyroid functions - FT3, TSH, and FT4). Radiological investigation involved hepatic ultrasound

MAFLD Score

MAFLD was identified in individuals who had FLD with the presence of any one of the following three conditions: overweight/obesity (body mass index [BMI] ≥ 25), type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation. Metabolic dysregulation was defined as the presence of at least two metabolic risk abnormalities (10):

- Central obesity (waist circumference $\geq 102/88$ cm in men and women).
- Hypertension (blood pressure $\geq 130/85$ mmHg or specific drug treatment).
- Triglyceride ≥ 150 mg/dl.
- HDL-cholesterol < 40 mg/dl for men and < 50 mg/dl for women.
- Prediabetes (fasting glucose levels = 100–125

mg/dl or hemoglobin A1c = 5.7%–6.4%).

- Insulin resistance (homeostasis model assessment of insulin resistance score ≥ 2.5).
- C-reactive protein (CRP) level > 2 mg/L.

BMI was calculated using the body weight (kg) and the square of the height (m^2). Waist to hip ratio was waistline (cm)/hipline (cm).

The value of modified homeostasis model assessment for insulin resistance (C-peptide) (CP).

Homa-IR (CP) was calculated by (fasting c-peptide) FCP instead of fasting insulin:

- Homa-IR (CP) = $1.5 + \text{FBG (mmol/L)} \times \text{FCP (pmol/L)} / 2800$.

Fatty Liver-index (FLI) was calculated according to the formula published by Bedogni.

- $\text{FLI} = (e^{0.953 \times \log_e(\text{triglycerides})} + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745) / (1 + e^{0.953 \times \log_e(\text{triglycerides})} + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745) \times 100$.

MAFLD liver fibrosis score (LFS) was calculated as:

- $\text{NFS} = (-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting glucose/presence of diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{PLT count (} \times 10^9/\text{L)} - 0.66 \times \text{ALB (g/dL)}) \times 99$.

Thyroid functions (FT3, TSH and FT4) were analyzed and association between the thyroid hormone levels and MAFLD was assessed.

Transabdominal ultrasonography with color doppler (USCD)

All patients underwent transabdominal USCD analysis for the assessment of morphological abnormalities, disease location, activity, and potential complications. Exams were performed with a Philips iU22 ultrasound system, using a linear (10–12 MHz) and convex (5–10 MHz) transducer. To avoid the potential effects of physical activity, body position, and meals, on hemodynamic status, all the assessments began after at least 15 minutes of rest, always in the supine position, and following 6 hours fasting.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the three groups utilizing ANOVA (F) test with post hoc test (Tukey) and compared between the two groups utilizing unpaired Student's t-test. Qualitative variables were presented as frequency and percentage

(%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed p value < 0.05 was considered statistically significant.

RESULTS

This study, 239 patients were assessed for eligibility, 33 patients did not meet the criteria and 26 patients refused to participate in the study. The remaining 180 patients were allocated into three equal groups (60 patients in each). All allocated patients were followed-up and analyzed statistically.

Age and Gender were insignificantly different among the three groups. BMI was significantly lower in group I than group II ($p < 0.001$) and higher in group II than group III ($p = 0.023$). Diabetes duration was highly significantly longer in group I than group II ($p < 0.001$).

Systolic blood pressure was significantly higher in Group II than group I and group III (p value = 0.020 and < 0.001 respectively). Diastolic blood pressure was significantly different among three groups ($p < 0.001$). Diastolic blood pressure was highly significantly lower in group II than group I and group III ($p < 0.001$) and insignificantly different between group I and III. Waistline was significantly different among three groups ($p < 0.001$). Waistline was significantly longer in group II than group I and group III ($p < 0.001$) and insignificantly different between group I and group III.

Hipline was significantly different among three groups ($p < 0.001$). Hipline was significantly longer in group I and group II than group III ($p < 0.001$) and insignificantly different between group I and group II.

Waist hip ratio was significantly different among three groups ($p < 0.001$). Waist/ hip ratio was significantly lower in group I than group II and group III ($p = 0.001$ and 0.014 respectively) and insignificantly different between group II and group III. PLT was significantly different among three groups ($p < 0.001$). PLT was significantly higher in group I than group II ($p < 0.001$) and lower in group I and group II than group III ($p < 0.001$). Albumin was significantly different among three groups ($p < 0.001$). Albumin was highly significantly lower in group II than group I and group III ($p < 0.001$) and insignificantly different between group I and group III. ALT was significantly different among three groups ($p < 0.001$). ALT was significantly higher in group II than I and group III ($p < 0.001$) and insignificantly different between group I and III.

AST was significantly different among three groups ($p < 0.001$). AST was significantly higher in group II than I and group III ($p < 0.001$) and insignificantly different between group I and III.

ALT/AST ratio was insignificantly different among three groups. GGT was significantly different among three groups ($p<0.001$). GGT was significantly higher in group II and group I than group III ($p<0.001$) and

insignificantly different between group I and II. AKP was significantly low normal in group II than group I and group III ($p<0.001$) and insignificantly different between group I and III (*table 1*).

Table 1 - Patient's demographic data and Clinical examination among the three groups

Variables		Group I	Group II (n = 60)	Group III (n = 60)	P value (n = 60)	Post Hoc
Age (years)	Mean± SD	65.9 ± 7.84	66.4 ± 6.31	63.4 ± 9.83		0.098
	Range	56 – 81	56 - 77	50 – 75		
Gender	Male	25(41.67%)	19(31.67%)	27 (45%)		0.298
	Female	35(58.33%)	41(68.33%)	33 (55%)		
BMI (< 25 kg/m ²)	Mean± SD	26 ± 4.4	28.1 ± 5.28	23 ± 2.95	<0.001*	P1<0.001* P2<0.001* P3= 0.023*
	Range	19.7 - 31.2	19.3 - 35.9	19.9 - 27.86		
Diabetes duration (years)	Mean± SD	13.5 ± 2.68	9.6 ± 3.73	---	<0.001*	
	Range	10 – 18	4 - 16			
Variables		Group I (n = 60)	Group II (n = 60)	Group III (n = 60)	P value	Post Hoc
Systolic blood pressure (≤ 130 mmHg)	Mean ±SD	139.1 ± 6.77	143.4 ± 7.35	134.8 ± 13.3	<0.001*	P1=0.037* P2= 0.044* P3<0.001*
	Range	127 – 148	132 - 156	36 – 140		
Diastolic blood pressure (≤ 85 mmHg)	Mean ± SD	88 ± 3.2	82.2 ± 5.66	89 ± 4.5	<0.001*	P1<0.001* P2= 0.455 P3<0.001*
	Range	81 – 92	71 - 90	83 – 96		
Waistline (102/88 cm)	Mean ± SD	85.6 ± 10.7	98 ± 13	82.8 ± 4.32	<0.001*	P1<0.001* P2=0.275 P3<0.001*
	Range	72 - 104.4	77.5 - 115	73 – 89		
Hipline (cm)	Mean ± SD	99.1 ± 3.39	101.7 ± 4.38	95.8 ± 11.23	<0.001*	P1= .129 P2=0.034* P3<0.001*
	Range	95 – 105	94 - 108	79 – 112		
Waist/ hip ratio	Mean ± SD	0.9 ± 0.12	1.2 ± 0.36	1.2 ± 0.13	<0.001*	P1<0.001* P2<0.001* P3 =.075
	Range	0.77 -1.15	0.62 - 1.69	0.91 - 1.35		
Variables		Group I (n = 60)	Group II (n = 60)	Group III (n = 60)	P value	Post Hoc
PLT (*109/L) Lab normal range (150 to 400)	Mean± SD	250.4 ± 59.73	141.3 ± 58.63	352.4 ± 39.71	<0.001*	P1<0.001* P2<0.001* P3<0.001*
	Range	156 -341	60 - 252	197 - 401		
Albumin (gm/dL) Lab normal range (3.4 to 5.4)	Mean± SD	4.4 ± 0.34	3.6 ± 0.68	4.5 ± 0.26	<0.001*	P1<0.001* P2=0.614 P3<0.001*
	Range	3.8 - 4.8	2.6 - 4.5	4.2 - 4.9		
ALT (U/L) Lab normal range (7 to 55)	Mean± SD	30.6 ± 4.08	77.6 ± 20.69	31.6 ± 5.05	<0.001*	P1<0.001* P2=0.900 P3<0.001*
	Range	25 – 39	55 - 107	28 – 42		
AST (U/L) Lab normal range (8 to 33)	Mean± SD	22 ± 2.07	71.7 ± 41.31	22.9 ± 3.11	<0.001*	P1<0.001* P2=0.976 P3<0.001*
	Range	19 – 27	31 - 145	18 – 28		
ALT/AST ratio	Mean± SD	1.4 ± 0.23	1.5 ± 0.87	1.4 ± 0.32	0. <0.668	
	Range	0.93 - 1.86	0.46 - 3.35	1.04 - 2.1		
GGT (U/L) Lab normal Range (5 to 40)	Mean± SD	31.3 ± 8.66	29.5 ± 6.1	21.1 ± 7.49	<0.001*	P1=0.362 P2<0.001* P3<0.001*
	Range	22 – 45	21 - 39	12 – 37		
AKP (U/L) Lab normal Range (44 to 147)	Mean ± SD	107.7 ± 10.64	97.6 ± 12.82	106.4 ± 9.72	<0.001*	P1=0.001* P2=0.817 P3<0.001*
	Range	88 - 124	80 - 118	89 – 123		

* Significant as p value <0.05, P1: P value between groups I and II, P2: P value between groups I and III, P3: P value between groups II and III. Group I =Diabetic without MAFLD, Group II = Diabetic with MAFLD Group III=Control group, ALT Alanine aminotransferase, AST Aspartic acidaminotransferase, GGT Glutamytransferase, AKP Alkaline phosphatase, Group I =Diabetic without MAFLD, Group II = Diabetic with MAFLD, Group III=Control group.

TG was significantly different among three groups ($p<0.001$). TG was significantly higher in group II than group I and group III ($p<0.001$) and insignificantly different between group I than group III. HDL was significantly different among three groups ($p<0.001$). HDL was significantly lower in group II than group I and group III ($p<0.001$). LDL was significantly different among the three groups ($p=0.035$). LDL was significantly higher in group II than group III (p value= 0.03) and insignificantly different between group I and (group II and group III). TC was insignificantly different among the three groups.

FBG was significantly different among three groups ($p<0.001$). FBG was significantly lower in group III than group I and group II ($p<0.001$) and insignificantly different between group I and group II.

HBA1C was significantly different among three groups ($p<0.001$). HBA1C was significantly higher in

group I and group II than group III ($p<0.001$) and insignificantly different between group I and group II.

FCP was significantly different among three groups ($p<0.001$). FCP was significantly higher in group II than group I ($p<0.001$) and higher in group I and group II than group III ($p=0.005$ and <0.001 respectively).

HOMA-IR (CP) was significantly different among three groups ($p<0.001$). HOMA-IR (CP) was significantly higher in group II than group I and group III and significantly higher in group I than group III.

FT3 and FT4 were significantly different among three groups ($p<0.001$). FT3 and FT4 were significantly lower in group I and group II than group III ($p<0.001$) and insignificantly different between group I and group II (table 2).

FLI was significantly different between three groups ($p<0.001$). FLI was significantly higher in group II than group I and group III ($p<0.001$) and

Table 2 - Lipid profile, Blood glucose profile and Thyroid profile among the three groups

	Lab normal range		Group I (n = 60)	Group II (n = 60)	Group III (n = 60)	P value	Post Hoc
TG (mg/dl)	Below 150 mg/dL	Mean $\pm$ SD	99.4 $\pm$ 40.19	146.8 $\pm$ 56.38	110.7 $\pm$ 26.89	<0.001*	P1<0.001*
		Range	70 - 173.63	72.9 - 246.6	86.37 - 180.25		P2=0.389 P3<0.001*
TC (mg/dL)	125 to 200mg/dL	Mean $\pm$ SD	173.4 $\pm$ 49.88	180.8 $\pm$ 44.32	170.8 $\pm$ 42.62	0.463	
		Range	109 - 249	89 - 246	129 - 251		
HDL (mg/dL)	35 to 65 mg/dL	Mean $\pm$ SD	62.4 $\pm$ 2.3	49.5 $\pm$ 7.12	67.2 $\pm$ 2.16	<0.001*	P1<0.001*
		Range	58 - 66	40 - 65	62 - 70		P2<0.001* P3<0.001*
LDL (mg/dL)	Less than 100 mg/dl	Mean $\pm$ SD	119.7 $\pm$ 20.17	122.1 $\pm$ 13.41	114.8 $\pm$ 12.38	0.035*	P1=0.684
		Range	96 - 153	107 - 139	104 - 138		P2=0.198 P3=0.03*
FBG (mg/dL)	70-100 mg/dl	Mean $\pm$ SD	175.7 $\pm$ 19.65	180.2 $\pm$ 13.94	119.6 $\pm$ 21.08	<0.001*	P1<0.001*
		Range	146.48 - 210.92	157.72 - 197.5	93.4 - 158.4		P2=0.387 P3<0.001*
HBA1C (%)	4-5.6%	Mean $\pm$ SD	11.2 $\pm$ 1.15	9.2 $\pm$ 0.7	6.4 $\pm$ 0.79	<0.001*	P1=0.310
		Range	8.65 - 12.5	7.99 - 10.2	5.3 - 7.5		P2<0.001* P3<0.001*
FCP (Pmol/L)	174-660.9 pmol/L	Mean $\pm$ SD	870.9 $\pm$ 178.77	716.5 $\pm$ 149.3	631.6 $\pm$ 101.06	<0.001*	P1<0.001*
		Range	613 - 1136.33	526.67 - 953.33	517.33 - 767.33		P2=0.005 P3<0.001*
HOMA- IR (CP)	less than 1	Mean $\pm$ SD	5.3 $\pm$ 1.25	4.6 $\pm$ 0.62	2.6 $\pm$ 0.45	<0.001*	P1<0.001*
		Range	3.41 - 6.74	4.06 - 5.67	2 - 3.28		P2=0.480 P3<0.001*
FT3 (ng/dL)	60 to 180 ng/dL	Mean $\pm$ SD	60 $\pm$ 25	66 $\pm$ 21	71 $\pm$ 21	<0.001*	P1=0.680
		Range	35 - 86.6	40 - 89	50 - 95.3		P2<0.001* P3<0.001*
FT4 (ng/dL)	0.8 to 1.8 ng/dL	Mean $\pm$ SD	1.1 $\pm$ 0.6	1 $\pm$ 0.6	1.3 $\pm$ 0.6	<0.001*	P1=0.746
		Range	0.52 - 1.7	0.4 - 1.65	0.7 - 1.95		P2<0.001* P3<0.001*

Table 2 - Cont'd

	Lab normal range		Group I (n = 60)	Group II (n = 60)	Group III (n = 60)	P value	Post Hoc
TSH (uIU/L)	0.27 to 4.2 uIU/L	Mean $\pm$ SD	4.1 $\pm$ 1.29	5.1 $\pm$ 1.76	3.8 $\pm$ 1.33	<0.001*	P1<0.001* P2=0.023* P3<0.001*
		Range	2.5 – 6	2.57 - 7.8	2 - 6		

* Significant p value <0.05, P1: P value between groups I and II, P2: P value between groups I and III, P3: P groups II and III. TG: Triglyceride, TC: Total cholesterol, HDL High density lipoprotein, LDL Low density lipoprotein. FBG Fasting blood glucose. Homa-IR (CP) Homa-Insulin resistance (C- peptide), FCP: Fasting C-peptide, HbA1c Glycosylated hemoglobin. FT3 Free triiodothyronine, FT4 Free thyroxine. TSH Thyroid stimulating hormone Group I =Diabetic without MAFLD, Group II = Diabetic with MAFLD Group III=Control group

insignificantly different between group I and group III. MFS was significantly different between three groups ($p<0.001$). MFS was significantly higher in group II than group I and group III ($p<0.001$) and was significantly higher in group I than group III ($p<0.001$) (table 3).

There was a positive correlation between NAFLD fibrosis score and TSH ($r=0.459$ and p value < 0.001) (table 4).

TSH can significantly predict MAFLD ($p = 0.001$ and $AUC = 0.633$) at cut-off >2.6 uIU/L with 73.33% sensitivity, 41.67% specificity, 71.54% PPV and 43.86% NPV (table 5).

Group II: Includes 60 patients T2DM patients with

MAFLD, according to MAFLD Fibrosis score were divided to: 30 patients as a Group without progressive liver fibrosis.

Age was highly significantly and diabetes duration higher in group IIb than group IIa ($p<0.001$). BMI was highly significantly lower in group IIb than group IIa ($p<0.001$). Gender was insignificantly different between both groups. Systolic blood pressure (mmHg) was insignificantly different between both groups. Diastolic blood pressure (mmHg) was highly significantly lower in group IIb than group IIa ($p<0.001$). Waistline and hipline were highly significantly longer in in group IIb than group IIa ($p<0.001$). Waist/ hip ratio was significantly

Table 3 - Fatty Liver Indicator (FLI) and MAFLD fibrosis score (MFS) of the three groups

		Group I (n = 60)	Group II (n = 60)	Group III (n = 60)	P value	Post Hoc
FLI	Mean $\pm$ SD	13.2 $\pm$ 9.49	37.3 $\pm$ 16.95	11.3 $\pm$ 4.05	<0.001*	P1<0.001* P2=0.638
	Range	5.61 - 38.21	11.7 - 62.24	7.4 - 23.74		P3<0.001*
MFS	Mean $\pm$ SD	-1.2 $\pm$ 0.81	2.6 $\pm$ 1.1	-2 $\pm$ 0.77	<0.001*	P1<0.001* P2<0.001*
	Range	-2.29 - 0.11	1.3 - 4.71	-3.32 - 0.48		P3<0.001*

* Significant as p value <0.05, P1: P value between groups I and II, P2: P value between groups I and III, P3: P value between groups II and III Group I =Diabetic without MAFLD, Group II = Diabetic with MAFLD Group III=Control group

Table 4 - Correlation between MAFLD fibrosis score (MFS) and TSH of the three groups

NAFLD fibrosis score (NFS)		
TSH (uIU/L)	R	0.483
	P value	< 0.001*

Significant as p value <0.05, TSH: Thyroid stimulating hormone, r: Pearson coefficient

Table 5 - Role of TSH in prediction MAFLD of the three groups

Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P value
2.6 (uIU/L)	73.33%	41.67%	71.54%	43.86%	0.633	0.001*

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

higher in group IIb than group IIa ($p<0.001$). Platelet count was highly significantly lower in group IIb than group IIa ($p<0.001$). Albumin was significantly lower in group IIb than group IIa ($p<0.001$). ALT was highly significantly higher in group IIb than group IIa ($p<0.001$). AST was highly significantly higher in group IIb than group IIa ($p<0.001$). ALT/AST ratio was significantly lower in group IIb than group IIa ($p<0.001$). GGT was significantly lower in group IIb than group IIa ($p<0.001$).

TG was significantly lower in group IIb than group IIa ($p<0.001$). TC was insignificantly different between both groups. HDL and LDL were significantly higher in group IIb than group IIa ($p<0.001$).

AKP was insignificantly different between both groups. Blood glucose profile [FBG, HbA1C and HOMA-IR (CP)] were significantly lower in group IIb than group IIa ($p<0.001$). FCP was insignificantly different between both groups (*table 6*).

Thyroid profile (FT3 and FT4) was significantly lower

Table 6 - Patient's demographic data, Clinical examination Laboratory investigation, Lipid profile and Blood glucose profile between both groups

		Group IIa (n=30)	Group IIb (n=30)	P value
Age (years)	Mean $\pm$ SD	62.63 $\pm$ 5.88	70.2 $\pm$ 4.11	<0.001*
	Range	56 – 70	66 – 77	
Gender	Male	11 (36.67%)	8 (26.67%)	0.405
	Female	19 (63.33%)	22 (73.33%)	
BMI (kg/m ²)	Mean $\pm$ SD	32.09 $\pm$ 3.96	24.08 $\pm$ 2.79	<0.001*
	Range	24.5 – 35.9	19.3 – 28.2	
Diabetes duration (years)	Mean $\pm$ SD	7.07 $\pm$ 2.23	12.07 $\pm$ 3.24	<0.001*
	Range	4 – 10	6 – 16	
Systolic blood pressure (mmHg)	Mean $\pm$ SD	142.63 $\pm$ 4.8	144.17 $\pm$ 9.26	0.424
	Range	133 – 148	132 – 156	
Diastolic blood pressure (mmHg)	Mean $\pm$ SD	85.87 $\pm$ 3.09	78.43 $\pm$ 5.2	<0.001*
	Range	81 – 90	71 – 85	
Waistline (cm)	Mean $\pm$ SD	87.58 $\pm$ 5.13	108.43 $\pm$ 9.63	<0.001*
	Range	77.5 – 94	85 – 115	
Hipline (cm)	Mean $\pm$ SD	98.3 $\pm$ 3.59	105.1 $\pm$ 1.49	<0.001*
	Range	94 – 106	103 – 108	
Waist/ hip ratio	Mean $\pm$ SD	0.92 $\pm$ 0.02	1.58 $\pm$ 0.19	<0.001*
	Range	0.89 – 0.99	0.62 – 1.69	
PLT (*109/L)	Mean $\pm$ SD	193.37 $\pm$ 31.57	89.27 $\pm$ 19.77	<0.001*
	Range	153 – 252	60 – 113	
Albumin (gm/dL)	Mean $\pm$ SD	4.28 $\pm$ 0.18	3.01 $\pm$ 0.26	<0.001*
	Range	4 – 4.5	2.6 – 3.5	
ALT (U/L)	Mean $\pm$ SD	39.6 $\pm$ 6.58	77.13 $\pm$ 20.86	<0.001*
	Range	25 – 49	55 – 106	
AST (U/L)	Mean $\pm$ SD	34.77 $\pm$ 3.3	108.53 $\pm$ 25.44	<0.001*
	Range	31 – 44	84 – 145	
ALT/AST ratio	Mean $\pm$ SD	1.14 $\pm$ 0.18	0.73 $\pm$ 0.2	<0.001*
	Range	0.76 – 1.36	0.45 – 1.14	
GGT (U/L)	Mean $\pm$ SD	33.97 $\pm$ 5.08	24.97 $\pm$ 2.86	<0.001*
	Range	27 – 39	21 – 32	
AKP (U/L)	Mean $\pm$ SD	100.3 $\pm$ 8.83	94.83 $\pm$ 15.51	0.099
	Range	88 – 111	80 – 118	
TG (mg-dl)	Mean $\pm$ SD	183.36 $\pm$ 52.21	110.18 $\pm$ 31.15	<0.001*
	Range	114.6 – 246.6	72.9 – 158.8	
TC (mg/dL)	Mean $\pm$ SD	184.67 $\pm$ 46.27	178.9 $\pm$ 42.87	0.618
	Range	115 – 247	90 – 225	
HDL (mg/dL)	Mean $\pm$ SD	44.2 $\pm$ 4.63	54.7 $\pm$ 4.96	<0.001*
	Range	40 – 51	50 – 65	
LDL (mg/dL)	Mean $\pm$ SD	109.03 $\pm$ 2.11	135.13 $\pm$ 3.05	<0.001*
	Range	107 – 114	126 – 139	

Table 6 - (Cont'd)

		Group IIa (n=30)	Group IIb (n=30)	P value
FBG (mg/dL)	Mean $\pm$ SD	169.12 $\pm$ 21.58	150.04 $\pm$ 15.82	<0.001*
	Range	139 - 198.4	123.4 - 166.6	
HbA1C (%)	Mean $\pm$ SD	9.38 $\pm$ 0.74	8.49 $\pm$ 0.57	<0.001*
	Range	7.4 - 10	7.32 - 9.09	
FCP (Pmol/L)	Mean $\pm$ SD	891.67 $\pm$ 14.55	850.11 $\pm$ 225.85	0.372
	Range	680.67 - 1057.33	613 - 1136.33	
HOMA- IR (CP)	Mean $\pm$ SD	6.48 $\pm$ 0.32	4.16 $\pm$ 0.54	<0.001*
	Range	5.68 - 6.74	3.41 - 4.93	

*: significant as p value <0.05. Group IIa = Diabetic with MAFLD without progressive fibrotic liver Group IIb= Diabetic with MAFLD with progressive fibrotic liver, ALT Alanine aminotransferase, AST Aspartic acidaminotransferase, GGT Glutamyltransferase, AKP Alkaline phosphatase, TG: Triglyceride, TC: Total cholesterol, HDL High density lipoprotein, LDL Low density lipoprotein. HDL High density lipoprotein. LDL Low density lipoprotein, FBG Fasting blood glucose. Homa-IR (CP) Homa-Insulin resistance(C-peptide), FCP Fasting C-peptide, HbA1c Glycosylatedhemoglobin.

in group IIb than group IIa ($p < 0.001$) while TSH was significantly higher in group IIb than group IIa ($p < 0.001$) (table 7).

FLI was insignificantly different between both groups. NFS was significantly higher in group IIb than group IIa ($p < 0.001$) (table 8).

DISCUSSION

Our study reveals a significant decrease in thyroid hormones, specifically FT3 and FT4, in both Group I and Group II compared to Group III. TSH levels were significantly higher in Group II than in Group I and

Table 7 - Thyroid profile between both groups

		Group IIa (n=30)	Group IIb (n=30)	P value
FT3 (ng/dL)	Mean $\pm$ SD	65 $\pm$ 25	55 $\pm$ 22	<0.001*
	Range	39 - 91	32 - 81.6	
FT4 (ng/dL)	Mean $\pm$ SD	0.89 $\pm$ 0.3	0.81 $\pm$ 0.3	<0.001*
	Range	0.5 - 1.3	0.5 - 1.15	
TSH (uIU/L)	Mean $\pm$ SD	4.15 $\pm$ 1.48	6.02 $\pm$ 1.53	<0.001*
	Range	2.57 - 6.58	3.68 - 7.8	

*Significant as p value <0.05. FT3 Free triiodothyronine, FT4 Free thyroxine. TSH Thyroid stimulating hormone. Group IIa = Diabetic with MAFLD without progressive fibrotic liver Group IIb= Diabetic with MAFLD with progressive fibrotic liver

Table 8 - Fatty Liver Indicator (FLI) between both groups

		Group IIa (n=30)	Group IIb (n=30)	P value
FT3 (ng/dL)	Mean $\pm$ SD	65 $\pm$ 25	55 $\pm$ 22	<0.001*
	Range	39 - 91	32 - 81.6	
FLI	Mean $\pm$ SD	33.46 $\pm$ 13.82	41.12 $\pm$ 19.06	0.080
	Range	11.7 - 48.21	15.65 - 62.24	
MFS	Mean $\pm$ SD	1.64 $\pm$ 0.18	3.64 $\pm$ 0.63	<0.001*
	Range	1.3 - 1.79	2.81 - 4.71	

*Significant as p value <0.05. MFS Metabolic fatty liver disease fibrosis score. Group IIa = Diabetic with MAFLD without progressive fibrotic liver, Group IIb= Diabetic with MAFLD with progressive fibrotic liver

Group III, and lower in Group I compared to Group II. Furthermore, TSH exhibited significant differences among the three groups, with a notably higher level in Group II compared to Group I.

In terms of the thyroid profile, FT3 and FT4 were significantly lower in Group IIb compared to Group IIa, while TSH was significantly higher in Group IIb than in Group IIa.

Our findings are partially consistent with Zhang et al., (13), who observed that FT3 levels were higher in the MAFLD group compared to the non-MAFLD group, while FT4 levels were lower. Their results, after adjusting for factors such as diabetes duration, BMI, systolic pressure, triglycerides (TG), and high-density lipoprotein (HDL), indicated a significant increasing trend in MAFLD risk with elevated FT3 levels and a decreasing trend with rising FT4 levels. ROC curve analysis suggested the potential use of FT3 and FT4 as serological reference indices for predicting MAFLD risk.

Conversely, Huang et al., (15), reported statistically higher FT3 levels in T2DM patients with MAFLD compared to those without MAFLD. Additionally, several studies emphasized that the fluctuation of thyroid hormone levels within the normal range significantly correlates with the risk of MAFLD (9,16). The discrepancies between these studies might be attributed to the influence of different ethnicities, potentially reflecting variations in the genetic makeup of participants.

Bril et al., (17), conducted a study on 232 T2DM patients with normal thyroid function, demonstrating that reduced FT4 levels were linked to elevated triglyceride levels, thereby increasing the risk of MAFLD. This aligns with our current findings, indicating a noticeable increase in MAFLD incidence with decreasing FT4 levels.

It is widely recognized that hypothyroidism is correlated with an elevated MAFLD risk (18). The direct mechanism linking thyroid dysfunction to MAFLD is associated with the impact of thyroid hormones on hepatic lipid metabolism. Correcting hypothyroidism through levothyroxine replacement therapy has been shown to decrease MAFLD prevalence and improve outcomes (18).

Gu et al., (19), reported that high-normal FT3 levels were independently linked to a higher incidence of MAFLD in middle-aged and older euthyroid subjects. A sizable cross-sectional study in euthyroid individuals demonstrated a positive correlation between FT3 levels and the risk of MAFLD (20). Additionally, in euthyroid overweight/obese adults, increased FT3 levels were independently associated with a higher risk of hepatic

steatosis (13). A meta-analysis involving 44,140 individuals suggested that hypothyroidism was independently associated with an increased risk of MAFLD, irrespective of age, sex, BMI, and other known risk factors (21).

In 2012, a Korean study revealed a statistically significant association between MAFLD and hypothyroidism, even in a dose-dependent manner, independent of metabolic syndrome risk factors (22). Zhang et al., (23), found that higher normal TSH levels were linked to an increased risk of MAFLD. Huang et al., (15), also reported statistically higher TSH levels in T2DM patients with MAFLD compared to those without MAFLD. Liu et al., (20), demonstrated that TSH levels (OR = 1.108) were independently associated with the risk of MAFLD diagnosed by ultrasound.

A 2014 Chinese study analyzed the prevalence of MAFLD in euthyroid subjects and identified a positive association between TSH levels, even within the reference range, and MAFLD, independent of known metabolic risk factors assessed through multiple logistic regression (24). Furthermore, Zhang et al., (25), reported that when diagnosing fatty liver using abdominal color Doppler ultrasound, TSH levels in the MAFLD group showed no difference from the non-MAFLD group.

The clinical correlation between thyroid hormones and liver fibrosis has been substantiated by previous studies (16, 26). In a study by Liu et al., (27), which examined 1773 health evaluations, the independent association between FT3 levels and the risk of hepatic fibrosis among individuals with MAFLD was discussed, using a BARD score of ≥ 2 for liver fibrosis assessment. Kim et al., (28), similarly identified hypothyroidism as an independent predictor of progressive hepatic fibrosis. Notably, biopsy-confirmed fibrosis in MAFLD exhibited a strong association with elevated TSH levels in a dose-dependent manner, even within the normal thyroid reference range.

Studies have indicated that low FT3 levels are linked to advanced fibrosis in patients with T2DM (29) and those at high risk of nonalcoholic steatohepatitis (NASH) (30). However, it's important to note that these studies did not exclude patients with thyroid dysfunction, potentially contributing to variations in their conclusions. Another study based on an euthyroid population found a significant association between low-normal serum FT4 levels and advanced liver fibrosis in individuals with MAFLD (31).

The pathological mechanism of T2DM complicated by MAFLD may involve not only insulin resistance but also a manifestation resembling thyroid hormone resistance, specifically hypothyroidism.

This study aims to analyze the connection between thyroid hormones and Metabolic Associated Fatty Liver Disease (MAFLD) in Egyptian patients with type 2 diabetes mellitus (T2DM). Over the past two decades, the prevalence of MAFLD has markedly increased, underscoring the critical need for understanding this disease. Given the growing concerns about hypothyroidism-induced MAFLD and the necessity for effective management, a comprehensive grasp of the pathophysiology is crucial. Thyroid hormones play a pivotal role in the thyroid-liver axis and lipid metabolism. Disruptions in lipid metabolism can lead to the accumulation of lipids, triggering an inflammatory response in the liver and culminating in MAFLD. Although there is currently no FDA-approved treatment for hypothyroidism-induced MAFLD, ongoing developments in this field highlight the importance of understanding the disease's pathophysiology for accurate treatment.

Summary of our study

Comparisons within Groups:

- Diastolic blood pressure exhibited significant differences among the three groups, being higher in Group II than Group I and Group III ($p<0.001$), with no significant difference between Group I and Group III. Waistline was significantly longer in Group II than in Group I and Group III ($p<0.001$), and insignificantly different between Group I and Group III.
- Hipline was significantly longer in Group I and Group II than in Group III ($p<0.001$), with no significant difference between Group I and Group II. Waist/hip ratio was significantly lower in Group I than in Group II and Group III ($p=0.001$ and 0.014 , respectively), and insignificantly different between Group II and Group III.
- ALT was significantly higher in Group II than in Group I and Group III ($p<0.001$), with no significant difference between Group I and Group III.
- AST was significantly different among the three groups ($p<0.001$), being higher in Group II than in Group I and Group III ($p<0.001$), and insignificantly different between Group I and Group III.
- ALT/AST ratio and GGT were insignificantly different among the three groups. HDL was significantly lower in Group II than in Group I and Group III ($p<0.001$), and higher in Group I than in Group II (p value <0.001).
- FBG was significantly different among the three groups ($p<0.001$), being lower in Group III than in Group I and Group II ($p<0.001$), and insignificantly different between Group I and Group II.
- HbA1C was significantly different among the three groups ($p<0.001$), being higher in Group I and Group II than in Group III ($p<0.001$), and insignificantly different between Group I and Group II.
- FCP, HOMA-IR (CP), FT3, and FT4 were significantly different among the three groups ($p<0.001$). FCP was higher in Group II than in Group I ($p<0.001$) and higher in Group I and Group II than in Group III ($p=0.005$ and <0.001 , respectively). HOMA-IR (CP) was higher in Group II than in Group I and Group III, and higher in Group I than in Group III.
- FT3 and FT4 were significantly lower in Group I and Group II than in Group III ($p<0.001$), and insignificantly different between Group I and Group II. TSH was significantly higher in Group II than in Group I and Group III ($p<0.001$), and lower in Group I than in Group II ($p=0.023$).
- FLI was significantly higher in Group II than in Group I and Group III ($p<0.001$ and <0.001 , respectively), and insignificantly different between Group I and Group III.

Comparisons within subgroups:

- In the subanalysis, age and diabetes duration were significantly higher in Group IIb than in Group IIa ($p=0.041$ and 0.048 , respectively), while BMI was significantly lower in Group IIb than in Group IIa ($p=0.017$). Sex was insignificantly different between both groups.
- Diastolic blood pressure was significantly lower in Group IIb than in Group IIa ($p=0.042$). Waistline and hipline were significantly longer in Group IIb than in Group IIa ($p=0.005$ and 0.023 , respectively). Waist/hip ratio was significantly higher in Group IIb than in Group IIa ($p=0.03$).
- ALT and ALT/AST ratio were significantly higher in Group IIb than in Group IIa ($p=0.002$ and 0.003 , respectively).
- LDL was significantly higher in Group IIb than in Group IIa ($p<0.001$).
- Blood glucose profile (FBG, HbA1C, FCB, and HOMA-IR (CP)) was insignificantly different between both groups.
- Thyroid profile FT3 and FT4 were significantly lower in Group IIb than in Group IIa ($p=0.047$ and 0.034 , respectively), while TSH was significantly higher in Group IIb than in Group IIa ($p=0.041$).

Comparison with previous studies:

- The findings align with Zhang et al., 2022 (13), and Huang et al., 2020 (14), who reported

significant differences in diastolic blood pressure, waistline, hipline, and waist-to-hip ratio between T2DM patients with and without MAFLD.

- In agreement with Zhang et al., 2022 (13), HDL was significantly lower in T2DM with MAFLD compared to those without MAFLD.
- Discrepancies between studies regarding HDL, FBG, HbA1c, and HOMA-IR might be attributed to unmeasured confounding factors and the present study's relatively small sample size.

Recommendations and limitations:

- Further research is recommended to validate these results and explore novel solutions, addressing limitations such as sample size and variations in criteria for thyroid function and MAFLD diagnosis.
- The study limitations include a relatively small sample size, differences in the definition of normal thyroid function, and discrepancies in MAFLD diagnosis criteria, impacting the consistency of conclusions. The retrospective and single-centre design limits establishing definite cause-and-effect relationships between thyroid characteristics and MAFLD. Multiple studies are warranted to substantiate these findings.

CONCLUSION

Our study underscores significant associations between thyroid hormones, metabolic parameters, and the presence and progression of Metabolic Associated Fatty Liver Disease (MAFLD) in Type 2 Diabetes Mellitus (T2DM) Egyptian patients. The observed thyroid profile alterations and metabolic dysregulations, particularly in Group II with progressive liver fibrosis, suggest a potential link between thyroid dysfunction and the development of MAFLD in T2DM. These findings emphasize the need for further research to elucidate the complex interplay between thyroid function and MAFLD, offering insights for more effective management strategies in this high-risk population.

Conflicts of interest and source of funding

No conflicts of interest and no funds.

Ethical approval

Approval from the Local Ethical Committee of Menoufia University was obtained, and written

informed consent was acquired from all participants before their inclusion in the study.

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