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The Interrelation Between Hypothyroidism and Non-alcoholic Fatty Liver Disease, a Cross-sectional Study

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Background: **Thyroid hormones play an important role in the regulation of diverse metabolic processes and might play a crucial role in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). However, their association remains controversial. Therefore, our aim is to clarify whether overt or subclinical hypothyroidism was associated with NAFLD.** ***Methods:*** **This cross-sectional study included 60 participants with a new diagnosis of hypothyroidism and 30 age- and gender-matched healthy participants with thyroid-stimulating hormone (TSH) level <4.5 mIU/L. Anthropometric measurements, laboratory parameters, plasma fibroblast growth factor 21 (FGF21), and hepatic steatosis diagnosed via controlled attenuation parameter (CAP) using transient elastography between the hypothyroid groups and control group were analyzed.** ***Results:*** **Participants with hypothyroidism displayed significantly higher serum aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, total cholestrol, triglycerides, low-density lipoprotein cholesterol, TSH, hemoglobin A1c, fasting insulin, and homeostatic model assessment of insulin resistance (HOMA-IR) but significantly lower serum albumin, high-density lipoprotein cholesterol, and free thyroxine levels than the control group (P = <0.001). The CAP values were significantly higher in participants with overt and subclinical hypothyroidism than the control group (P = <0.001). The only significant independent predictors of steatosis in our study were free T4, body mass index, and HOMA-IR after using multivariate logistic regression. The mean serum FGF21 levels were increased in hypothyroid participants with hepatic steatosis than those without hepatic steatosis (126.9 ± 272.6) pg/ml vs. (106.8 ± 138.7) pg/ml, P = 0.8). Receiver operating characteristic (ROC) curve showed that FGF21 was not a significant marker for hepatic steatosis in hypothyroid participants (area under curve (AUC) = 0.44, P = 0.54).** ***Conclusion:*** **Individuals with subclinical or overt hypothyroidism were more likely to have NAFLD than those with normal thyroid function. Serum FGF21 levels were increased in hypothyroid individuals and its role as a marker of hepatic steatosis in hypothyroid individuals needs further assessment.** **(J Clin Exp Hepatol xxxx;xxx:xxx)**

Currently, non-alcoholic fatty liver disease (NAFLD) is a rapidly growing disease, and it represents the most common cause of chronic disorders of the liver worldwide. The NAFLD epidemic continues to grow in parallel with the ongoing rise in obesity.[1] NAFLD encompasses a wide clinical spectrum ranging from simple fatty liver or hepatic steatosis to non-alcoholic steatohepatitis (NASH) which may progress to liver fibrosis, cirrhosis, and complications of end-stage liver disease necessitating liver transplantation.[2] that will heavily burden the health care system; therefore, early identification of the risk factors for NAFLD is of clinical importance for undertaking preventive and therapeutic strategies against NAFLD.

Thyroid hormones play a crucial role in lipid metabolism[3] and mitochondrial function in the liver,[4] thereby subclinical or overt hypothyroidism, which are common diseases of the endocrine system that are associated with several health problems, including metabolic syndrome and cardiovascular disease,[5] have been reported to be related to the development of NAFLD.[6] In recent years, advances in our understanding of the cellular and molecular

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CAP: controlled attenuation parameter; DBP: diastolic blood pressure; FGF21: fibroblast growth factor 21; FBG: fasting blood glucose; FT4: free thyroxine; GGT: gamma glutamyl transferase; HbA1c: hemoglobin A1c; HDL-C: high density lipoprotein-cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; 2HPP: 2 hours post-prandial blood glucose; LDL-C: low density lipoprotein-cholesterol; LSM: liver stiffness measurement; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; SBP: systolic blood pressure; TE: transient elastography; TSH: thyroid-stimulating hormone; WC: waist circumference
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mechanisms of fatty acid, cholesterol synthesis, and metabolism have led to a better appreciation for the role of thyroid hormones and thyroid hormone receptors (THRs) in maintaining normal hepatic lipid homeostasis.[7]

The relationship between thyroid dysfunction, especially subclinical or overt hypothyroidism, and NAFLD has been discussed, varying from a strong correlation[8] to no correlation as reported by Eshraghian *et al.*, and Lee KW *et al.*[9,10] Therefore, the association between hypothyroidism and NAFLD risk remains a challenge up to now.

To address this issue, this study aimed to clarify whether thyroid dysfunction either overt or subclinical hypothyroidism was associated with NAFLD and if fibroblast growth factor 21 (FGF21) can be used as a marker for NAFLD and its relation to thyroid functions in hypothyroid participants.

PARTICIPANTS AND METHODS

Participants

This was a cross-sectional study conducted on a total of 90 participants, who attended the endocrinology outpatient clinic at Kasr Al Ainy Hospital, Cairo University between April 2019 and June 2020. This study aimed to be exploratory, so sample size was not calculated in prior. This purposive sample based on the availability of patients who fulfill the inclusion criteria at that time The study was conducted according to the principles of the Declaration of Helsinki and was approved by Institutional Review Board (IRB) of the Faculty of Medicine, Cairo University (N-2-2019).

Those 90 participants were subdivided into three groups. Group (1) included thirty participants with a new diagnosis of overt hypothyroidism, (with high thyroid-stimulating hormone [TSH] level >4.5 mIU/L and low free thyroxine [FT4] <0.9 ng/dl). Group (2) included thirty participants with new diagnosis of subclinical hypothyroidism, [with high TSH level >4.5 mIU/L and normal FT4 (0.9 ng/dl–1.7 ng/dl)]. Group (3) included thirty age- and gender-matched apparently healthy volunteers, who attended the outpatient for routine check-up were considered as the control group with TSH level less than 4.5 mIU/L. Inclusion criteria were an age between 20 and 60 years and participants with subclinical hypothyroidism and recent diagnosis of hypothyroidism. Exclusion criteria were the presence of coexistent underlying chronic liver diseases (autoimmune hepatitis, viral-induced hepatitis, or metabolic disease), pregnant participants, and the presence of type 1 or 2 diabetes mellitus. Alcohol is not normally consumed by the included participants due to religious thoughts.

All participants underwent a detailed history, physical examination including measurements of weight, standing height to calculate body mass index (BMI; kg/m^2), waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP). WC was measured at the midpoint between the lowest rib and the iliac crest at the end of a normal expiration while the participants were in a standing position. After an overnight fasting period, blood samples were taken for the estimation of complete blood count, liver function parameters (serum levels of transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), total bilirubin, gamma glutamyl transferase [GGT], and albumin), kidney function tests (serum urea and creatinine), serum uric acid and anti-hepatitis C antibody, and hepatitis B virus surface antigen. Metabolic panels including serum lipids (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]), fasting blood glucose (FBG), 2 h postprandial blood glucose, hemoglobin A1c (HbA1c), and fasting serum insulin were measured. Homeostatic model assessment of insulin resistance (HOMA-IR), developed by Matthews *et al.*[11], was calculated using the formula "fasting glucose (mg/dL) × fasting insulin (mIU/L)]/405 mg"[12] whereas, the thyroid parameters including TSH, FT4. In addition, FGF21, transient elastography was performed.

FGF21 Measurement

Serum FGF21 concentrations were determined with commercially available human FGF21 immunoassay kits [Bioassay Technology Laboratory, Shanghai, China (Cat. No: E1983Hu)]. The assay used enzyme-linked immune sorbent assay based on the Biotin double antibody sandwich technology to assay the human FGF21. The assay range was 5–1500 pg/ml. The intra- and inter-assay coefficients of variation were <10% and <12%, respectively.

Transient Elastography

Liver stiffness (LS) and controlled attenuation parameter (CAP) measurements were performed by transient elastography (TE, Echosens, Fibro Scan 502, Paris, France). Based on the manufacturer's instructions, examinations were considered reliable when the median value of 10 liver stiffness measurement (LSM) with a success rate (SR) >60% and interquartile range <30%.[13] The CAP was measured only on validated measurements according to the same criteria used for LSM, which measured the same liver area measured by LSM. The final CAP value was the median of 10 individual CAP values regardless of the SR. The LSM was expressed as kilopascal (kPa) and the CAP measurements were expressed as decibel per meter (dB/m). The presence of fibrosis was defined as LSM ≥8 kPa at TE.[14] Steatosis grades were assigned as follows: S0 (no

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steatosis, CAP 0–238 dB/m), S1 (mild steatosis, CAP 238–260 dB/m), S2 (moderate steatosis, CAP 261–290 dB/m), and S3 (severe steatosis, CAP ≥ 290 dB/m).[15]

Criteria for Metabolic Syndrome

For the American Heart Association (AHA),[16] metabolic syndrome was diagnosed as having at least three of the following criteria: elevated WC (≥102 cm in males or ≥88 cm females); elevated serum TGs (≥150 mg/dl); low serum HDL-C (<40 mg/dl for men; <50 mg/dl for females); history of hypertension (systolic ≥130 mm Hg or diastolic ≥85 mm Hg); elevated fasting glucose (≥100 mg/dl).

Statistical Method

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal–Wallis and Mann–Whitney tests.[17] For comparing categorical data, chi-square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5.[18] Correlations between quantitative variables were done using spearman correlation coefficient.[19] Logistic regression was done to detect independent predictors.[20] *P*-values <0.05 were considered as statistically significant.

RESULTS

A total of 90 participants were included. The age of the participants ranged from 20 to 60 years with 83.3% were females. Anthropometric measurements, laboratory parameters, and non-invasive methods between the hypothyroid groups and control group were summarized in Table 1. The age, BMI, WC, and SBP were significantly different between the studied groups. However, this relation was insignificant in terms of gender, DBP, hemoglobin, and platelet count. Participants with overt or subclinical hypothyroidism displayed significantly higher serum AST, ALT, GGT, TC, TGs, LDL-C, FBS, 2HPP, HbA1c, TSH but significantly lower serum albumin, HDL-C, and FT4 levels than the control group (P = <0.001 for all). Although, some participants had prediabetes values, none of them were in the diabetic range. Similarly, serum fasting insulin and HOMA-IR were significantly higher in overt and subclinical groups than the control group with 53.6% and 43.3% had an early IR (HOMA-IR > 1.9) and 33.3% and 26.7% had definitive IR (HOMA-IR > 2.9) in overt and subclinical groups, respectively, indicating more insulin resistance (P = <0.001).

No significant difference was noted in the TE values and serum FGF21 levels between the studied groups (P = 0.15 and 0.6, respectively); however, the CAP values measured by TE were significantly higher in participants with overt and subclinical hypothyroidism compared to the control group (P = <0.001). Moreover, the proportion of participants with hepatic fibrosis and steatosis were 10% and 73.3%, respectively, in the overt hypothyroidism group compared to 10% and 56.7%, respectively, in the subclinical hypothyroidism group.

As shown in Table 2, overt hypothyroid participants with hepatic steatosis exhibited significantly higher values in body weight (P = 0.003), BMI (P = <0.001), WC (P = 0.005), serum fasting insulin level (P = 0.007), HOMA-IR (P = 0.01), and CAP measurements (P = <0.001) than those without hepatic steatosis. Subclinical hypothyroid participants with hepatic steatosis exhibited significantly higher values in body weight (P = <0.001), BMI (P = 0.001), WC (P = 0.001), DBP (P = 0.03), TSH (P = 0.001), and HbA1c (P = 0.01) but significantly lower free T4 level (P = 0.005) than those without hepatic steatosis.

Correlation analysis was performed between thyroid function (TSH and FT4) and different parameters in overt and subclinical hypothyroid groups (Table 3). In the overt hypothyroid group, FT4 was negatively associated with lipid profiles (TC, LDL-C). In the subclinical hypothyroid group, serum TSH was positively associated with BMI and CAP measurements. On the other hand, FT4 was negatively associated with age and CAP measurements but it was positively associated with serum albumin.

When multivariate logistic regression used to detect independent predictors of steatosis in all cases using TSH, free T4, BMI, WC, HOMA-IR, HbA1c, and FBG, we found that the only significant independent predictors of steatosis were free T4, BMI, and HOMA-IR. BMI and HOMA-IR increase the risk as OR > 1, free T4 decreases the risk as OR < 1. That prove our results that decrease in thyroid hormone in patients with hypothyroidism increase the risk for liver steatosis besides elevated BMI and HOMA-IR which mainly occur secondary to impaired metabolism in patients with hypothyroidism. Other variables including WC, HbA1C, and FBG were not risk factors for liver steatosis in our included study subjects (Table 4).

Participants were further subdivided into two groups according to the presence or absence of metabolic syndrome in each category based on the criteria from the National Heart, Lung, and Blood Institute and the AHA.[16] 33.3% of overt hypothyroid participants and 33.3% of subclinical hypothyroid participants exhibit the typical

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Table 1 Comparison of Anthropometric Measurements, Laboratory Parameters, and Non-invasive Methods Between the Hypothyroid Groups and Control Group.

Variables	Overt hypothyroidism group (n = 30)	Subclinical hypothyroidism group (n = 30)	Control group (n = 30)	*P*-value*
Age, years	35 (30–40)	35 (23–42)	25 (20–32)	**0.0004**
Gender, n (%)				
Males	4 (13.3%)	3 (10%)	4 (13.3%)	
Females	26 (86.7%)	27 (90%)	26 (86.7%)	1
Anthropometric measurements				
Body weight (kg)	84.12 (13.96)	82.63 (19.8)	59.95 (11.22)	**<0.001**
BMI (kg/m^2)	31.94 (5.43)	31.7 (6.95)	22.5 (3.02)	**<0.001**
Waist circumference (cm)	98.33 (10.14)	92.62 (15.1)	73 (6.64)	**<0.001**
Blood pressure				
SBP (mmHg)	113 (16.2)	115.5 (17.24)	104.33 (10.1)	**0.02**
DBP (mmHg)	74.33 (11.04)	75.83 (8.52)	70.83 (6.96)	0.11
Laboratory parameters				
Hemoglobin (g/dl)	11.8 (1.9)	12.12 (1.53)	12.5 (1.34)	0.4
Platelet count (10^3/mm^3)	278.63 (90.7)	299.2 (82.6)	295.4 (61.3)	0.4
Albumin (g/dl)	4.2 (0.3)	4.25 (0.3)	4.6 (0.3)	**<0.001**
ALT (U/L)	26.6 (19.4)	18.83 (7.5)	12.83 (4.32)	**<0.001**
ALT >35 U/L	7 (23.3%)	1 (3.3%)	0 (0%)	**0.001**
AST (U/L)	28.1 (19.02)	20.9 (7.2)	15.23 (5.6)	**<0.001**
AST >35 U/L	7 (23.3%)	2 (6.7%)	0 (0%)	**0.005**
GGT (U/L)	38.1 (26.6)	22.2 (8.7)	13.2 (4.04)	**<0.001**
GGT >42 U/L	7 (23.3%)	0 (0%)	0 (0%)	**0.0003**
Triglycerides, (mg/dl)	132.7 (56.12)	103.4 (48.5)	73.5 (33.8)	**<0.001**
Total cholesterol (mg/dl)	203.93 (50.7)	188.8 (40.1)	157.97 (28.64)	**<0.001**
HDL-C (mg/dl)	42.13 (8.2)	49.12 (11.3)	54.8 (14.9)	**0.001**
LDL-C (mg/dl)	135.5 (48.1)	119.32 (37.04)	90.6 (28.2)	**<0.001**
TSH (uIU/ml) (0.4–4.2)	64.9 (87.8)	8.24 (2.81)	1.8 (0.8)	**<0.001**
FT4 (ng/dl) (0.9–1.7)	0.56 (0.16)	1.07 (0.13)	1.27 (0.13)	**<0.001**
FBG (mg/dl)	86.3 (9.9)	82.13 (10.5)	71.9 (4.1)	**<0.001**
2HPP (mg/dl)	127.73 (12.5)	116.97 (16.7)	100.1 (6.8)	**<0.001**
HbA1c (%)	5.37 (0.36)	5.03 (0.33)	4.7 (0.3)	**<0.001**
Fasting insulin (mIU/l)	13.12 (8.7)	11.7 (9.42)	5.2 (1.8)	**<0.001**
HOMA-IR	2.9 (2.10)	2.43 (2.10)	0.91 (0.3)	**<0.001**
Early IR >1.9, n (%)	16 (53.3%)	13 (43.3%)	0 (0%)	**<0.001**
Definitive IR > 2.9, n (%)	10 (33.3%)	8 (26.7%)	0 (0%)	**<0.001**
Metabolic syndrome, n (%)	10 (33.3%)	10 (33.3%)	0 (0%)	**0.0002**
Blood urea nitrogen level (mg/dl)	23.5 (9.83)	23.4 (6.81)	20.1 (4.5)	0.2
Creatinine (mg/dl)	0.82 (0.2)	0.77 (0.11)	0.65 (0.12)	**<0.001**
Uric acid (mg/dl)	4.84 (1.3)	4.41 (1.14)	2.95 (0.38)	**<0.001**
FGF21 (pg/ml), median (IQR).	62.5 (56.3–71.6)	63.7 (51.1–88.8)	55.6 (50.5–121.8)	0.6

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Table 1 (*Continued*)

Variables	Overt hypothyroidism group (n = 30)	Subclinical hypothyroidism group (n = 30)	Control group (n = 30)	*P*-value*
Non-invasive methods				
TE values, (kPa)	4.1 (1.4)	4.4 (1.4)	4.6 (0.9)	0.15
Presence of fibrosis (≥8 kPa), n (%)	3 (10%)	3 (10%)	0 (0%)	0.24
CAP, dB/m	261.4 (77.93)	247.97 (75.24)	184.2 (36.62)	**<0.001**
Presence of steatosis, n (%)	22 (73.3%)	17 (56.7%)	0 (0%)	**<0.001**

Unless otherwise stated numerical data are expressed as mean (SD) or median (IQR).
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BL+ve: borderline positive: −ve: negative; BMI: body mass index; CAP: controlled attenuation parameter; DBP: diastolic blood pressure; FBG: fasting blood glucose: FGF21: fibroblast growth factor 21; FT4: free thyroxine; GGT: gamma glutamyl transferase; HbA1c: hemoglobin A1c; HDL-C: high density lipoprotein-cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; 2HPP: 2 hours post-prandial blood glucose; IR: insulin resistance; kPa: Kilopascal; LDL-C: low density lipoprotein-cholesterol; SBP: systolic blood pressure; TE: transient elastography; TSH: thyroid-stimulating hormone.
*P**-value for comparison among three groups.
Statistically significant values are in bold.

features of metabolic syndrome. Overt hypothyroid group with metabolic syndrome exhibited significantly higher values of TGs (P = <0.001), serum fasting insulin (P = 0.04), HOMA-IR (P = 0.04), TE values (P = 0.001), and CAP measurements (P = 0.01) than those without metabolic syndrome whereas subclinical hypothyroid group with metabolic syndrome exhibited significantly higher values of BMI (P = 0.02), TGs (P = <0.001), TC (P = 0.005), LDL-C (P = 0.008), HOMA-IR (P = 0.002), and CAP measurements (P = 0.003) but significantly lower HDL-C (P = 0.01) than those without metabolic syndrome as shown in Supplementary Table (1). In addition, 90% (9/10) of overt hypothyroidism participants with metabolic syndrome had hepatic steatosis and 65% (13/20) of them without metabolic syndrome had hepatic steatosis. In subclinical hypothyroidism participants, hepatic steatosis was 90% (9/10) and 40% (8/20) in those with metabolic syndrome and without metabolic syndrome, respectively.

The mean serum FGF21 levels were increased in hypothyroid participants (subclinical and overt hypothyroidism) with hepatic steatosis (126.9 ± 272.6 pg/ml) than those without hepatic steatosis (106.8 ± 138.7 pg/ml), with no significant difference between them (P = 0.8). Correlation analysis of serum FGF21 levels revealed a significant negative association with platelet count and TGs; however, its levels did not show any further association with other parameters in hypothyroid participants as shown in Supplementary Table (2). A ROC curve was constructed to evaluate the performance of FGF21 as a marker of hepatic steatosis in hypothyroid participants (subclinical and overt hypothyroidism); it showed that FGF21 was not a significant marker for hepatic steatosis in hypothyroid participants (AUC = 0.44, P = 0.54) as shown in Figure 1.

DISCUSSION

As reported by others, our results demonstrated that participants with overt or subclinical hypothyroidism displayed significantly higher BMI, SBP, dyslipidemia featuring hypertriglyceridemia; raised TC and LDL-C; low HDL-cholesterol, and insulin resistance than the control group.[21,22] It is worth mentioning that lower levels of thyroid hormones can affect lipid metabolism through increasing the levels of cholesterol, low-density lipoproteins, and TG due to increased esterification of hepatic fatty acids but decreasing the level of HDL-C.[23] In addition, increased levels of TSH can directly increase hepatic gluconeogenesis, repress hepatic bile acid synthesis, and cause hypercholesterolemia by decreasing HMG-CoA reductase phosphorylation, which further can affect lipid metabolism in the liver.[7] Moreover, insulin resistance in the setting of hypothyroidism has been documented and this due to low levels of thyroid hormones influences certain adipocytokines levels.[24]

Thyroid hormones also regulate calorigenesis in all cells, including hepatocytes and thereby modulate hepatic function; the liver, in turn, metabolizes the thyroid hormones and contributes to the regulation of their systemic endocrine effects. Meanwhile, elevated TSH levels may affect liver function causing more liver cell damage and elevation of the liver enzymes and thus liver disease affects thyroid hormone metabolism, and a variety of systemic diseases affect both organs.[25] Within this context, we found that participants either with overt or subclinical hypothyroidism had significantly higher serum levels of ALT, AST, and GGT than the control group; therefore, our findings confirm previous observations suggesting that hypothyroidism is frequently associated with abnormalities in

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Table 2 Comparison of Anthropometric Measurements, Laboratory Parameters, and Non-invasive Methods Between the Hypothyroid Groups (overt or subclinical) According to the Presence or Absence of Hepatic Steatosis.

Variables	Overt hypothyroidism group (n = 30)			Subclinical hypothyroidism group (n = 30)		
	Presence of steatosis (n = 22)	Absence of steatosis (n = 8)	*P*-value	Presence of steatosis (n = 17)	Absence of steatosis (n = 13)	*P*-value
Age, years	36.41 (10.7)	40.13 (7.4)	0.3	36.41 (6.6)	29.92 (11.74)	0.09
Anthropometric measurements						
Body weight (kg)	88.2 (13.6)	7.92 (73.02)	**0.003**	93.23 (15.09)	68.8 (16.5)	**<0.001**
Height (cm)	161.73 (8.7)	164.8 (7.6)	0.4	161.82 (10.73)	160 (10.3)	0.77
BMI (kg/m^2)	33.8 (4.95)	26.95 (3.1)	**<0.001**	35.34 (5.3)	26.8 (5.9)	**0.001**
WC (cm)	101.61 (8.6)	89.31 (8.84)	**0.005**	100.53 (11.63)	82.3 (12.8)	**0.001**
SBP (mmHg)	113.4 (17.6)	111.9 (12.5)	1	121.5 (19.7)	107.7 (9.3)	0.053
DBP (mmHg)	75 (12.3)	72.5 (7.1)	0.9	79.12 (9.1)	71.5 (5.6)	**0.03**
Laboratory parameters						
Hemoglobin (g/dl)	11.73 (1.6)	11.99 (1.24)	0.6	12.04 (1.4)	12.24 (1.8)	0.9
Platelet (10^3/mm^3)	261.6 (72.4)	325.4 (122.3)	0.4	299 (73.1)	299.4 (96.73)	0.96
Albumin (g/dl)	4.2 (0.29)	4.2 (0.21)	0.7	4.22 (0.27)	4.3 (0.24)	0.3
ALT (U/L)	28.2 (21.3)	22.13 (12.9)	0.7	18.6 (6.4)	19.2 (8.97)	1
AST (U/L)	29 (21)	25.5 (12.9)	0.6	20.3 (6.7)	21.62 (7.95)	0.5
GGT (U/L)	41.1 (30.3)	29.9 (9.3)	0.7	23.82 (8.63)	20.1 (8.62)	0.3
TGs (mg/dl)	138.6 (62.2)	116.5 (32.42)	0.4	112.53 (46.4)	91.5 (50.31)	0.3
TC (mg/dl)	200.1 (40.9)	214.4 (73.8)	0.9	199.6 (36.7)	174.7 (41.4)	0.1
HDL-C (mg/dl)	41.82 (7.64)	43 (10.10)	0.6	48.62 (11.38)	49.8 (11.6)	0.9
LDL-C (mg/dl)	130.9 (33.2)	148 (77.7)	0.98	129.04 (35.92)	106.62 (35.9)	0.1
TSH (uIU /ml)	61.1 (97.9)	75.3 (55.11)	0.2	9.6 (2.9)	6.48 (1.43)	**0.001**
FT4 (ng/dl)	0.57 (0.2)	0.54 (0.19)	0.6	1.02 (0.12)	1.14 (0.13)	**0.005**
FBG (mg/dl)	87.5 (10.63)	82.9 (6.8)	0.32	84.3 (12.32)	79.31 (6.94)	0.3
2HPP (mg/dl)	130 (13.73)	121.5 (4.63)	0.06	122.1 (17.52)	110.31 (13.4)	0.07
HbA1c (%)	5.43 (0.36)	5.21 (0.33)	0.34	5.16 (0.32)	4.9 (0.24)	**0.01**
Fasting insulin (mIU/l)	15.12 (8.92)	7.61 (5.11)	**0.007**	11.4 (8.48)	12.1 (10.9)	0.96
HOMA-IR	3.38 (2.21)	1.51 (0.9)	**0.01**	2.5 (2.23)	2.33 (1.99)	0.96
Creatinine (mg/dl)	0.81 (0.21)	0.83 (0.2)	0.8	0.76 (0.12)	0.79 (0.11)	0.71
FGF21 (pg/ml), Median (IQR)	61.4 (55.6–73.2)	63.6 (61.6–71.9)	0.6	62.6 (51.8–102.2)	69.5 (49.8–90.8)	0.7
Non-invasive methods						
TE values (kPa)	4.2 (1.41)	3.7 (1.3)	0.4	4.5 (1.6)	4.3 (1.01)	0.8
CAP (dB/m)	298.8 (43.4)	158.5 (54.9)	**<0.001**	301.6 (38.8)	177.9 (47.7)	**<0.001**

Data are expressed as mean (SD) or median (IQR). Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CAP: Controlled attenuation parameter; DBP: Diastolic blood pressure; FBG: Fasting blood glucose: FGF21: Fibroblast growth factor 21; FT4: Free thyroxine; GGT; gamma glutamyl transferase; HbA1c: hemoglobin A1c; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; 2HPP: 2 hours post-prandial blood glucose; kPa: Kilopascal; LDL-C: Low density lipoprotein-cholesterol; TC: Total cholesterol; TE: Transient elastography; TGs: Triglycerides; TSH: Thyroid-stimulating hormone; SBP: Systolic blood pressure; WC: waist circumference.
Statistically significant values are in bold.

liver function tests. This was reported also by others e.g., Ambiger S. *et al.*[26,27] However, we detected no consistent association of serum TSH and FT4 levels with these parameters this was due to the small number of patients included in each group.

In the present study, the prevalence of hepatic steatosis as determined by TE was significantly higher in participants with overt or subclinical hypothyroidism than in those with normal thyroid function. In addition, 90% (9/10) of clinical hypothyroidism subjects with metabolic

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Table 3 Correlation Between TSH and FT4 With Different Parameters in Overt and Subclinical Hypothyroidism Groups.

		TSH		FT4	
		Overt hypothyroidism group	Subclinical hypothyroidism group	Overt hypothyroidism group	Subclinical hypothyroidism group
Age (years)	Correlation coefficient	−0.2	0.17	0.0002	−0.47
	P-value	0.3	0.34	0.99	**0.01**
BMI (kg/m^2)	Correlation coefficient	−0.07	0.38	−0.09	−0.26
	P-value	0.7	**0.04**	0.63	0.17
Waist circumference (cm)	Correlation coefficient	0.07	0.22	−0.083	−0.32
	P-value	0.72	0.2	0.7	0.08
SBP (mm Hg)	Correlation coefficient	0.05	0.23	−0.33	−0.09
	P-value	0.8	0.21	0.07	0.61
DBP (mm Hg)	Correlation coefficient	0.038	0.28	−0.26	0.02
	P-value	0.83	0.13	0.17	0.93
Total bilirubin (mg/dl)	Correlation coefficient	−0.35	−0.195	0.3	0.17
	P-value	0.06	0.30	0.11	0.38
Albumin (g/dl)	Correlation coefficient	0.149	−0.15	0.11	0.49
	P-value	0.43	0.4	0.56	**0.005**
GGT (U/L)	Correlation coefficient	−0.22	0.15	−0.06	−0.04
	P-value	0.25	0.42	0.75	0.85
ALT (U/L)	Correlation coefficient	−0.2	0.17	0.05	−0.03
	P-value	0.4	0.36	0.78	0.85
AST (U/L)	Correlation coefficient	−0.2	−0.08	0.03	0.11
	P-value	0.4	0.65	0.87	0.56
T.Cholesterol (mg/dl)	Correlation coefficient	0.14	0.014	−0.4	−0.02
	P-value	0.5	0.94	**0.03**	0.91
Triglycerides (mg/dl)	Correlation coefficient	−0.02	−0.13	0.07	0.2
	P-value	0.94	0.5	0.7	0.4
HDL-C (mg/dl)	Correlation coefficient	−0.083	0.21	−0.16	0.002
	P-value	0.7	0.3	0.41	0.99
LDL-C (mg/dl)	Correlation coefficient	0.13	0.02	−0.42	−0.104
	P-value	0.5	0.9	**0.02**	0.6
FBG (mg/dl)	Correlation coefficient	−0.02	−0.19	0.038	0.05
	P-value	0.93	0.29	0.84	0.8
HbA1c (%)	Correlation coefficient	0.086	0.22	−0.18	−0.26
	P-value	0.64	0.24	0.33	0.16
Fasting insulin (mIU/l)	Correlation coefficient	−0.038	−0.19	0.09	0.23
	P-value	0.8	0.30	0.61	0.23
HOMR-IR	Correlation coefficient	−0.036	−0.22	0.09	0.23
	P-value	0.85	0.24	0.61	0.22
CAP (dB/m)	Correlation coefficient	−0.16	0.42	0.13	−0.48
	P-value	0.37	**0.02**	0.51	**0.007**
TE values (kPa)	Correlation coefficient	−0.4	−0.27	0.41	−0.14
	P-value	**0.03**	0.15	**0.02**	0.47

Abbreviations: Anti-TG: Antit-thyroglobulin; Anti-TPO: Anti-thyroperoxidase autoantibodies; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CAP: Controlled attenuation parameter; DBP: Diastolic blood pressure; FBG: Fasting blood glucose: FT4: Free thyroxine; GGT; gamma glutamyl transferase; HbA1c: hemoglobin A1c; HDL-C: High density lipoprotein-cholesterol; HOMA-IR: Homeostatic model assessment of insulin Resistance; 2HPP: 2 hours post-prandial blood glucose; INR: International normalized ratio; kPa: Kilopascal; LDL-C: Low density lipoprotein-cholesterol; SBP: Systolic blood pressure; TE: Transient elastography; TSH: Thyroid-stimulating hormone.
Statistically significant values are in bold.

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Table 4 Multivariate Logistic Regression to Detect Independent Predictors of Steatosis in all Cases Using TSH, FREE T4, BMI, WAIST CIRCUMFERENCE, HOMA IR, HbA1c and FBG.

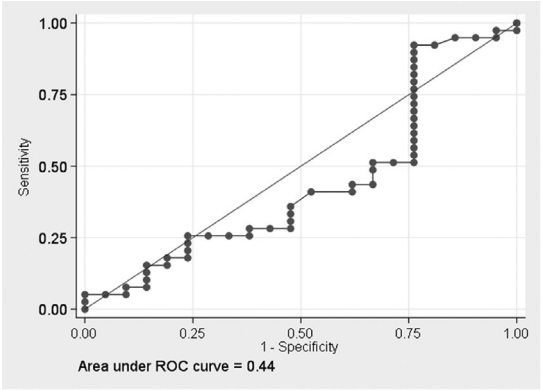
		P value	OR	95% C.I.	
				Lower	Upper
Steatosis	TSH	0.060	0.985	0.969	1.001
	FREET4	**0.038**	0.008	0.000	0.757
	BMI	**0.016**	1.447	1.070	1.956
	Waist	0.082	1.100	0.988	1.226
	Homa IR	**0.028**	2.186	1.089	4.387
	HBA1C	0.491	4.620	0.059	361.521
	FBG	0.073	0.867	0.741	1.013

Abbreviations: BMI: body mass index; FBG: fasting blood glucose; Free T4: free thyroxine; HbA1c: hemoglobin A1c; HOMA IR: homeostatic model assessment of insulin resistance; TSH: thyroid stimulating hormone.
Statistically significant values are in bold.

syndrome had hepatic steatosis and 65% (13/20) of them without metabolic syndrome had hepatic steatosis. In the subclinical hypothyroidism subjects, hepatic steatosis was 90% (9/10) and 40% (8/20) in those with metabolic syndrome and without metabolic syndrome, respectively. We also noted a significant inverse association between serum FT4 level and hepatic steatosis represented by CAP values ($r = -0.48$, $P = 0.007$), whereas serum TSH and hepatic steatosis showed a significant positive association ($r = 0.4$, $P = 0.02$) in the subclinical hypothyroid group. These findings explain a relevant clinical relationship between these two disease entities. This could be related to elevated TSH levels which result in diminished hepatic lipoprotein lipase activity and cause an increase influx of TGs within hepatocytes to promote hepatic steatosis by binding to TSH receptor on hepatocytes and then triggers hepatic sterol regulatory element binding transcription factor 1 activity via the cAMP (cyclic adenosine monophosphate)/PKA (prorein kinase A)/PPARα (peroxisome proliferate activated receptor alpha) pathway associated with decreased AMPK, which further increases the expression of genes associated with lipogenesis.[28]

As reported by Mantovani A *et al.* and Guo *et al.*, individuals with hypothyroidism are prone to develop hepatic steatosis and subsequent liver fibrosis.[29,30] In the current study, we found that the proportion of participants with thyroid dysfunction either overt or subclinical that had hepatic fibrosis was higher than in the control group. Little is known regarding the underlying link for this association, but thyroid dysfunction may mediate hepatic fibrosis via oxidative stress and mitochondrial dysfunction.[31] In addition, the thyroid hormone receptor may activate hepatic stellate cells and hepatic fibrogenesis according to the recent report.[32,33]

FGF21, a member of endocrine FGF family, emerged as a hormone involved in the regulation of glucose, lipid, and energy metabolism which share great similarities with the metabolic actions of thyroid hormones. The role of FGF21 has been recently proposed in NAFLD/NASH[34] and may serve as a promising marker of hepatic apoptosis. In the current study, we demonstrated that hypothyroid participants had higher serum FGF21 levels than the controls. The mechanisms by which serum FGF21 levels are increased in hypothyroid individuals are unclear. One possible explanation is that the increase in serum FGF21 levels might be a compensatory mechanism in response to altered metabolism by thyroid hormones such as changed basal metabolic rate or body fat accumulation. Alternatively, the increase in serum FGF21



Parameter	Area Under the Curve	*P*-value	95% Confidence Interval
Serum FGF21	0.44	0.54	0.28 - 0.60

Figure 1 ROC curve of serum FGF21 as a marker of hepatic steatosis in hypothyroid participants.

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levels might be a response to local regulation by thyroid hormones.[35] Thyroid hormones synthesis is under the influence of many systemic factors and local factors, which include the actions of deiodinases that convert T4 to T3. Therefore, an increase in hepatic deiodinase activity, promoting a local increase in T3, might account for increased FGF21 synthesis in the liver. Lastly, although the mechanism of FGF synthesis and clearance is unclear, the elevation of serum FGF21 in hypothyroid individuals might arise from an altered balance between synthesis and clearance of FGF21.[35]

Moreover, as FGF21 is liver-derived protein, studies have demonstrated that FGF21 signaling is a key pathological step in the development and progression of NAFLD and its levels are elevated in subjects with NAFLD.[36] This study confirmed such observation that serum FGF21 levels were elevated in hypothyroid participants (subclinical and overt hypothyroidism) with hepatic steatosis (126.9 ± 272.6 pg/ml) than those without hepatic steatosis (106.8 ± 138.7 pg/ml). The elevation of serum FGF21 levels in individuals with hepatic steatosis is explained by dysfunctional PPARα signaling as PPARα is activated by intrahepatic fatty acids that are increased by the up regulation of genes which regulate lipogenesis and cholesterol metabolism.[37,38] On the other hand, our study reported a negative correlation between serum FGF21 levels and TGs in hypothyroid groups. Because both FGF21 and thyroid hormones are associated with altered lipid metabolism. It was found that FGF21 has a central role in lipid metabolism through increasing the deposition and catabolism of TG-rich lipoproteins in WAT and BAT, thus reducing plasma TGs.[39] FGF21 also alters the hepatic expression of genes involved in hepatic lipid metabolism, it up-regulates anti-lipogenic genes (Lepr and Igfbp2) and represses genes involved in lipid synthesis (Scd1 and Gck).[40]

In conclusion, hypothyroid individuals are more likely to have metabolic abnormalities such as obesity, hypertension, dyslipidemia, and IR putting them at a high risk of cardiovascular events and even mortality. This may lead us to screen individuals with thyroid dysfunction for biochemical parameters, hepatic steatosis and fibrosis, as thyroid dysfunction either overt or subclinical is a modifiable risk factor and can be treated with thyroid hormone replacement. Serum FGF21 level was increased in hypothyroid individuals and inversely correlated with TGs; however, serum FGF21 was not a significant marker for hepatic steatosis in hypothyroid participants. Therefore, more prospective cohort studies are needed to further strengthen the relationship between NAFLD and hypothyroidism and the role of FGF21 as a marker in the diagnosis of hepatic steatosis in hypothyroid individuals.

Limitations of the Study

1. The small number of included individuals with hypothyroid.
2. Although liver biopsy represents the gold standard for diagnosis of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), the diagnosis of hepatic fibrosis and steatosis was based on transient elastography examination, a non-invasive method commonly used in diagnosis of hepatic fibrosis and steatosis in clinical practice.
3. Individuals with hyperthyroidism were not included. Hence, further studies are needed to explore the relationship between NAFLD/NASH and thyroid dysfunction including hyperthyroidism.
4. History of alcohol consumption has not been documented because this is a sensitive issue as self-reported history of alcohol consumption is under reported because some individuals in our country are unlikely to disclose their high-risk behaviors especially in conservative communities.
5. Other thyroid metabolites were not assessed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the results are available from the corresponding author upon reasonable request.

INFORMED CONSENT

Written informed consent was obtained from each participant prior to sample collection and transient elastography as well as thyroid ultrasound were performed.

CONSENT FOR PUBLICATION

Not applicable.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

All authors have substantially contributed to the conception and design, acquisition of data, data analysis and interpretation. All authors have agreed on the content of the manuscript. SE: data collection, acquisition and manuscript writing; HE: conception and study design, data analysis and interpretation; SAA: Fibro scan operator, data analysis, interpretation and manuscript writing; OS: investigation; RS: data analysis, interpretation and manuscript revision; AY: investigation; IE: conception and study design, interpretation of results and manuscript revision.

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CONFLICTS OF INTEREST

No conflict of interest.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.03.004.

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