Original Article

# Association of Subclinical Hypothyroidism with Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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## Abstract

**Background:** Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are recognized as two common health problems. Metabolic diseases, such as dyslipidemia, obesity, and hypertension are known risk factors for NAFLD. In addition to these risk factors, other risk factors have been recently suggested, such as thyroid dysfunction.

**Materials and Methods:** In this study, adult patients with T2DM were recruited. Various clinical and biochemical parameters including thyroid function tests, liver function tests, and liver sonography in all participants were assessed and compared between with and without NAFLD groups.

**Results:** Data from 926 diabetic patients were analyzed; of which, 744 (80.3%) had fatty liver. The prevalence of subclinical hypothyroidism (SCH) in patients with NAFLD was 11.6% and in patients without NAFLD was 6.0% ($P = 0.029$). Furthermore, the prevalence of overt hypothyroidism was higher in diabetic patients with NAFLD (3.9% vs. 1.6%); this difference was not statistically significant. In univariate logistic regression analysis, hemoglobin A1c (odds ratio [OR]: 8.13); history of insulin consumption (OR: 5.35); duration of diabetes (OR: 2.20); family history of diabetes (OR: 2.85); history of antihypertensive drug use (OR: 2.14) as well as SCH (OR: 2.03) were significant variables for NAFLD. According to the multivariate logistic model, after eliminating the confounding effect of age, sex, and body mass index; the chance of developing NAFLD in patients with SCH was 2.32 times higher than patients without SCH ($P = 0.014$).

**Conclusion:** NAFLD is extremely common in patients with T2DM. The relationship between hypothyroidism and NAFLD is independent of other risk factors.

**Keywords:** Diabetes mellitus, hypothyroidism, nonalcoholic fatty liver disease, type 2

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## Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as an increase in triglyceride accumulation in the liver (>5% of liver weight) in the absence of excessive alcohol consumption or other known causes of steatosis. NAFLD in its progressive course can lead to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. For the past two decades, NAFLD has been one of the most important causes of morbidity and mortality worldwide, and in future, it will become the first cause of liver transplantation. Recent research has shown that hepatocellular carcinoma and end-stage liver disease can result from mild degrees of steatosis and

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inflammation. Experts believe that a significant proportion of participants diagnosed with cryptogenic cirrhosis have NAFLD or NASH as an underlying disease.[1-3]

NAFLD and type 2 diabetes mellitus (T2DM) have been known as major public health concerns. The prevalence of NAFLD in Western countries is 46.2% and is the most common liver disease. Its prevalence in some specific groups, such as obese people and patients with T2DM, reaches 75% to 90%. In recent decades, the prevalence of NAFLD has increased along with obesity worldwide; reaching 46.2% in Europe, 33% in North America, and 31.8% in Asia. It is estimated that about one-fourth of the world's population suffers from NAFLD.[4-8] Furthermore, the global prevalence of diabetes in 2019 was 9.3% (463 million people), which is expected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. Notably, patients with NAFLD experience T2DM and vice versa. About 25% of patients with NAFLD and 50% of patients with NASH have T2DM, while NAFLD is reported in about 70% of patients with T2DM.[9] These two conditions have mutual effects on each other. In patients with T2DM, NAFLD increases the risk of mortality. Furthermore, the presence of T2DM causes a threefold increase in the risk of progressive liver fibrosis and a two-fold increase in the risk of hepatocellular carcinoma. It is also an independent predictor of liver disease mortality and all-cause mortality.[10]

What links the two diseases is insulin resistance, and NAFLD is recognized as the hepatic component of metabolic syndrome. Metabolic diseases, such as dyslipidemia, obesity, and hypertension, are known risk factors for NAFLD. In addition to these risk factors, other risk factors have been recently suggested, such as thyroid dysfunction.[11-14]

Thyroid hormones are involved in regulating the metabolism of carbohydrates, proteins, and lipids. The decreased levels of thyroid hormones are associated with the reduced basal metabolic rate, decreased resting energy expenditure and weight gain, increased cholesterol levels, decreased gluconeogenesis, and reduced lipolysis.[15] Thyroid hormones are also involved in lipid metabolism and insulin resistance in the liver. On the other hand, hypothyroidism can lead to insulin resistance, dyslipidemia, and obesity, all of which are components of metabolic syndrome. Subclinical hypothyroidism (SCH) is associated with metabolic syndrome, lipid metabolism disorders, and cardiovascular mortality. Furthermore, hypothyroidism, both overt and subclinical, is prevalent in patients with NAFLD or NASH.[16-18]

Regarding the metabolic manifestations of hypothyroidism, several studies have examined the association between NAFLD and thyroid dysfunction and reported conflicting results.[19,20] There is no information available on the association between thyroid dysfunction and NAFLD in diabetic patients, and it is not clear whether hypothyroidism is a risk factor for NAFLD in patients with type 2 diabetes. Therefore, this cross-sectional study aimed to evaluate the association between overt and SCH and NAFLD in a group of patients with type 2 diabetes.

## Materials and Methods

This cross-sectional study was performed on patients with T2DM who referred to endocrinology clinics in Zahedan, Southeastern Iran, between April 2018 and August 2020. Patients with T2DM of at least age 30 years were included in the study by sequential sampling. Then, for each patient, information including age, sex, duration of diabetes, other comorbidities, and medications were recorded by a physician. Diabetes was diagnosed based on American Diabetes Association criteria.[21]

Participants with evidence of chronic liver diseases such as autoimmune hepatitis, viral hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson, and cirrhosis were excluded. Participants with other types of diabetes, including T1DM, latent autoimmune diabetes of adults, and gestational diabetes, were also excluded. Participants with impaired kidney function (estimated glomerular filtration rage <60 ml/min/1.73 $m^2$ or plasma creatinine >2 mg/dL), malignancy, acute infectious disease, a history of thyroid dysfunction, or other endocrine diseases that affect thyroid function tests such as acromegaly and Cushing syndrome were excluded from the study. People with a history of consuming any amount of alcohol, or taking drugs that affect thyroid function tests, such as antithyroid drugs, tamoxifen, amiodarone, isoniazid, antiviral drugs, corticosteroid, methotrexate, and sodium valproate in the last 6 months have been excluded from the study, too. Pregnant and lactating women were also excluded.

Participants were evaluated in terms of height, weight, and blood pressure measurement. Bodyweight with minimal clothing with a digital scale and height in the standing position using a Stadiometer was measured. Body mass index (BMI) was determined using this formula: weight in kilograms divided by the square of height in meters. Blood pressure using a manual sphygmomanometer and after 15 min of rest in a sitting position, before blood sampling was measured.

For all participants, liver ultrasonography was performed by a sonologist after 12 h of fasting. Fatty liver was determined found on standard criteria including liver illumination, variation between the liver and kidneys echogenicity, and the degree of ambiguity of blood vessels. Grading of the fatty liver based on the amount of fat deposition in the liver was determined as follows; Grade I– observable periportal and diaphragmatic echogenicity in association with increased liver echogenicity; Grade II– nonobservable periportal echogenicity in association with increased liver echogenicity without diaphragmatic ambiguity; Grade III-nonobservable periportal echogenicity in association with increased liver echogenicity with diaphragmatic ambiguity.[22] Fatty liver was diagnosed according to US criteria. NAFLD was diagnosed according to the American Gastroenterological Association criteria: (1) Presence of hepatic steatosis on imaging or histology; (2) Lack of excessive consumption of alcohol; (3) No other reason for hepatic steatosis, and (4) No other synchronic cause for chronic liver disease.[23]

Fasting venous blood was collected for measurement of the glycemic profile, thyroid function tests, and other biochemical tests. All blood samples were collected between 8 and 9 am and after 12 h of fasting. Plasma Glucose was measured by the glucose oxidase method. Measurement of Glycated hemoglobin A1c (HbA1c) was carried out using high-performance liquid chromatography. Lipids were measured using enzymatic colorimetric tests. Blood urea nitrogen, creatinine, liver function tests were assessed using enzymatic colorimetric assays. Serological tests for hepatitis B and C rejection were performed in patients with elevated liver enzymes. The normal AST and ALT were defined as <40 u/l. FT4, FT3, and thyroid-stimulating hormone (TSH) using immunochemoluminescent assays were measured. Antithyroid peroxidase (normal range <16 U/ml), antithyroglobulin (normal range <100) were measured by immunochemoluminescent assays. SCH was defined as an elevated level of (TSH: 4.3–10 mIU/L; normal range: 0.4–4.2 mIU/L) in the presence of normal serum free thyroxine (FT4; normal: 0.8–1.8 ng/ml, normal FT3: 2.3–4.2 pg/ml) level. Overt hypothyroidism was defined as an elevated level of thyroid-stimulating hormone (TSH ≥10 mIU/L) in the presence of low serum FT4 and FT3 levels.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. The Zahedan University Ethics Committee for Human Studies approved the protocol. All participants provided informed consent.

### *Statistical analysis*

The study variable is described with descriptive statistics, like the frequency with percentage and mean with standard deviation. The normality of variables was assessed with Shapiro–Wilk test and graphical approaches. The mean difference of a numerical variable in with and without NAFLD groups was analyzed with an independent sample *t*-test. We used of Chi-square test for testing the association between two categorical variables. The association between independent factors and NAFLD was assessed with a univariate and multivariate logistic regression model. $P < 0.05$ was considered statistically significant. All of the analyses were conducted with Stata statistical software: Release 14. College Station, TX: StataCorp LP.

## Results

Clinical and laboratory characteristics of patients with and without NAFLD are shown in Table 1. In this study, data from 926 diabetic patients were analyzed, of which 744 (80.3%) had fatty liver. Of the total patients, 65% were female patients; but gender distribution was not significantly different between patients with and without fatty liver. The mean age of diabetic patients with NAFLD was significantly higher than patients without NAFLD. Furthermore, the mean duration of diabetes in diabetic patients with NAFLD (10.64 years) was twice that of diabetic patients without NAFLD (5.84 years) and this difference was statistically significant ($P < 0.001$). The mean BMI in diabetic patients with and without NAFLD was 27.39 and 26.10, respectively, and this difference was statistically significant ($P < 0.001$). Mean fasting plasma glucose and HbA1c in diabetic patients with NAFLD were significantly higher than in diabetic patients without NAFLD.

The prevalence of SCH in diabetic patients with NAFLD was almost twice that of patients without NAFLD (11.6% vs. 6.0%) and this difference was also statistically significant ($P = 0.029$). Furthermore, although the prevalence of overt hypothyroidism was higher in diabetic patients with NAFLD (3.9% vs. 1.6%), this difference was not statistically significant [Figure 1].

In univariate logistic regression analysis, HbA1c with an odds ratio (OR) of 8.13 and history of insulin use with OR = 5.35 showed the highest OR for NAFLD. Furthermore, duration of diabetes (OR = 2.20), family history of diabetes (OR = 2.85), history of antihypertensive drug use (OR = 2.14) as well as SCH (OR = 2.03) are significant variables with OR > 2 for NAFLD [Table 2].

According to the multivariate logistic model, after eliminating the confounding effect of age, sex, and BMI, the chance of developing NAFLD in patients with SCH is 2.32 times higher than patients without SCH ($P = 0.014$). In the final model, the simultaneous effects of age, BMI, family history of diabetes, duration of diabetes, history of antihypertensive drug use, subclinical and overt hypothyroidism on NAFLD were evaluated. In this model, the OR of subclinical and overt hypothyroidism for NAFLD were 2.14 and 3.35, respectively. In this model, the effect of other variables on increasing the chance of NAFLD in diabetic patients was also significant. History of antihypertensive drug use (OR = 2.87), duration of diabetes (OR = 2.37), and family history of diabetes (OR = 2.05) were the strongest predictors [Table 3].

## Discussion

This cross-sectional study showed that overt and SCH are more common in type 2 diabetic patients with NAFLD than

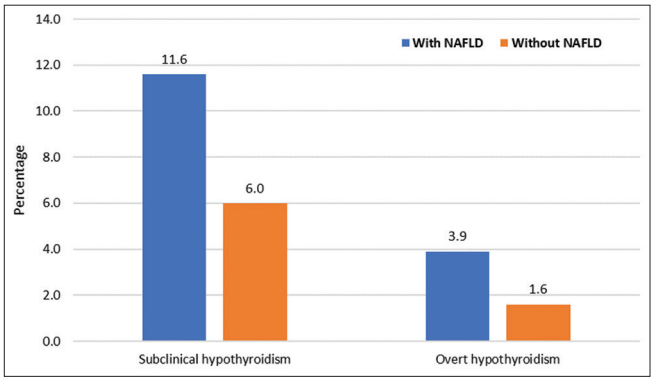


**Figure 1:** Prevalence of subclinical and overt hypothyroidism in patients with and without nonalcoholic fatty liver disease

**Table 1: Clinical and laboratory characteristics of type 2 diabetic patients with and without nonalcoholic fatty liver disease**

| | All ($n=926$) | Nonalcoholic fatty liver disease | | *P* |
|---|---|---|---|---|
| | | With ($n=744$) | Without ($n=182$) | |
| Age (years) | 53.15 (10.63) | 54.12 (11.22) | 49.17 (6.39) | <0.001 |
| Sex, female | 602 (65.0) | 488 (65.6) | 114 (62.6) | 0.454 |
| Diabetes duration (years) | 9.69 (4.25) | 10.64 (4.16) | 5.84 (1.67) | <0.001 |
| Positive family history of DM | 662 (71.5) | 566 (76.1) | 96 (52.7) | <0.001 |
| Use of antihypertensive drug | 511 (55.2) | 438 (58.9) | 73 (40.1) | <0.001 |
| Use of statin | 784 (84.7) | 632 (84.9) | 152 (83.5) | 0.631 |
| Use of OHA | 530 (57.2) | 400 (53.8) | 130 (71.4) | <0.001 |
| Use of insulin | 316 (34.1) | 296 (39.8) | 20 (11.0) | <0.001 |
| BMI (kg/m$^2$) | 27.14 (2.92) | 27.39 (2.93) | 26.10 (2.65) | <0.001 |
| Systolic BP (mmHg) | 133.28 (10.93) | 133.55 (11.23) | 132.16 (9.57) | 0.091 |
| Diastolic BP (mmHg) | 81.50 (9.48) | 81.44 (9.66) | 81.75 (8.76) | 0.696 |
| Hypertension, BP ≥140/90 (%) | 424 (45.8) | 341 (45.8) | 83 (45.6) | 0.956 |
| Fasting plasma glucose (mg/dL) | 164.37 (27.58) | 167.55 (27.96) | 151.38 (21.57) | <0.001 |
| HbA1c | 8.43 (0.93) | 8.65 (0.89) | 7.57 (0.54) | <0.001 |
| Total cholesterol (mg/dL) | 183.69 (47.59) | 186.87 (49.04) | 170.70 (38.60) | <0.001 |
| Triglycerides (mg/dL) | 117.71 (62.06) | 118.55 (63.32) | 114.32 (56.65) | 0.379 |
| LDL cholesterol (mg/dL) | 117.70 (44.44) | 120.52 (46.03) | 106.19 (35.03) | <0.001 |
| HDL cholesterol (mg/dL) | 45.71 (10.38) | 45.65 (10.33) | 43.33 (10.40) | 0.007 |
| VLDL (mg/dL) | 23.38 (12.42) | 23.56 (12.69) | 22.65 (11.29) | 0.340 |
| BUN (mg/dL) | 14.62 (3.53) | 14.63 (3.56) | 14.61 (3.43) | 0.959 |
| Creatinine (mg/dL) | 1.11 (0.17) | 1.11 (0.17) | 1.10 (0.17) | 0.829 |
| ALT (IU/l) | 37.06 (12.91) | 39.24 (12.72) | 28.14 (9.40) | <0.001 |
| AST (IU/l) | 33.39 (12.61) | 35.48 (12.43) | 24.84 (9.30) | <0.001 |
| AlkPH (IU/l) | 109.37 (27.58) | 109.50 (21.18) | 107.72 (22.11) | 0.315 |
| FT3 (pg/ml) | 3.53 (0.72) | 3.52 (0.76) | 3.54 (0.52) | 0.735 |
| FT4 (ng/dl) | 1.27 (0.28) | 1.26 (0.29) | 1.29 (0.24) | 0.186 |
| TSH (mIU/l) | 5.29 (13.34) | 5.87 (14.62) | 2.93 (5.07) | <0.001 |
| SCH | 97 (10.5) | 86 (11.6) | 11 (6.0) | 0.029 |
| Overt hypothyroidism | 32 (3.5) | 29 (3.9) | 3 (1.6) | 0.136 |
| Anti-TPO titer (IU/l) | 28.35 (35.45) | 29.19 (37.55) | 24.96 (24.85) | 0.149 |
| Positive Anti-TPO (≥16) | 434 (46.9) | 359 (48.3) | 75 (41.2) | 0.088 |
| Anti-Tg titer (IU/l) | 54.29 (29.87) | 53.35 (30.10) | 58.13 (28.67) | 0.053 |
| Positive anti-Tg (≥100) | 58 (6.3) | 47 (6.3) | 11 (6.0) | 0.892 |

*P*-values were determined by independent *t*-test or Pearson $\chi^2$ test, Data are shown as *n* (%) or mean±SD. AST: Aspartate transaminase, ALT: Alanine transaminase, AlkPH: Alkaline phosphatase, BMI: Body mass index, BP: Blood pressure, DM: Diabetes mellitus, FT3: Free triiodothyronine, FT4: free thyroxine, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very-LDL, TSH: Thyroid-stimulating hormone, OHA: Oral hypoglycemic agents, BUN: Blood urea nitrogen, SCH: Subclinical hypothyroidism, TPO: Thyroid peroxidase, Tg: Thyroglobulin

in diabetic patients without NAFLD. There was a strong association between hypothyroidism and NAFLD. These findings suggest that hypothyroidism, regardless of other known metabolic risk factors, is closely related to NAFLD in patients with T2DM.

NAFLD as a common disease is associated with metabolic syndrome and its components, including insulin resistance, hypertriglyceridemia, diabetes, hypertension, and obesity. On the other hand, type 2 diabetes is a common metabolic disease, with an increasing prevalence worldwide.[24,25] In recent years, many studies have been conducted on the association between type 2 diabetes and NAFLD.[10,26] In the present study, the prevalence of NAFLD in patients with T2DM was estimated at 80%, while similar studies have reported prevalence rates of 21% to 75%.[10]

Besides the known risk factors for NAFLD, some other risk factors have been also introduced, such as hypothyroidism. The present results are consistent with the findings of some similar previous studies. In a large population-based study of 9500 participants, it was found that both overt and SCH were significantly associated with NAFLD, even after adjustments for age, sex, BMI, blood pressure, diabetes, lipids, smoking, and alcohol consumption.[27] Similar results were reported in a prospective case-control study of 327 patients with SCH and 327 euthyroid individuals (matched in terms of age, sex, and BMI).[28] Moreover, in a study of 232 euthyroid patients with T2DM, it was found that in the presence of normal TSH, a decrease in the level of free thyroid hormones was significantly associated with an increase in the intrahepatic fat content, based on magnetic resonance spectroscopy.[29]

**Table 2: Univariate logistic regression analyses of nonalcoholic fatty liver disease in participants**

| Variable | OR (95% CI) | *P* |
|---|---|---|
| Age | 1.05 (1.03-1.06) | <0.001 |
| Sex, female | 1.14 (0.812-1.59) | 0.454 |
| Diabetes duration | 2.20 (1.93-2.51) | <0.001 |
| Positive family history of DM | 2.85 (2.04-3.99) | <0.001 |
| Use of antihypertensive drug | 2.14 (1.54-2.97) | <0.001 |
| Use of statin | 1.11 (0.717-1.73) | 0.631 |
| Use of OHA | 0.465 (0.327-0.662) | <0.001 |
| Use of insulin | 5.35 (3.29-8.71) | 0.001 |
| BMI | 1.16 (1.10-1.23) | <0.001 |
| Systolic BP | 1.01 (0.997-1.03) | 0.124 |
| Diastolic BP | 0.997 (0.980-1.01) | 0.696 |
| Hypertension, BP ≥140/90 | 1.01 (0.729-1.40) | 0.956 |
| Fasting plasma glucose | 1.02 (1.02-1.03) | <0.001 |
| HbA1c | 8.13 (5.89-11.22) | <0.001 |
| Total cholesterol | 1.01 (1.0-1.01) | <0.001 |
| Triglycerides | 1.0 (0.998-1.0) | 0.410 |
| LDL cholesterol | 1.01 (1.0-1.01) | <0.001 |
| HDL cholesterol | 1.02 (1.01-1.04) | 0.007 |
| VLDL | 1.0 (0.993-1.02) | 0.373 |
| BUN | 1.0 (0.956-1.05) | 0.959 |
| Creatinine | 1.11 (0.435-2.83) | 0.828 |
| ALT | 1.11 (1.09-1.14) | <0.001 |
| AST | 1.11 (1.08-1.13) | <0.001 |
| ALKPH | 1.0 (0.996-1.01) | 0.315 |
| FT3 | 0.962 (0.770-1.20) | 0.734 |
| FT4 | 0.70 (0.385-1.27) | 0.241 |
| TSH | 1.05 (1.02-1.09) | 0.039 |
| SCH | 2.03 (1.06-3.89) | 0.032 |
| Overt hypothyroidism | 2.42 (0.729-8.03) | 0.149 |
| Anti-TPO titer | 1.01 (0.999-1.01) | 0.124 |
| Anti-Tg titer | 0.995 (0.989-1.0) | 0.053 |

OR: Odds ratio, CI: Confidence interval, ALT: Alanine transaminase, AST: Aspartate transaminase, AlkPH: Alkaline phosphatase, BMI: Body mass index, BP: blood pressure, DM: Diabetes mellitus, FT3: Free triiodothyronine, FT4: free thyroxine, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very-LDL, TSH: Thyroid-stimulating hormone, OHA: Oral hypoglycemic agents, SCH: Subclinical hypothyroidism, BUN: Blood urea nitrogen, TPO: Thyroid peroxidase, Tg: Thyroglobulin

**Table 3: Multivariate logistic regression analyses of nonalcoholic fatty liver disease**

| Independent variable | OR (95% CI) | *P* |
|---|---|---|
| Model 1 | | |
| Age, years | 1.05 (1.03-1.07) | <0.001 |
| Sex, female | 1.05 (0.739-1.50) | 0.780 |
| BMI | 1.18 (1.11-1.25) | <0.001 |
| SCH, yes | 2.32 (1.19-4.54) | 0.014 |
| Hypothyroid, yes | 2.29 (0.673-7.79) | 0.185 |
| Model 2 | | |
| Family history of DM | 2.33 (1.52-3.58) | <0.001 |
| DM duration | 2.23 (1.95-2.55) | <0.001 |
| SCH, yes | 2.10 (0.927-4.77) | 0.075 |
| Hypothyroid, yes | 4.90 (1.26-19.05) | 0.022 |
| Model 3 | | |
| Age, years | 1.07 (1.04-1.10) | <0.001 |
| BMI | 1.22 (1.12-1.32) | <0.001 |
| Family history of DM | 2.05 (1.29-3.26) | <0.001 |
| DM duration | 2.37 (2.04-2.74) | <0.001 |
| Use of antihypertensive drug | 2.87 (1.82-4.54) | <0.001 |
| SCH, yes | 2.14 (0.861-5.32) | 0.101 |
| Hypothyroid, yes | 3.35 (0.827-13.59) | 0.090 |

OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, DM: Diabetes mellitus, SCH: Subclinical hypothyroidism

Conversely, our findings are inconsistent with some previous studies. According to a large longitudinal cohort study of 18,500 people in South Korea, it was shown that neither overt hypothyroidism nor SCH was associated with an increased risk of NAFLD.[30] In our study, there was a strong association between SCH and NAFLD, while no association was found between overt hypothyroidism and NAFLD, which may be due to the lower prevalence of overt hypothyroidism in the study population. This study does not have enough power to show this association. The discrepancy between these observational studies can be attributed to differences in the exact criteria for diagnosis of hypothyroidism and NAFLD, characteristics of study participants, and study design. Therefore, prospective studies with large sample sizes, based on accurate NAFLD and hypothyroidism diagnostic criteria, are needed to investigate the association between hypothyroidism and NAFLD and to determine its pathogenesis.

It is not yet known exactly by what biological mechanism patients with hypothyroidism are more prone to fatty liver disease, but the mechanisms that have been proposed include insulin resistance, metabolic syndrome, dyslipidemia, a direct effect of TSH on hepatocytes, and oxidative stress.[31-33]

Patients with clinical and SCH often have manifestations of metabolic syndrome, including prediabetes, dyslipidemia, weight gain, and obesity.[34] On the other hand, NAFLD is associated with the impairment of glucose metabolism, lipid metabolism, and energy homeostasis.[35] Therefore, there are similarities between hypothyroidism and NAFLD. Experimental studies have shown that overweight or obesity alone can prevent the effects of thyroid hormones on the liver and may have some significant effects on glucose metabolism, as well as fat and energy homeostasis in these patients.[31-33]

Moreover, hypothyroidism is associated with atherogenic dyslipidemia, involving decreased serum high-density lipoprotein-cholesterol, hypertriglyceridemia, elevated serum low-density lipoprotein (LDL)-cholesterol and very LDL-cholesterol levels and increased apolipoprotein B;[36] therefore, hypothyroidism may exacerbate dyslipidemia in NAFLD patients.[33] On the other hand, hypothyroidism is often associated with insulin resistance, which can exacerbate fat metabolism disorders.[31,33] Previous research shows that high levels of adipokines, such as visfatin, leptin, interleukin-1, and tumor necrosis factor-α, besides increased oxidative stress in hypothyroidism, may contribute to insulin resistance

in these patients.[31-33] Changes in the serum levels of some specific cytokines, increase in lipid peroxidation and oxidative stress are common in patients with hypothyroidism,[31,33] and NAFLD,[36] and may explain the common pathophysiological mechanism underlying the association between hypothyroidism and NAFLD.

Besides the changes in glucose and lipid metabolism in the liver due to decreased thyroid hormones in hypothyroidism, the findings of epidemiological studies, indicating that SCH increases the risk of NAFLD, may be explained by the fact that the elevated serum concentration of TSH can lead to the development and progression of NAFLD by stimulating hepatic lipogenesis.[31-33] The biological activity of TSH is exerted by binding to TSH receptors, which can be found in some extrathyroid tissues, such as hepatocytes as well as the thyroid cell membranes.[33] Interestingly, an increase in TSH following an increase in the triglyceride content of hepatocytes can directly induce NAFLD in patients with hypothyroidism.[31,33]

The molecular mechanism proposed for hepatic steatosis in hypothyroidism is increased peroxisome proliferator-activated receptor-α pathway activity, protein kinase A, and increased cyclic adenosine monophosphate (AMP) that activate the hepatic sterol regulatory element-binding protein 1 (SREBP-1). On the other hand, a decrease in the AMP-activated protein kinase leads to an increase in gene expression, which results in an increase in hepatic steatogenesis.[32,33,37]

There are some limitations in the present study. First, this was a cross-sectional study that could not indicate a cause-and-effect relationship between hypothyroidism and NAFLD in patients with type 2 diabetes. Second, we used ultrasound to diagnose NAFLD, not liver biopsy. It should be noted that liver biopsy is recognized as the gold standard for diagnosing NAFLD and differentiating it from NASH. However, considering the invasiveness of liver biopsy, we used ultrasound to diagnose NAFLD, similar to most previous observational studies. Overall, the sensitivity of medical ultrasound to diagnose steatosis is estimated at 60% to 94%, depending on the degree of steatosis.[38]

On the other hand, this is one of the first studies to investigate the association between hypothyroidism and NAFLD in patients with type 2 diabetes. Furthermore, fatty liver grading was performed by an experienced radiologist, and other causes of elevated liver enzymes were excluded from this study. This study also had an acceptable sample size.

## Conclusion

The results of the present study, investigating the relationship between hypothyroidism and NAFLD in patients with T2DM, showed that NAFLD is extremely common in patients with type 2 diabetes and that the relationship between hypothyroidism and NAFLD is independent of other risk factors. However, large prospective studies with larger sample sizes and precise definitions of hypothyroidism and NAFLD are necessary to investigate the role of hypothyroidism risk factors in the development of NAFLD in patients with T2DM.

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### Conflicts of interest

There are no conflicts of interest.

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