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ORIGINAL RESEARCH

Association of Euthyroid Thyroid Hormone Levels with Hepatic Steatosis in Patients with Nonalcoholic Fatty Liver Disease

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Purpose: The frequency of nonalcolic fatty liver disease (NAFLD), a major health issue that affects people all over the world, has been rising recently. Numerous studies have demonstrated the tight connection between NAFLD and thyroid function. In this study, we aimed to evaluate the relationship between thyroid function tests and the degree of liver steatosis in patients with biopsy proven NAFLD.

Patients and Methods: We retrospectively evaluated data of living donor applicants who received liver biopsies. Three hundred sixty seven patients were included in the study. According to the liver biopsy results, the patients were divided into two groups; 227 patients biopsy-proven NAFLD and 145 control subjects without NAFLD. Demographic, anthropometric and laboratory parameters were compared between two groups.

Results: All groups thyroid function tests fall within the normal range. However, in patients with NAFLD, serum FT3 and FT4 levels were significantly higher than control group. In addition negative relationship was found between the levels of FT3, FT4, and the stage of NAFLD. In patients with NAFLD, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, triglyceride, total cholesterol levels, homeostasis model assessment of insulin resistance (HOMA-IR), body mass index were significantly high.

Conclusion: In this retrospective study, we showed that in patients with NAFLD, serum FT3 and FT4 levels were significantly lower than the control group. Our findings support that low levels of serum FT3 and FT4 might be a risk factor for liver steatosis in euthyroid patients with NAFLD.

Keywords: nonalcolic fatty liver disease, thyroid function, hepatic steatosis

Introduction

An urgent public health issue called nonalcolic fatty liver disease (NAFLD) can result in cirrhosis, hepatocellular cancer, and chronic liver disease, affects around 30% of the population and is continuously becoming more prevalent.[1,2] NAFLD is the primary contributor of abnormal liver tests, according to population-based research.[3] The rising prevalence of diabetes, obesity, and other metabolic risk factors are the main causes of nonalcolic steatohepatitis (NASH).[4] Some studies have shown that the prevalence of NAFLD in patients with diabetes and obesity reaches 80%.[5,6] According to the American Association for the Study of Liver Diseases, numerous conditions, including hypothyroidism, have been reported to increase the risk of NAFLD/NASH.[7] The thyroid and NAFLD have a close relationship, according to numerous clinical investigations.[8] The regulation of hepatic lipid, cholesterol, and glucose metabolism is greatly influenced by thyroid hormones. Ampirde thyroid hormone signaling decreases the liver's ability to use fatty acids, which causes the fatty acids to be esterified and build up as triglycerides.[9,10] As a result, abnormal thyroid hormone levels predispose to NAFLD/NASH.[11] However, the role of FT3 and FT4 levels within the normal range in NAFLD

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patients remains unclear. Our study's objective was to assess how thyroid hormone levels affected the emergence of NAFLD.

Materials and Method

In this study, we retrospectively assessed the data of living liver donor candidates who underwent liver biopsies between January 2010 and January 2019. Donor candidates who underwent biopsy due to the finding of moderate to severe liver steatosis on imaging and whose steatosis was histopathologically verified were included in the study. The study was approved by the Ethics Committee of Demiroglu Bilim University (No: 20191603) and performed in accordance with National Institute of Health guidelines and conducted in accordance with good clinical practice principles and the Declaration of Helsinki. Since the patients had given systematic consent upon applying to the physician, it was deemed unnecessary to obtain written consent with an ethics committee decision. All of the patients had imaging procedures, such as abdominal ultrasonography, computed tomography, and magnetic resonance, prior to liver biopsy. A liver biopsy was done when imaging techniques revealed moderate to severe fatty liver disease. The same expert liver pathologist assessed each liver biopsy sample and categorized them all using the NASH Clinical Research Network.[12] Three hundred and seventy two patients with liver biopsy-proven NAFLD or those without NAFLD based on histopathological investigations made up the study population (Figure 1).

Male or female participants between the ages of 18 and 65 were required to meet the following criteria: normal thyroid function, non-obesity (body mass index (BMI) <30), lack of history of binge drinking (ethyl alcohol consumption is greater than 30 grams for men and 20 grams for women per day), and the hepatitis B surface antigen and hepatitis C virus antibody have been tested negative. Patients with any thyroid diseases or using drug for these diseases, any other chronic liver diseases, diabetes mellitus, heart failure, asthma, hemathologic problems, acute or chronic infections, a history of malignancy, drug-associated fatty liver, or refusal to participate in the study were the exclusion criteria. Data on anthropometric traits (such as age, gender, and BMI) and biochemistry were gathered. Total cholesterol (TC), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin (TB), albumin, free triiodothyronine (FT4), free thyroxine (FT3), thyroid-stimulating hormone (TSH), glucose, and insulin were all included as biochemical parameters. Formula: (22.5

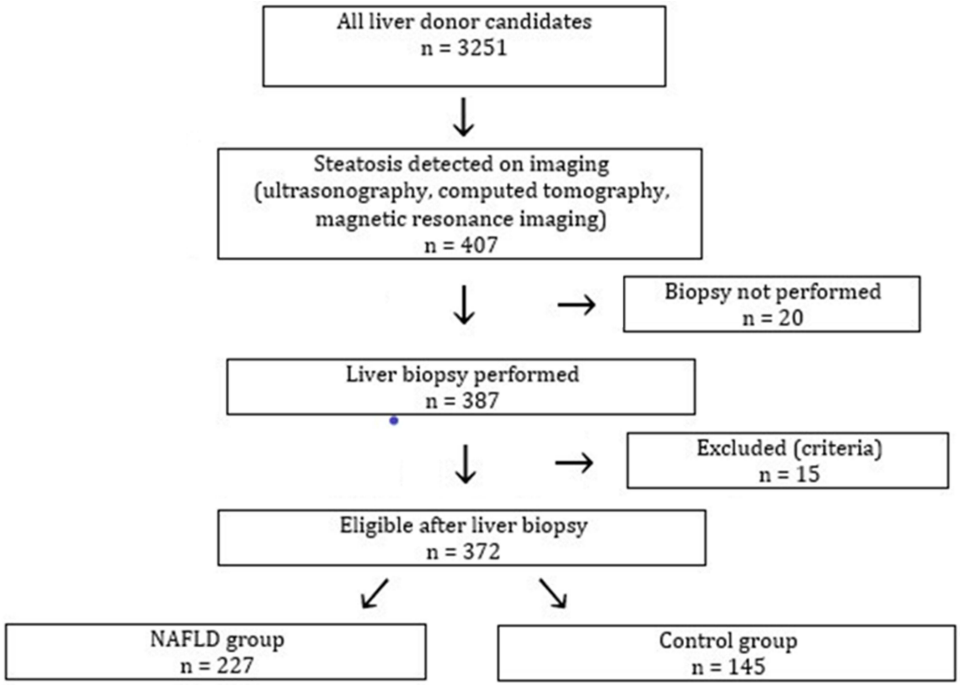

Figure 1 Flowchart of the number of patients included in the study.

fasting insulin [mU/mL] glucose [mmol/L]) was used to calculate the insulin resistance score (HOMA-IR). Insulin resistance was identified using HOMA-IR 2.5.[13] Age, gender, BMI, the levels of ALT (IU/L), AST (IU/L), ALP (U/L), GGT (U/L), total biluribin (mg/dl), albumin (g/dl), triglyceride (mg/dL), and total cholesterol (mg/dl) were compared statistically between the NAFLD and control groups. Additionally, HOMA-IR, FT3, and FT4 levels were compared statistically between the NAFLD and control groups.

The study used SPSS 21.0 for statistical analysis, examining mean values, standard deviations, ranges, and percentages. Normality was assessed using Kolmogorov–Smirnov test, Mann Whitney *U*-test, and $\chi 2$ test for categorical parameters. Spearman coefficient was used for bivariate correlation.

Results

There were 372 patients overall (145 in the control group and 227 in the NAFLD group). The patients median (IQR) ages were 34.00 (26.00–46.00) years for NAFLD and 34.00 (27.00–46.00) years for controls. In both the NAFLD and control groups, each patient had a BMI below 30. The median body mass index was 27.10 (24.50–30.00) in the NAFLD group and 24.1 (22.50–27.00) in the control group, and it was statistically higher in the NAFLD group ($p < 0.001$). HOMA-IR, ALT, AST, ALP, triglyceride, and total cholesterol levels were significantly higher in the NAFLD group compared to the control group ($p < 0.05$). However, there were no statistically significant differences in GGT, total biluribin, and albumin levels between the two groups ($p > 0.05$) (Table 1).

Table 1 Clinical, Laboratory, and Demographic Data of NAFLD Patients Compared to Controls

	NAFLD (n = 227) Median (IQR)	Control (n = 145) Median (IQR)	P*
Age	34.00 (26.00–46.00)	34.00 (27.00–46.00)	0.84
Gender (female/male, n)	89/138	62/83	0.41**
Body mass index (kg/m2)	27.10 (24.50–30.00)	24.1 (22.50–27.00)	**<0.001**
ALT (IU/L)	19.00 (14.00–26.00)	16.00 (12.00–22.00)	**0.001**
AST (IU/L)	18.00 (14.00–21.00)	16.0 (13.75–19.00)	**0.021**
ALP (U/L)	71.00 (55.00–86.00)	64.00 (44.30–76.25)	**0.008**
GGT (U/L)	17.00 (11.00–25.00)	14.00 (10.00–22.00)	0.12
Total Biluribin (mg/dl)	0.52 (0.40–0.70)	0.50 (0.40–0.72)	0.16
Albumin (g/dll)	4.70 (4.50–4.90)	4.70 (4.40–4.80)	0.22
Triglyceride (mg/dL)	103.00 (70.00–151.00)	84.00 (62.00–119.00)	**0.03**
Total cholesterol (mg/dl)	183.00 (158.00–214.00)	171.00 (155.00–204.00)	**0.03**
HOMA-IR	2.37 (1.63–3.02)	1.52 (1.15–2.04)	**<0.001**
FT3	3.86 (3.36–5.07)	4.81 (4.10–5.40)	**<0.001**
FT4	4.31 (1.36–15.37)	15.20 (12.45–17.30)	**<0.001**
TSH	1.80 (1.23–2.44)	1.70 (1.19–2.65)	0.56

Notes: Statistically significant variables were identified using in the bolded values Mann–Whitney *U*-Test and the $\chi 2$ Test ($p < 0.05$). *Mann–Whitney Test, **χ^2 Test.

Abbreiations: ALT, Alanine aminotransferase; AST, Aspartat aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transferase; HOMA-IR, Homeostatic model assessment insulin resistance; FT3, Free triiodothyronine; FT4, Free thyroxine; TSH, Thyroid-stimulating hormone.

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Table 2 Correlation Analysis Between Thyroid Hormones and NAFLD Stage

	r	P*
TSH	0.072	0.350
FT3	−0.276	**<0.001**
FT4	−0.206	**<0.001**

Notes: Statistically significant variables were identified using in the bolded values Spearman Correlation ($p < 0.05$). *Spearman Correlation.
Abbreviations: TSH, Thyroid-stimulating hormone; FT3, Free triiodothyronine; FT4, Free thyroxine.

Additionally, FT3, and FT4 levels were significantly lower in the NAFLD group compared to the control group ($p < 0.001$), while there was no statistically significant difference in TSH levels between the two groups ($p > 0.05$) (Table 1).

NAFLD stage was observed to have negative relationship between the values of serum FT3, and FT4 (FT3: r = −0.276, P 0.001; FT4: r = −0.207, P 0.001). TSH levels and NAFLD stage did not correlate (TSH: r = 0.072, P = 0.350) (Table 2).

The ROC curve for FT4 and FT3 in estimating NAFLD was constructed, and the area under the curve of FT4 0.681 (95% CI = 0.624 to 0.737, P < 0.001) and FT3 0.645 (95% CI = 0.625 to 0.739, P < 0.001) were found. The cut-off values of FT4 were 13.92 mg/dl with sensitivity of 65.6% and specificity of 65.8%. The cut-off values of FT3 were 4.58 mg/dl with sensitivity of 63.6% and specificity of 62.0% (Figure 2).

Discussion

In our study, we found that in patients with NAFLD, serum FT3 and FT4 levels were significantly lower than the control group. Moreover, stage of NAFLD was negatively correlated with serum FT3 and FT4 levels. In addition, serum triglyceride, total cholesterol levels and HOMA-IR were both higher in patients with NAFLD. However, serum TSH levels were not statistically different between NAFLD and control group.

It is suggested that Non-Alcoholic Fatty Liver Disease (NAFLD), which underlies diseases such as increasing obesity and insulin resistance, may be associated with thyroid dysfunction.[14–17] Despite the physiological mechanism that appears to underlie NAFLD development, it is still unknown how thyroid dysfunction and the metabolic syndrome are related to NAFLD. Thyroid hormones play a critical role in regulating metabolism, particularly lipid metabolism in the liver. The patients with subclinical and clinical hypothyroidism have a considerably increased chance of developing NAFLD than people with euthyroidism. Patients with hypothyroidism have elevated triglyceride and LDL cholesterol levels due to decreased plasma lipoprotein lipase activity. According to these mechanism, fatty accumulation and cellular oxidative stress might be associated with the development of NAFLD.[18] In another study, it was discovered that people with euthyroidism had considerably greater FT3 and lower FT4 levels, which increased their chance of developing NAFLD.[19] Liu et al was showed that the development of NAFLD and FT3, TSH levels were found to be correlated, whereas FT4 levels were not[20] Also in the other studies showed that the FT3/FT4 ratio, HOMA-IR, uric acid and waist circumference width are both as risk factors for the onset of NAFLD.[21,22] Significantly different from these studies, in our study NASH was diagnosed histopathologically. Moreover, we investigated only euthyroid patients with NASH. Therefore, patient selection is one of the strongest aspect of our study and provided a more accurate interpretation of the results.

Some researchers have shown that TH and THR agonist therapies effectively lowered serum levels of triglycerides and free fatty acids and decreased the stage of hepatic stetaosis.[23–25] Levothyroxine treatment is effective in terms of lowering liver enzymes and hepatic fat content by thyroid receptor in individuals with hypothyroidism and NAFLD.[26] It is interesting to note

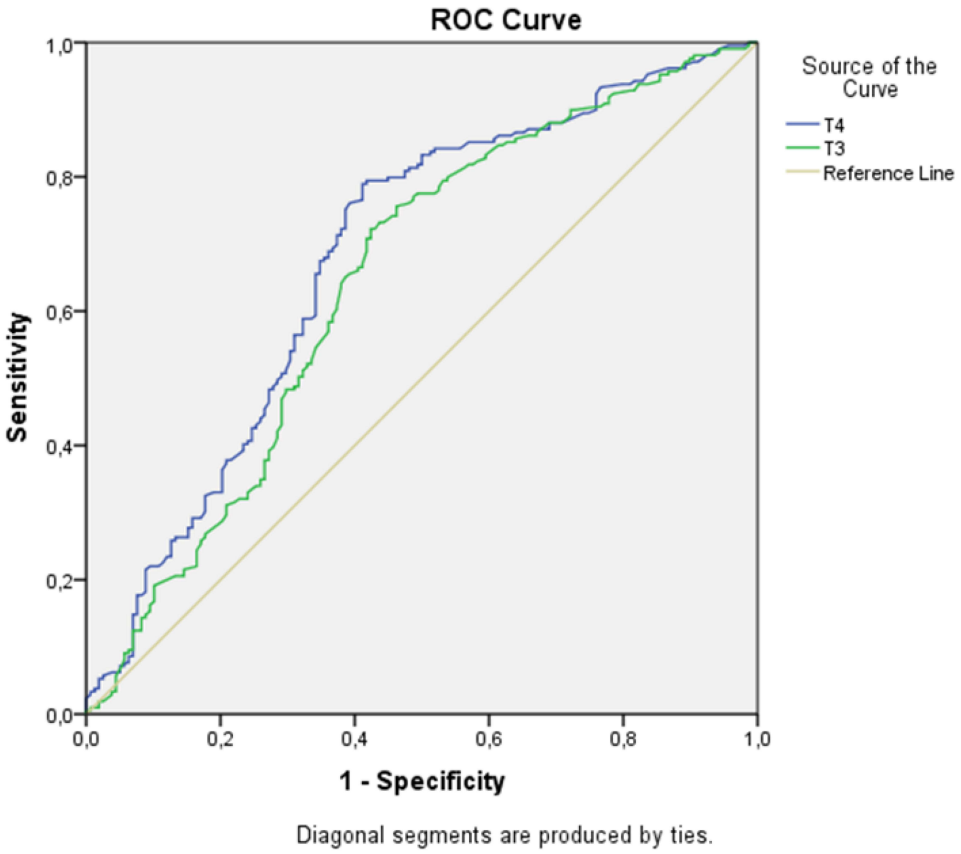

Figure 2 Curve for the prediction of NAFLD by FT4 and FT3. The ROC curve for FT4 and FT3 in estimating NAFLD was constructed, and the area under the curve of FT4 0.681 (95% CI = 0.624 to 0.737, P < 0.001) and FT3 0.645 (95% CI = 0.625 to 0.739, P < 0.001) were found. The cut-off values of FT4 were 13.92 mg/dl with sensitivity of 65.6% and specificity of 65.8%. The cut-off values of FT3 were 4.58 mg/dl with sensitivity of 63.6% and specificity of 62.0%.

that this effect was also seen in people who were euthyroid in a study on animals.[27] This study differs from other studies by demonstrating that NAFLD is a treatable and reversible condition with a specific therapeutic intervention.[28,29] Even while TSH and TH levels were within the normal range in NAFLD patients with the disease verified by biopsy, the NAFLD group in our study had considerably lower FT4 and FT3 values. The most significant finding of our study is that, despite normal TSH levels, lower FT3 and FT4 may be related with fatty liver. In addition, it may be inferred that TH and TRH agonists can be utilized to treat hepatic steatosis, and it would be beneficial to check not just TSH but also FT3 and FT4 levels when monitoring people with NAFLD and hypothyroidism.

Our study has some limitations. This study includes only living donor candidates who had moderate-severe steatosis on who underwent liver biopsies. This might not be representative of the general population with NAFLD. Secondly, it is a retrospective study.

Conclusion

Low levels of serum FT3 and FT4 might be a risk factor for liver steatosis in euthyroid patients with NAFLD. Clinicians may concentrate on the involvement of thyroid functions in the development of liver fibrosis from fatty liver disease. In the future, the relationship between thyroid disease and fatty liver can be more clearly revealed with prospective studies involving a larger number of patients.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

AO: Methodology, Validation, Funding acquisition, Writing – review and editing

BCT: Resources, Supervision, Project Administration, Methodology

EA: Methodology

TS: Investigation, Writing – original draft

EK: Software

FT: Conceptualization, Formal analysis, Project Administration, Writing – original draft. All authors took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflicts of interest in this study.

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