

FT3/FT4 ratio predicts non-alcoholic fatty liver disease independent of metabolic parameters in patients with euthyroidism and hypothyroidism

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OBJECTIVE: This study was performed to evaluate the effects of metabolic parameters and thyroid dysfunction on the development of non-alcoholic fatty liver disease (NAFLD).

METHODS: The current study evaluated a total of 115 patients, 75 female and 40 male. Physical examination and anthropometric measurements were applied to all participants. Hypothyroidism was considered at a thyroid stimulating hormone level ≥ 4.1 mIU/L. Patients with euthyroidism and patients with hypothyroidism were compared. Abdominal ultrasonography was used to diagnose non-alcoholic fatty liver disease. The participants were further compared with regard to the presence of non-alcoholic fatty liver disease. Logistic regression modeling was performed to identify the relationship between non-alcoholic fatty liver disease and independent variables, such as metabolic parameters and insulin resistance.

RESULTS: Non-alcoholic fatty liver disease was identified in 69 patients. The mean waist circumference, body mass index, fasting plasma insulin, HOMA-IR ($p < 0.001$) and FT₃/FT₄ ratio ($p = 0.01$) values were significantly higher in the patients with NAFLD compared to those without it. Multivariate regression analysis revealed that FT₃/FT₄ ratio, waist circumference and insulin resistance were independent risk factors for non-alcoholic fatty liver disease.

CONCLUSION: Insulin resistance, enlarged waist circumference, elevated body mass index, higher FT₃/FT₄ ratio and hypertriglyceridemia are independent risk factors for NAFLD, whereas hypothyroidism is not directly related to the condition.

KEYWORDS: FT₃/FT₄ ratio; Insulin resistance; Non-alcoholic fatty liver disease; Hypothyroidism; Euthyroidism.

Gökmen FY, Ahabab S, Ataoğlu HE, Türker BÇ, Çetin F, Türker F, et al. FT3/FT4 ratio predicts non-alcoholic fatty liver disease independent of metabolic parameters in patients with euthyroidism and hypothyroidism. Clinics. 2016;71(4):221-225

Received for publication on November 12, 2015; First review completed on December 18, 2015; Accepted for publication on February 2, 2016

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a pathological spectrum of chronic liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) with inflammation, has a high risk for progression to cirrhosis (1-3). NAFLD is a growing diagnosis and the most commonly encountered liver pathology in clinical practice (4,5). NAFLD is commonly asymptomatic and discovered incidentally. The diagnosis of NAFLD is based on exclusion criteria, such as alcohol consumption (more than 20 g/day), autoimmune liver disease, viral hepatitis infection, hemochromatosis, Wilson's disease, and drug consumption. All of these must be excluded before

considering NAFLD (6). The prevalence of NAFLD is associated with abdominal obesity, diabetes mellitus and other metabolic risk factors (7, 8). NAFLD is a strong determinant for the development of metabolic syndrome, which has potentially relevant clinical implications with regard to diagnosis, prevention and treatment (9,10). Moreover, metabolic syndrome, insulin resistance, diabetes, obesity and mixed hyperlipidemia are major metabolic risk factors for NAFLD (11). Because of the hyperinsulinism, pro-thrombotic potential, and subclinical inflammation associated with NAFLD, patients with this condition are at increased risk for cardiovascular mortality (12). In addition, the correction of insulin resistance may not be sufficient to successfully treat NASH in the majority of patients, conflicting with previous studies on NAFLD pathogenesis (13).

The thyroid gland is significantly involved in lipid and carbohydrate metabolism, regulation of body weight and adipogenesis (14). Recent studies have suggested that thyroid dysfunction may play a role in NAFLD. Subclinical hypothyroidism is associated with metabolic syndrome, cardiovascular mortality, and disturbance of lipid metabolism

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No potential conflict of interest was reported.

DOI: 10.6061/clinics/2016/04/08



(15, 16). Thyroid dysfunctions in the form of overt or subclinical hypothyroidism are prevalent among patients with NAFLD/ NASH (17).

NAFLD is a risk factor for the development of type 2 diabetes, which is, in turn, a major contributor to progressive liver disease (18). In contrast, chronic infections, such as that caused by hepatitis C virus, have an association with the development of NAFLD, insulin resistance and metabolic parameters (19). The identification of risk factors is essential for preventing NAFLD. Therefore, in the current study, we evaluated the effects of metabolic parameters and thyroid dysfunction on the development of NAFLD.

METHODS

Participants

The current study evaluated 115 individuals, 75 female and 40 male, who were admitted to the Haseki Training and Research Hospital's outpatient clinic for routine care from July 2014 through January 2015. Anthropometric measurements were taken, and thyroid function tests were performed. Hypothyroidism was described according to Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association (20). Euthyroidism (ET) was described as a thyroid stimulating hormone (TSH) level of 0.5–4 mIU/L and no history of chronic disease. Hypothyroidism (HT) was described as a TSH level of ≥ 4.1 mIU/L. Patients meeting the following criteria were excluded: chronic liver and kidney disease, viral hepatitis, diabetes mellitus, undergoing corticosteroid treatment, malignancy, alcohol consumption greater than 20 g/d, and pregnancy. Informed consent was obtained from all participants. The study protocol was approved by the local ethics committee of Istanbul Haseki Training and Research Hospital.

Measurements

All patients underwent physical examination. Blood pressure was measured using a mercury sphygmomanometer. Height (m), weight (kg), and waist circumference (WC) were also measured. WC was measured between the lowest rib and the crista iliaca superior. Body mass index (BMI) was calculated as weight (kg)/height (m)². Plasma TSH, free T3 (FT3), free T4 (FT4), alanine aminotransferase (ALT), aspartate alanine aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), glucose, insulin, total cholesterol, triglycerides, HDL and LDL cholesterol, uric acid and creatinine were measured after an 8-hour fast using an Abbot Architect Analyzer System (IL, USA). The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using the following formula: fasting blood glucose (mmol/l) \times [insulin (mU/l)/22.5].

Abdominal Ultrasonography

The presence of qualitative steatosis was determined using a standard 2D abdominal ultrasonography (USG). All participants underwent abdominal USG (Philips Active Array, 2D-Clearvue 550 device). NAFLD was characterized by the presence of hepatic brightness, hepatorenal echo contrast, deep attenuation and vascular blurring on USG (21).

Statistical Analysis

Numeric values were expressed as the mean \pm standard deviation. Statistical analysis was performed using SPSS 16.0

for Windows. The Kolmogorov-Smirnov Z test was used to determine the distributions of variables. Regular variances were assessed using a t test, and irregular variables were assessed using the Mann-Whitney U test. Logistic regression modeling was performed to assess independent risk factors of NAFLD. A *p* value <0.05 was considered statistically significant.

RESULTS

In total, 115 participants were enrolled in this study: 54 presented with HT (F/M, 39/15) and 61 presented with ET (F/M, 36/25). The anthropometric and metabolic parameters of the patients with ET and HT were compared and are presented in Table 1. No significant differences were found in gender, age, mean BMI, systolic BP, diastolic BP, ALT, AST, ALP, GGT, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, uric acid, fasting glucose, fasting insulin, HOMA-IR, NAFLD or ferritin in the subjects with ET (30.28 ± 5.19) versus those with HT. The mean FT₃/FT₄ ratio of the patients with HT was higher than that of the subjects with ET, at 4.61 ± 1.38 versus 3.63 ± 0.68 , respectively ($p < 0.001$). There was no difference in NAFLD status between the patients with ET and those with HT. NAFLD was identified in 69 of total 115 subjects: 33 patients with ET and 36 patients with HT.

The participants were compared according to the presence of NAFLD, and the parameters of the comparison are presented in Table 2. The mean WC, BMI, systolic and diastolic blood pressure values were statistically higher in the patients with NAFLD than those without the condition ($p < 0.001$, <0.001 , 0.049 and 0.003, respectively). Additionally, the patients with NAFLD had significantly higher triglyceride levels (164.96 ± 77.27 mg/dl) than those without NAFLD (112.61 ± 89.80 mg/dl) ($p = 0.001$). The patients with NAFLD also had significantly higher uric acid, fasting insulin, HOMA-IR and FT₃/FT₄ ratios.

The subjects with ET or HT in this study were also compared according to the presence or absence of NAFLD, as shown in Table 3. The patients with ET and NAFLD had higher WC ($p = 0.001$), total cholesterol ($p = 0.042$), triglycerides ($p < 0.001$), fasting insulin ($p < 0.001$) and HOMA-IR ($p = 0.001$) levels compared to the subjects with ET without NAFLD. While the FT₄ levels in the patients with ET and NAFLD were lower than those in the patients with ET without NAFLD, the patients with ET and NAFLD had increased FT₃/FT₄ ratios, as well as uric acid, fasting insulin and HOMA-IR levels, compared to the patients with ET without NAFLD ($p = 0.01$).

The patients with HT and NAFLD had lower FT₄ levels compared to the patients with HT without NAFLD (Table 3). Additionally, the patients with HT and NAFLD had higher WC, total cholesterol, triglycerides, fasting insulin and HOMA-IR levels than the patients with HT without NAFLD.

Logistic regression analysis was performed to delineate the nature of the relationships that exist between NAFLD, metabolic parameters and insulin resistance as independent variables (Table 4). WC (OR: 1.087, $p = 0.01$), HOMA-IR (OR: 2.978, $p = 0.005$), and FT₃/FT₄ ratio (OR: 1.834, $p = 0.02$) were independent risk factors for NAFLD in all study participants. Additional regression analysis was performed to evaluate HT patients with NAFLD with respect to metabolic parameters (Table 5). WC (OR: 1.189, $p = 0.02$), triglycerides (OR: 1.031, $p = 0.04$), uric acid (OR: 0.318, $p = 0.03$), HOMA-IR

**Table 1** - Parameters compared between patients with euthyroidism and those with hypothyroidism.

Parameters	Patients with ET (n:61)	Patients with HT (n:54)	p value
Gender, male %	41%	27.8%	0.138
Age	48.44 ± 13.19	47.98 ± 11.87	0.845
WC (cm)	94.34 ± 11.00	92.11 ± 12.59	0.312
BMI	30.28 ± 5.19	30.05 ± 6.54	0.831
Systolic BP (mm/Hg)	123.20 ± 18.14	118.24 ± 18.14	0.162
Diastolic BP (mm/Hg)	77.05 ± 11.45	73.61 ± 11.30	0.109
TSH (mIU/L)	1.63 ± 0.91	22.48 ± 15.91	<0.001
FT ₃ (pg/ml)	0.86 ± 0.11	0.62 ± 0.17	<0.001
FT ₄ (ng/dl)	3.07 ± 0.44	2.66 ± 0.37	<0.001
FT ₃ /FT ₄ ratio	3.63 ± 0.68	4.61 ± 1.48	<0.001
ALT (mg/dl)	24.64 ± 15.67	21.76 ± 11.53	0.261
AST (mg/dl)	24.98 ± 8.14	24.37 ± 9.87	0.719
ALP (mg/dl)	79.96 ± 24.51	86.11 ± 28.26	0.22
GGT (mg/dl)	28.96 ± 20.42	28.40 ± 25.46	0.896
Total cholesterol (mg/dl)	203.77 ± 48.74	208.19 ± 43.87	0.613
Triglycerides (mg/dl)	131.11 ± 88.01	158.59 ± 82.20	0.088
LDL cholesterol (mg/dl)	127.92 ± 39.25	126.83 ± 36.89	0.879
HDL cholesterol (mg/dl)	51.04 ± 9.97	49.66 ± 11.05	0.484
Uric acid (mg/dl)	5.10 ± 1.40	4.96 ± 1.54	0.705
Fasting glucose (mg/dl)	99.69 ± 21.04	103.41 ± 39.09	0.52
Fasting insulin (mIU/ml)	8.83 ± 5.23	8.59 ± 4.87	0.804
HOMA-IR	2.15 ± 1.32	2.11 ± 1.26	0.894
NAFLD (n - %)	36 - 59%	33 - 64%	0.819
Ferritin (ng/ml)	61.79 ± 91.20	29.12 ± 18.77	0.099

Euthyroidism, hypothyroidism n: number of patients. WC: waist circumference. BMI: body mass index. BP: blood pressure. ALT: alanine aminotransferase. AST: aspartate aminotransferase. ALP: alkaline phosphatase. GGT: gamma glutamyl transferase. HOMA-IR: homeostasis model assessment for insulin resistance. NAFLD: non-alcoholic fatty liver disease.

(OR: 8.042, $p=0.02$) and FT₃/FT₄ ratio (OR: 3.540, $p=0.01$) were independent risk factors for NAFLD in patients with HT.

DISCUSSION

NAFLD is a burgeoning health problem and is currently recognized as the most common metabolic liver disease. Insulin resistance and obesity contribute to the development of NAFLD, which has become the most prevalent liver disease worldwide, affecting one-third of the global adult population (22,23). NAFLD can lead to NASH and/or hepatocellular cancer (24).

It has been suggested that a relationship exists between NAFLD and thyroid dysfunction (25). Despite the precise physiological mechanism underlying the development of NAFLD, the relationship between NAFLD, hypothyroidism and metabolic syndrome remains unclear. Because of the importance of thyroid hormones in lipid metabolism (26), HT may result in hyperlipidemia, thereby initiating the development of NAFLD. Several studies have indicated that hypothyroidism is a risk factor for NAFLD and can result in metabolic syndrome (16,27,28). FT₃/FT₄ ratio can be considered an indicator of peripheral deiodinase activity. Bilgin and Pirgon (29) suggested that augmented conversion from FT₄ to FT₃ due to increased deiodinase activity is a compensatory mechanism for fat accumulation to improve energy expenditure. FT₃/FT₄ ratio positively correlates with HOMA-IR in patients with NAFLD (18). Moreover, positive associations have been reported between FT₃/FT₄ ratio and both waist circumference and BMI in patients with obesity (30). Ittermann and Haring (31) reported that low FT₄ levels,

but not low TSH and FT₃ levels, are associated with hepatic steatosis. In the present study, the mean BMI values in patients with ET and patients with HT were similar; however, the patients with HT had significantly higher FT₃/FT₄ ratios ($p<0.001$). The patients with NAFLD had significantly elevated BMI, WC, HOMA-IR values and FT₃/FT₄ ratios; their FT₄ levels were low, leading to increased FT₃/FT₄ ratios, but their TSH levels were unaffected. The results of this study suggest that elevated FT₃/FT₄ ratio is an independent risk factor for NAFLD.

Patients with HT have elevated triglyceride and LDL cholesterol levels due to decreased plasma lipoprotein lipase activity. Hyperlipidemia associated with fatty accumulation in the liver and cellular oxidative stress is one potential mechanism underlying the development of NAFLD (32,33). The results of the present study support this relationship, as TC ($p=0.002$), LDL cholesterol ($p=0.001$), triglyceride ($p=0.008$), and uric acid ($p=0.006$) levels were significantly higher and HDL cholesterol levels lower ($p=0.022$) in the patients with NAFLD.

The prevalence of NAFLD did not significantly differ between the ET (n:36, 59%) and HT (n:33, 64%) groups. Mazo and Lima (34) previously reported that no association exists between HT, hepatosteatosis and NASH. In addition, Eshraghian and Dabbaghmanesh (35) reported that no association exists between autoimmune thyroid disorder and elevated anti-thyroid peroxidase levels, anti-tiroglobulin levels and NAFLD. Furthermore, NAFLD was not correlated with thyroid dysfunction in the current study, as the included patients with ET and HT did not show significant differences in NAFLD prevalence, insulin resistance, abdominal obesity or BMI. The mean BMI of the patients with ET and HT was above 30, and abdominal obesity was considered to be more important to the development of NAFLD than HT. WC, FT₃/FT₄ ratio, triglyceride level and serum uric acid level were independent risk factors for

Table 2 - Comparison of study parameters between patients with and without non-alcoholic fatty liver disease.

Parameters	Without NAFLD (n:46)	With NAFLD (n:69)	p value
Gender, male %	28.3%	39.1%	0.231
Age	45.76 ± 12.30	49.87 ± 12.51	0.085
WC (cm)	86.20 ± 12.73	98.03 ± 8.27	<0.001
BMI	27.11 ± 5.29	32.21 ± 5.30	<0.001
Systolic BP (mm/Hg)	116.63 ± 17.80	123.70 ± 19.24	0.049
Diastolic BP (mm/Hg)	71.63 ± 9.95	77.97 ± 11.77	0.003
TSH (mIU/L)	9.51 ± 10.33	13.81 ± 20.30	0.138
FT ₃ (pg/ml)	2.91 ± 0.34	2.85 ± 0.52	0.479
FT ₄ (ng/dl)	0.80 ± 0.16	0.72 ± 0.20	0.025
FT ₃ /FT ₄ ratio	3.78 ± 0.82	4.32 ± 1.42	0.015
ALT (mg/dl)	18.02 ± 9.34	26.80 ± 15.32	<0.001
AST (mg/dl)	21.62 ± 5.87	26.74 ± 10.05	0.001
ALP (mg/dl)	79.46 ± 24.38	84.98 ± 27.54	0.28
GGT (mg/dl)	21.97 ± 18.29	33.15 ± 24.43	0.01
Total cholesterol (mg/dl)	189.89 ± 42.22	216.48 ± 46.23	0.002
Triglycerides (mg/dl)	112.61 ± 89.80	164.96 ± 77.27	0.001
LDL cholesterol (mg/dl)	115.93 ± 33.98	135.06 ± 38.83	0.008
HDL cholesterol (mg/dl)	53.22 ± 11.41	48.50 ± 9.41	0.022
Uric acid (mg/dl)	4.58 ± 1.46	5.36 ± 1.40	0.006
Fasting glucose (mg/dl)	102.17 ± 46.61	100.94 ± 12.20	0.862
Fasting insulin (mIU/ml)	5.72 ± 2.30	10.58 ± 5.38	<0.001
HOMA-IR	1.37 ± 0.60	2.62 ± 1.36	<0.001
Ferritin (ng/ml)	23.83 ± 12.62	54.80 ± 79.08	0.187

Non-alcoholic fatty liver disease. WC: waist circumference. BMI: body mass index. BP: blood pressure. ALT: alanine aminotransferase. AST: aspartate aminotransferase. ALP: alkaline phosphatase. GGT: gamma glutamyl transferase. HOMA-IR: homeostasis model assessment for insulin resistance.



Table 3 - Comparison of parameters between patients with ET or HT according to presence or absence of non-alcoholic fatty liver disease.

	Parameters	with NAFLD	without NAFLD	p value
Patients with euthyroidism	N	36	25	-
	Age	49.78 ± 12.77	46.52 ± 13.80	0.347
	FT ₃ (pg/ml)	3.09 ± 0.52	3.04 ± 0.29	0.645
	FT ₄ (ng/dl)	0.84 ± 0.11	0.90 ± 0.10	0.046
	FT ₃ /FT ₄ ratio	3.78 ± 0.78	3.42 ± 0.47	0.01
	TSH (mIU/L)	1.71 ± 0.96	1.50 ± 0.83	0.381
	WC (cm)	98.86 ± 7.69	87.84 ± 11.90	<0.001
	Total cholesterol (mg/dl)	215.25 ± 51.83	187.24 ± 39.20	0.026
	LDL cholesterol (mg/dl)	137.56 ± 41.72	114.04 ± 31.18	0.02
	HDL cholesterol (mg/dl)	49.06 ± 8.21	53.88 ± 11.65	0.082
	Triglycerides (mg/dl)	143.72 ± 66.64	112.96 ± 110.93	0.18
	Glucose (mg/dl)	101.97 ± 11.69	96.40 ± 29.79	0.313
	Uric acid (mg/dl)	5.50 ± 1.42	4.48 ± 1.15	0.006
	Fasting insulin (mIU/ml)	10.53 ± 5.82	6.05 ± 2.14	<0.001
Patients with hypothyroidism	HOMA-IR	2.62 ± 1.43	1.39 ± 0.53	<0.001
	N	33	21	-
	Age	49.97 ± 12.42	44.86 ± 10.48	0.124
	FT ₃ (pg/ml)	27.01 ± 23.02	19.04 ± 79	0.075
	FT ₄ (ng/dl)	2.59 ± 0.37	2.76 ± 0.35	0.103
	FT ₃ /FT ₄ ratio	0.59 ± 0.19	0.68 ± 0.13	0.036
	TSH (mIU/L)	4.89 ± 1.72	4.20 ± 0.94	0.27
	WC (cm)	97.12 ± 8.89	84.24 ± 13.67	0.001
	Total cholesterol (mg/dl)	217.82 ± 40.00	193.05 ± 46.34	0.042
	LDL cholesterol (mg/dl)	132.33 ± 35.85	118.19 ± 37.69	0.172
	HDL cholesterol (mg/dl)	47.89 ± 10.64	52.43 ± 11.34	0.14
	Triglycerides (mg/dl)	188.12 ± 82.28	112.19 ± 58.08	<0.001
	Glucose (mg/dl)	109.05 ± 61.09	99.82 ± 12.81	0.502
	Uric acid (mg/dl)	5.19 ± 1.38	4.70 ± 1.76	0.259
	Fasting insulin (mIU/ml)	10.64 ± 4.94	5.38 ± 2.44	<0.001
	HOMA-IR	2.61 ± 1.30	1.34 ± 0.67	<0.001

NAFLD: non-alcoholic fatty liver disease. FT₃: free T₃. FT₄: free T₄. TSH: thyroid stimulating hormone. WC: waist circumference. HOMA-IR: homeostasis model assessment for insulin resistance.

NAFLD in the patients with HT in our study. Abdominal obesity is a substantial component of metabolic syndrome and increases the risk for cardiovascular events. Visceral fat can be considered an important predictive factor for NAFLD (36).

The mean WC ($p < 0.001$), BMI ($p < 0.001$), systolic and diastolic blood pressure ($p = 0.049$ and $p = 0.003$) values were higher in the patients with NAFLD in the present study. Fatty liver disease has been associated with anthropometric findings. Moreover, abdominal obesity and increased WC have been associated with NAFLD (37). Huang and Beilin (38) demonstrated that systolic and diastolic blood pressure are elevated in patients with NAFLD compared to controls. Concordant with the referenced results, in the current study, AST, ALT and GGT were increased in patients with NAFLD. Chung and Kim (25) reported that

both the prevalence of NAFLD and ALT levels were higher in patients with HT. Serum ALT level is a surrogate marker for NAFLD in the absence of other causes of liver disease (17). In the current study, fasting insulin and HOMA-IR values were elevated in patients with NAFLD. Furthermore, insulin resistance and fasting insulin level formed a strong relationship with NAFLD, independent of HT. Additionally, it has been reported that hyperinsulinemia and HT can separately result in the development of NAFLD (39,40).

In the current study, abdominal USG was applied to diagnose NAFLD via the qualitative detection of steatosis. Abdominal USG detects changes in fatty accumulation in the liver of as low as $\geq 20\%$ and closely mirrors coronary and carotid atherosclerosis burden. In contrast, semi-quantitative USG indices (to exclude NASH) and sonoelastography (to

Table 4 - Logistic regression analysis of the association between non-alcoholic fatty liver disease and metabolic variables in all participants.

Variables	p value	OR	95% CI
WC	0.01	1.087	1.018 - 1.061
Triglycerides	0.12	1.010	0.997 - 1.031
Total cholesterol	0.21	1.009	0.995 - 0.921
Uric acid	0.79	1.056	0.706 - 51.283
HOMA-IR	0.005	2.978	1.397 - 9.575
FT ₃ /FT ₄ ratio	0.02	1.834	1.089 - 3.569

WC: waist circumference. HOMA-IR: homeostasis model assessment for insulin resistance. OR: odds ratio. CI: confidence interval.

Table 5 - Logistic regression analysis of the association between non-alcoholic fatty liver disease and metabolic variables in patients with HT.

Variables	p value	OR	95% CI
WC	0.02	1.189	1.024 - 1.381
Triglycerides	0.04	1.031	1.001 - 1.061
Total cholesterol	0.78	1.004	0.977 - 1.031
Uric acid	0.03	0.318	0.11 - 0.921
HOMA-IR	0.02	8.042	1.261 - 51.283
FT ₃ /FT ₄ ratio	0.01	3.540	1.309 - 9.575

WC: waist circumference. HOMA-IR: homeostasis model assessment for insulin resistance. OR: odds ratio. CI: confidence interval.



quantify fibrosis) help predict liver histology and can be used to help select patients to submit to liver biopsy (41). According to the above, semi-quantitative steatosis indices must be further investigated.

In conclusion, FT₃/FT₄ ratio, HOMA-IR and WC are risk factors for the development of NAFLD. FT₃/FT₄ ratio is a predictor of NAFLD independent of insulin resistance both in patients with ET and in patients with HT. Elevated serum triglyceride and uric acid levels are independent risk factors for NAFLD in patients with HT.

AUTHOR CONTRIBUTIONS

Gökmen FY and Ahbab S participated in the study design, study coordination and drafting of the manuscript. Ataöğlu HE participated in statistic analysis and helped in drafting the manuscript. Türker BÇ, Çetin F, Türker F and Mamaç RY participated in data collection. Yenigün M participated in study design and coordination.

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