Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(11) 1–7

DOI: 10.1177/03000605211056841
journals.sagepub.com/home/imr
SAGE

Does the FT3-to-FT4 ratio easily predict the progression of NAFLD and NASH cirrhosis?

Fatih Türker[1], Alihan Oral[2], Tolga Şahin[3], Betül Çavuşoğlu Türker[4], Erdem Koçak[5], Hayriye Esra Ataoğlu[1] and Süleyman Ahbab[1]

Abstract

Background: Factors causing progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH) and liver cirrhosis remain relatively unknown. We aimed to evaluate the power and effectiveness of the free triiodothyronine (FT3)-to-free thyroxine (FT4) ratio to predict nonalcoholic fatty liver disease (NAFLD)/liver fibrosis and NASH cirrhosis severity.

Methods: Patients (n = 436) with NASH-associated liver cirrhosis (n = 68), patients with liver biopsy-proven NAFLD (n = 226), or healthy participants (n = 142) were enrolled between January 2010 and January 2020. The aspartate aminotransferase-to-thrombocyte ratio (APRI), NAFLD fibrosis score, albumin–bilirubin score (ALBI), aspartate aminotransferase (AST)-to-alanine aminotransferase (ALT) ratio, FT3-to-FT4 ratio, and Fibrosis-4 (FIB-4) were calculated and evaluated.

Results: All parameters were significantly higher in NASH cirrhosis than in the healthy group. Body mass index, ALT, fasting insulin, homeostatic model assessment for insulin resistance, and triglyceride levels were significantly higher in liver biopsy-proven NAFLD than in the healthy group. The APRI, NAFLD fibrosis score, ALBI, AST-to-ALT ratio, FT3-to-FT4 ratio, and FIB-4 were significantly higher in the NASH cirrhosis group than in the healthy group. In patients with biopsy-proven NAFLD, the FT3-to-FT4 ratio was significantly lower than in the healthy group.

[1]University of Health Sciences Turkey, Haseki Health Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey
[2]Medicana Hospital Bahçelievler, Internal Medicine Clinic, Istanbul, Turkey
[3]Demiroğlu Bilim University Department of Gastroenterology, Istanbul, Turkey
[4]Istanbul Taksim Training and Research Hospital, Internal Medicine Clinic, Istanbul, Turkey
[5]Istinye University Department of Gastroenterology, Istanbul, Turkey

Corresponding author:
Fatih Turker, University of Health Sciences Turkey, Haseki Health Training and Research Hospital, Department of Internal Medicine, Dr. Adnan Adıvar ST. No. 9, Aksaray Fatih Istanbul 34130, Turkey.
Email: fatihturker1985@hotmail.com

Conclusion: The FT3-to-FT4 ratio is an effective and useful indicator to predict NAFLD/liver fibrosis and NASH cirrhosis severity.

Keywords
FT3-to-FT4 ratio, liver fibrosis score, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, aspartate aminotransferase, alanine aminotransferase, Fibrosis-4, albumin–bilirubin score, free triiodothyronine, free thyroxine

Date received: 29 June 2021; accepted: 12 October 2021

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as fatty liver disease due to non-alcoholic causes. It includes two disease groups, nonalcoholic steatohepatitis (NASH) and steatosis. The frequency of NASH in the community varies between 25% and 56% on the basis of the diagnostic criteria that are used.[1] The NAFLD prevalence is higher in known risk groups, and type II diabetes mellitus, obesity, and hyperlipidemia are among the most important risk factors. NAFLD gradually progresses within the etiology of liver cirrhosis due to the increase in the NAFLD rate in the population.[2]

The factors responsible for the progression from NAFLD to NASH and liver cirrhosis are still relatively unknown. Various scoring systems such as Fibrosis-4 (FIB-4), the aspartate aminotransferase (AST)-to-thrombocyte ratio (APRI), and the NAFLD fibrosis score have been developed to predict progression to liver fibrosis.[3–5] Neither liver biopsy nor various parameters such as alanine aminotransferase (ALT), AST, or platelets alone are effective in detecting liver damage.[6] The critical roles of thyroid stimulating hormone (TSH), triiodothyronine (T3), and L-thyroxine (T4) in tissue and organ development, growth, differentiation, and metabolism are known. Studies have shown that subclinical and clinical hypothyroidism are associated with chronic liver disease. Additionally, free T3 (FT3) and free T4 (FT4) levels are significantly reduced among those with liver cirrhosis.[7–9] In this study, liver fibrosis scoring and the FT3-to-FT4 ratio were compared between healthy participants and patients with NAFLD or NASH cirrhosis.

Methods

Study participants

This retrospective cohort study was performed using data from living donor candidates who underwent liver biopsies and patients with NASH-associated cirrhosis between January 2010 and January 2020 at the Gastroenterology and Internal Medicine Department, Florence Nightingale Hospital, Demiroglu Bilim University. It was conducted in accordance with principles of good clinical practice and the Declaration of Helsinki. The study was approved by the clinical research ethics committee at Florence Nightingale Hospital (approval number 2019-16-03; approved on 8 June 2019) and was performed in accordance with the National Institute of Health guidelines. All data were collected anonymously without including patient-identifying information,

and written informed consent was obtained from the patients whose data were used in the analysis. Standardized data collection includes patient demographic information, medical history, and laboratory examination results. Demographic data, medical history, vital signs at admission, medications, and the final diagnosis were obtained from the patients' electronic medical records.

This study was performed in patients with NASH-associated liver cirrhosis, patients with liver biopsy-proven NAFLD, and healthy participants between January 2010 and January 2020. NAFLD patients enrolled into this study included patients who were liver transplant donor candidates and who had liver biopsy-proven steatosis or NASH. Patients with NASH-associated cirrhosis were Child B and Child C patients for whom a biopsy was contraindicated. Liver transplant donor candidates without biopsy-proven steatosis were included in the healthy group. Liver histology specimens were assessed by an experienced liver pathologist. The inclusion criteria for the NASH-associated liver cirrhosis, NAFLD, and healthy groups were no excessive alcohol intake (considered as an average daily consumption of alcohol >30 g/day in men and >20 g/day in women), negative test results for the presence of the hepatitis B surface antigen and hepatitis C virus antibody, and no drug treatments that are known to affect liver steatosis (e.g., corticosteroids and estrogens). Patients with thyroid-related diseases and TSH levels that were outside the laboratory reference range were excluded.

Patients under 18 years old or patients with cardiovascular disease (congenital heart disease, valvular heart disease, and coronary heart disease), diabetes mellitus, thrombo-embolism, kidney disease, or active infection were excluded in the study group. Additionally, patients with liver disease that had other causes (e.g., hemochromatosis, autoimmune hepatitis, viral hepatitis, and Wilson's disease) or cirrhosis that had other causes except NAFLD were also excluded.

Laboratory measurements

Routine blood samples were drawn between 6:00 am and 7:00 am after a 12-hour fast and analyzed immediately thereafter. Total cholesterol, triglycerides, ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), fasting glucose, albumin, glycosylated hemoglobin (HbA1c), fasting insulin, homeostatic model assessment for insulin resistance (HOMA-IR; calculated as follows: fasting insulin [mU/mL] $\times$ glucose [mmol/L]/22.5), TSH, free T3 (FT3), and free T4 (FT4) levels were analyzed at the Department of Laboratory Medicine, Florence Nightingale Hospital, Demiroglu Bilim University. The laboratory findings were obtained from the patients' electronic medical records. Biochemical parameters (ALT, AST, GGT, ALP, albumin, fasting glucose, HbA1c, fasting insulin, HOMA-IR, total cholesterol, triglycerides, TSH, FT3, and FT4), age, and metabolic parameters (body mass index [BMI]) were evaluated for all participants in the three groups. The APRI, NAFLD fibrosis score, albumin–bilirubin score (ALBI), AST-to-ALT ratio, FT3-to-FT4 ratio, and FIB-4 were calculated for all participants, and superiority was evaluated between the three groups.

Statistical analysis

Data are expressed as the mean $\pm$ standard deviation. A statistical analysis was performed using SPSS 24.0 (IBM Corp., Armonk, NY, USA). Basic descriptive statistics were measured including the mean, standard deviation, range, and percentage. Normality of the distribution was examined using the Kolmogorov–Smirnov test.

Mean values between two independent groups were compared using the Mann–Whitney U test for continuous variables and using the χ^2 test for categorical parameters. Comparisons between more than two subgroups were performed using an analysis of variance and the Kruskal–Wallis h test. Bivariate correlations were explored using Pearson's test (continuous variables). Differences were considered to be statistically significant if the two-tailed P value was less than 0.05.

Results

There were 436 participants (269 men and 167 women) who were enrolled into this study, with 226 patients in the liver biopsy-proven NAFLD group, 68 patients in the NASH-associated liver cirrhosis group, and 142 participants in the healthy group. There were 81 men (57%) in the healthy group, 139 men (61.5%) in the biopsy-proven NAFLD group, and 49 men in the NASH-associated liver cirrhosis group. The mean age was 34.08 ± 9.00 years in healthy group, 34.25 ± 8.7 years in the liver biopsy-proven NAFLD group, and 59.93 ± 6.7 years in the NASH-associated liver cirrhosis group. All parameters were significantly higher (including age, BMI, ALT, AST, ALP GGT, albumin, fasting glucose, fasting insulin, HbA1c, HOMA-IR, total cholesterol, and triglycerides) in the NASH-associated liver cirrhosis group compared with the healthy group ($P < 0.001$) (Table 1). BMI, ALT, fasting insulin, HOMA-IR, and triglycerides were significantly higher in the liver biopsy-proven NAFLD compared with the healthy group ($P < 0.001$). FIB-4, APRI, and the AST-to-ALT ratio were significantly higher, while the NAFLD fibrosis score, ALBI, and FT3-to-FT4 ratio were significantly lower in the NASH-associated liver cirrhosis group than in the healthy group ($P < 0.001$ for all; Table 2). Only the FT3-to-FT4 ratio was significantly lower in the liver biopsy-proven NAFLD group compared with the healthy group ($P < 0.001$; Table 2). We examined the correlation analysis between liver fibrosis scores and the FT3-to-FT4 ratio. We found that a low FT3-to-FT4 ratio correlated with FIB-4 ($r = 0.122$, $P = 0.012$), APRI ($r = 0.106$, $P = 0.029$), and NAFLD fibrosis scores ($r = 0.146$, $P = 0.04$) (Table 3).

Discussion

In this single-center study, we aimed to evaluate the FT3-to-FT4 ratio, which is a new simple marker to assess liver fibrosis in patients with NAFLD. When the APRI, NAFLD fibrosis score, ALBI, AST-to-ALT ratio, FT3-to-FT4 ratio, and FIB-4 were evaluated together, we found that the FT3-to-FT4 ratio was the best predictor for developing NAFLD and NASH cirrhosis. Various studies have investigated the best method to evaluate liver fibrosis using non-invasive tests.[10,11] These researchers compared various scoring systems and concluded that no scoring system were superior to the others; however, few studies have compared these scoring systems. The relationship between NAFLD and the FT3-to-FT4 ratio has always been an area of interest and investigation for researchers.[12] T4 levels were shown to be generally within normal limits, but in cirrhosis, FT4 levels increase due to decreased serum T4 binding protein levels.[13] T3 and FT3 concentrations generally decrease with increasing disease severity. However, this issue remains controversial. Studies on this subject have mostly been conducted in patients with alcoholic cirrhosis. In this study, we added the FT3-to-FT4 ratio to the fibrosis scoring systems and determined the parameter that best shows disease progression from the healthy group to NASH cirrhosis. Thyroid hormones play a critical role in regulating metabolism including lipid metabolism,

Table 1. Clinical, laboratory, and demographic data compared between the healthy, liver biopsy-proven NAFLD, and NASH-related liver cirrhosis groups.

	Healthy group (n = 142)	Biopsy-proven NAFLD group (n = 226)	NASH-related liver cirrhosis group (n = 68)	P
Age (years)	34.08 ± 9.00	34.25 ± 8.7	**59.93 ± 6.7***	**<0.001**
BMI (kg/m^2)	24.70 ± 3.30	**27.20 ± 4.00****	**30.30 ± 5.11***	**<0.001**
ALT (U/L)	18.42 ± 10.81	**22.7 ± 14.1*****	**31.9 ± 26.1***	**<0.001**
AST (U/L)	16.9 ± 4.6	18.4 ± 5.6	**47.9 ± 25.8***	**<0.001**
ALP (U/L)	66.1 ± 20.0	72.8 ± 24.4	**130.1 ± 84.9***	**<0.001**
GGT (U/L)	18.2 ± 12.3	120.7 ± 15.7	**123.8 ± 23.8***	**<0.001**
Albumin (g/dL)	4.6 ± 0.3	4.6 ± 0.3	**2.9 ± 0.6***	**<0.001**
Fasting glucose (mg/dL)	92.4 ± 9.1	95.1 ± 9.4	**125.6 ± 45.4***	**<0.001**
HbA1c (%)	5.2 ± 0.5	5.3 ± 0.5	**6.1 ± 1.5***	**<0.001**
Fasting insulin (μIU/mL)	7.4 ± 2.9	**11.0 ± 6.1****	**24.0 ± 14.2***	**<0.001**
HOMA-IR (mU/mL)	1.7 ± 0.8	**2.6 ± 1.6****	**7.3 ± 4.1***	**<0.001**
Total cholesterol (mg/dL)	178.9 ± 45.1	**186.0 ± 41.4**	**127.0 ± 42.1***	**<0.001**
Triglycerides (mg/dL)	96.5 ± 43.8	**118.0 ± 66.1*****	**91.1 ± 52.2***	**<0.001**
TSH (mIU/L)	2.72 ± 8.13	2.00 ± 1.20	2.58 ± 2.73	0.340
FT3 (mIU/L)	4.11 ± 1.22	**4.82 ± 1.56****	**3.34 ± 0.83***	**<0.001**
FT4 (mIU/L)	8.14 ± 7.10	**13.74 ± 10.28****	**13.41 ± 6.32***	**<0.001**

*P < 0.001 for the NASH-related liver cirrhosis group vs. the healthy group.
**P < 0.001 for the biopsy-proven NAFLD group vs. the healthy group.
***P < 0.005 for the biopsy-proven NAFLD group vs. the healthy group.
NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance, calculated as follows: fasting insulin (mU/mL) × glucose (mmol/L)/22.5; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

Table 2. Comparison of liver fibrosis scores and the FT3-to-FT4 ratio between the healthy, liver biopsy-proven NAFLD, and NASH cirrhosis groups.

	Healthy group (n = 142)	Biopsy-proven NAFLD group (n = 226)	NASH-related liver cirrhosis group (n = 68)	P
FIB-4	0.6 ± 0.2	0.6 ± 0.2	6.4 ± 4.0*	<0.001
APRI	0.22 ± 0.08	0.22 ± 0.08	1.7 ± 1.1*	<0.001
NAFLD	−3.8 ± 1.0	−3.5 ± 1.1	1.0 ± 0.9*	<0.001
FT3-to-FT4 ratio	1.4 ± 1.1	0.8 ± 1.4**	0.4 ± 0.6*	<0.001
ALBI	10.5 ± 5.7	10.0 ± 5.4	1.8 ± 1.6*	<0.001
AST-to-ALT ratio	1.0 ± 0.3	0.9 ± 0.3	1.6 ± 0.4*	<0.001

*P<0.001 for the NASH-related liver cirrhosis group vs. the healthy group.
**P<0.001 for the biopsy-proven NAFLD group vs. the healthy group.
FT3-to-FT4 ratio, free T3/free T4 ratio; FT3, free triiodothyronine; FT4, free thyroxine; FIB-4, Fibrosis-4; APRI, aspartate aminotransferase-to-thrombocyte ratio; NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Correlation analysis between liver fibrosis scores and the FT3-to-FT4 ratio.

	FT3-to-FT4 ratio	
	r	P
FIB-4	−0.122	0.012
APRI	−0.106	0.029
NAFLD	−0.146	0.04
ALBI	0.42	0.381
AST-to-ALT ratio	−0.68	0.160

FT3, free triiodothyronine; FT4, free thyroxine; FT3-to-FT4 ratio, free T3/free T4 ratio; FIB-4, Fibrosis-4; APRI, aspartate aminotransferase-to-thrombocyte ratio; NAFLD, non-alcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

especially in the liver.[14] FT3 and FT4 levels were shown to decrease in proportion to the severity of the disease in liver cirrhosis, but the etiology of cirrhosis patients was unclear and only a small number of patients were enrolled into the study.[15]

Thyroid dysfunction may also be associated with an increased risk of fibrosis because it is associated with metabolic abnormalities such as dyslipidemia and obesity.[16,17] Kim et al. evaluated 425 subjects with biopsy-proven NAFLD. They showed that low thyroid function was significantly associated with advanced fibrosis.[18] Another study conducted in the Netherlands supported the relationship between chronic liver disease severity and hypothyroidism.[19] Unlike our study, these other two studies did not examine the relationship between FT3 levels and liver fibrosis. Vincken et al.[15] showed that thyroid function test results were lower in the cirrhosis group compared with the healthy group. FT4 and FT3 levels were within normal limits, which is similar to our study, but these levels were significantly lower in patients with cirrhosis compared with healthy controls. TSH levels in patients with cirrhosis in our study did were not significantly different and were within normal limits. However, from the healthy group to NASH cirrhosis in our study, we found a significantly larger decrease in FT3 levels compared with FT4 levels. Thus, we showed that the FT3-to-FT4 ratio is an effective way to predict the severity of NAFLD/liver fibrosis and NASH cirrhosis. Another advantage of our study is that the diagnosis of NAFLD and NASH was made via liver biopsy, and we also included healthy people. These findings show the relationship between a low FT3-to-FT4 ratio and NAFLD and NASH cirrhosis. Therefore, the FT3-to-FT4 ratio could be used as a noninvasive marker for liver fibrosis in patients with NAFLD and NASH cirrhosis.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Fatih Türker https://orcid.org/0000-0002-8281-0319

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