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Original paper

Factors related to the presence of nonalcoholic fatty liver disease in patients with type 2 diabetes: a single center study

Seydahmet Akin, Oguzhan Gungor, Banu Boyuk, Hande Erman

Department of Internal Medicine, Istanbul Kartal Dr Lutfi Kirdar City Hospital, Turkey

Abstract

Aim of the study: There is a close relationship between the development of diabetes and nonalcoholic fatty liver disease (NAFLD). The aim of the study was to determine the frequency and associated factors of NAFLD in type 2 diabetes mellitus (T2DM) patients according to the ultrasound examination and noninvasive hepatic fibrosis indices.

Material and methods: 316 patients who were followed up in the Internal Medicine Diabetes clinic, over the age of 18, diagnosed with T2DM were included retrospectively. NAFLD was noted using ultrasound. NAFLD fibrosis score (NFS), fibrosis-4 index (FIB-4) and AST to platelet ratio index (APRI) were used as non-invasive hepatic fibrosis indices.

Results: The prevalence of NAFLD with hepatic ultrasound was 89.7% in T2DM patients. Among non-invasive fibrosis indices, NFS and FIB-4 were similar, but APRI was significantly higher in moderate-severe hepatosteatosis group (p values = 0.355, 0.246 and 0.003 respectively). In logistic regression analysis, while mild hepatosteatosis was associated with BMI and NFS ($p = 0.004$, $p = 0.008$), moderate to severe hepatosteatosis as associated with BMI and serum triglycerides ($p < 0.001$, $p = 0.019$).

Conclusions: The prevalence of NAFLD is high in patients with T2DM. The frequency and degree of NAFLD is associated with the NFS, BMI and hypertriglyceridemia. While NFS is associated with mild hepatosteatosis; moderate to severe hepatosteatosis is associated with BMI and serum triglycerides.

Key words: APRI, non-alcoholic fatty liver disease, FIB-4, type 2 diabetes mellitus, NFS.

Address for correspondence:

Hande Erman, Department of Internal Medicine, Istanbul Kartal Dr Lutfi Kirdar City Hospital, Turkey,
e-mail: handeerman@yahoo.com

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as fatty liver disease without secondary causes that cause fat accumulation in the liver, such as excessive alcohol intake, use of drugs that cause adiposity, or hereditary diseases [1]. The incidence of NAFLD/nonalcoholic steatohepatitis (NASH) is increasing in parallel with the increase in type 2 diabetes mellitus (T2DM), obesity, high-calorie diet, fructose-containing beverages, and sedentary lifestyle habits worldwide. NASH is seen as the liver involvement of metabolic syndrome (MetS), and it is rapidly becoming one of the most important causes of cryptogenic cirrhosis [2]. NAFLD is found in 75-80% of patients with obesity, 56-87% of patients with T2DM, approximately 70% of patients with MetS, and 70% of patients with dyslipidemia [1, 3].

A recent study revealed that moderate to advanced fibrosis affects nearly 15% of patients with T2DM [4]. American Diabetes Association guidelines support the screening for clinically significant fibrosis in T2DM patients or fatty liver on ultrasound in outpatient clinics [5]. The noninvasive tests NAFLD fibrosis score

(NFS) and fibrosis-4 (FIB-4) score are the commonly used and recommended hepatic fibrosis scores for screening liver fibrosis [5]. Although there is no consensus on cut-off values for non-invasive tests, especially in specific patient groups such as diabetes and obesity, recent studies suggest certain values [6]. While NFS scores greater than 0.640 predict NAFLD with a sensitivity of 86% and a specificity of 71% [7], FIB-4 upper cut-off of < 1.3 suggests better diagnostic accuracy [8]. Recent studies have validated the diagnostic and predictive value of non-invasive liver fibrosis indices in NAFLD disease [9]. Aspartate aminotransferase to platelet ratio (APRI) is also used to assess fibrosis degree and an APRI score ≤ 1.0 indicates low risk for liver fibrosis (negative predictive value [NPV] = 84%) [6]. In our study, we aimed to determine the frequency of NAFLD in T2DM patients and determine the factors affecting its presence.

Material and methods

Study population

We retrospectively evaluated patients aged > 18 years, diagnosed with T2DM who attended on a regular basis our diabetes outpatient clinic between 2018 and 2021. Patients with the following were excluded: alcohol intake > 30 g for men and > 20 g for women per day; being seropositive for hepatitis B or C; history of acute illness and malignancy; pregnancy.

Anthropometric, ultrasound, and laboratory measurements

Age, gender, duration of diabetes, body mass index (BMI), and medications of the patients were analyzed from the patient files and hospital system. Diabetes was defined according to the American Diabetes Association criteria. Hepatic ultrasonography (USG) scanning was performed in all patients by experienced radiologists. Patients without hepatosteatosis were included in the first group, patients with mild hepatosteatosis were included in the second group, and patients with moderate to severe hepatosteatosis were included in the third group. The following criteria are used in radiologic assessment of fatty liver: 1 – increased echogenicity of the liver parenchyma relative to that of the cortex of the right kidney, 2 – deep beam attenuation, 3 – blurring of the intrahepatic vessels. Mild hepatosteatosis was diagnosed by a minimal diffuse increase in hepatic echogenicity with normal visualization of the diaphragm and intrahepatic vessel border. Moderate hepatosteatosis was diagnosed by a diffuse increase in hepatic echogenicity with slightly impaired visualization of the intrahepatic vessels and diaphragm. Severe hepatosteatosis was diagnosed by a marked increase in echogenicity with poor penetration of the posterior segment of the right lobe of the liver and poor or no visualization of hepatic vessels and diaphragm [10].

Risk of advanced fibrosis was estimated using the FIB-4 score and the NFS score [6].

FIB-4 score: (age × AST [U/l])/(platelet count [10^9] × $\sqrt{}$ALT [U/l]). FIB-4 score of < 1.3 indicates low risk for advanced fibrosis [6]. NFS: –1.675 + (0.037 × age) + (0.094 × BMI) + (1.13 × presence of diabetes [present = 1, no = 0]) + (0.99 × AST/ALT) – (0.013 × platelet count [10^9]/l]) – (0.66 × albumin [g/dl]) [6]. NFS score of < –1.455 represents low risk, values between –1.455 and 0.675 represent intermediate risk, and > 0.675 indicates high risk for advanced fibrosis [6]. The patients were compared by dividing them into three groups according to the cut-off values of the NAFLD fibrosis score and the FIB-4 score. APRI was calculated as the AST to platelet ratio. An APRI score of ≤ 1.0 indicates low risk and > 1.0 indicates indeterminate and high risk [6]. The study has been approved by the Medical Ethics Committee of the University of Health Science, Istanbul Kartal Dr. Lutfi Kirdar City Hospital (2021/514/197/4-2021, 03, 10). A waiver of informed consent was approved by the ethics committee due to the retrospective design of the study.

Statistical analysis

Frequency and percentage values were given for categorical variables. Mean, standard deviation, median, minimum and maximum values were given for continuous variables. The normal distribution test of continuous variables was performed with the Kolmogorov-Smirnov test. Chi-square (χ^2) analysis was used for the relationships between categorical variables. Where appropriate, categorical variables were evaluated with Fisher-Freeman-Halton test. The Mann-Whitney *U* test was used in the comparison of two independent groups for the variables that did not fulfill the assumption of normal distribution. The Kruskal-Wallis H test was used in comparison of more than two groups. Dunn's multiple comparison test with Bonferroni correction was used to determine the source of the difference in the Kruskal-Wallis H test. Logistic regression analysis was used to determine the effect of independent variables on NAFLD. $P < 0.05$ was considered statistically significant. Analyses were performed with the SPSS 23 package program (IBM Corp. released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY).

Results

Table 1 represents the baseline characteristics for patients according to hepatic steatosis degree according to ultrasound assessment. Among 316 T2DM patients, 89.8% had varying degrees of NAFLD. The proportion of subjects with mild hepatic steatosis was 56.01%, moderate to severe fibrosis 33.86% and no steatosis 10.2%. Patients in the group with mild steatosis were significantly older and had longer duration of diabetes than the other groups ($p < 0.05$). BMI, triglycerides, APRI, and insulin dose were significantly higher in the group with definite steatosis (moderate to severe) ($p < 0.001$, $p = 0.001$ and $p = 0.003$ respectively). SGLT2-i use was more common in the patients with mild steatosis ($p = 0.041$). In addition, fenofibrate usage was significantly higher in the moderate to severe steatosis group ($p = 0.004$).

Table 2 represents the comparative analysis in terms of demographics and laboratory characteristics according to both FIB-4 score and NFS score. Patients with FIB-4 < 1.3 were more frequently men ($p = 0.041$), younger ($p < 0.001$) and had longer duration of diabetes ($p = 0.05$). In addition, patients with FIB-4 score ≥ 1.3 had higher APRI than the other groups ($p < 0.001$). According to NFS, patients with NFS ≥ 0.675 were older and more likely to have a higher BMI ($p < 0.001$), HbA_{1c} ($p = 0.004$) and APRI ($p < 0.001$). Diabetes duration of the NFS < –1.455 group was significantly lower than the other groups ($p = 0.001$).

Table 1. Demographic, laboratory, and clinical characteristics of type 2 diabetes mellitus patients according to degree of hepatosteatosis in ultrasound evaluation

Parameter	Without hepatosteatosis *n* = 32	Mild hepatosteatosis *n* = 177	Moderate- severe hepatosteatosis *n* = 107	*P*-value
Age (years), mean ±SD	58.38 ±9.04	61.12 ±9.19	58.51 ±8.56	0.041
Male, *n* (%)	14 (43.75)	73 (41.24)	50 (46.72)	0.664
BMI (kg/m^2), mean ±SD	29.09 ±3.99	31.15 ±4.87	33.32 ±5.0	< 0.001
DM duration (years), mean ±SD	14.28 ±5.75	15.5 ±7.24	13.36 ±6.37	0.024
Laboratory findings, mean ±SD				
FBG (mg/dl)	153.75 ±51.49	153.06 ±46.40	165.93 ±52.39	0.084
HbA1c (%)	7.87 ±1.49	7.86 ±1.22	8.09 ±1.22	0.123
Total cholesterol (mg/dl)	189.41 ±44.26	200.67 ±47.55	201.87 ±47.76	0.453
LDL-C (mg/dl)	113.53 ±37.27	118.75 ±40.21	114.35 ±36.89	0.566
Non-HDL-C (mg/dl)	141.09 ±41.21	152.32 ±46.63	156.26 ±45.67	0.285
TG (mg/dl)	137.72 ±65.66	164.65 ±76.26	221.81 ±158.81	0.001
TSH (mIU/l)	2.09 ±0.57	3.03 ±5.66	2.21 ±1.30	0.976
APRI	0.21 ±0.06	0.22 ±0.17	0.26 ±0.23	0.003
NFS	–0.63 ±0.85	–0.9 ±1.24	–0.7 ±1.26	0.355
FIB-4 score	1.13 ±0.31	1.11 ±0.79	1.11 ±0.54	0.246
Drug usage, *n* (%)				
Metformin	27 (84.37)	155 (87.57)	98 (91.58)	0.428
Pioglitazone	1 (3.1)	2 (1.12)	1 (0.93)	0.545
Sulfonylurea	6 (18.75)	32 (18.07)	17 (15.88)	0.875
DPP4i	14 (43.75)	104 (58.75)	69 (38.98)	0.110
SGLT2i	0 (0)	30 (16.94)	18 (16.82)	0.041
GLP-1RA	0 (0)	5 (2.82)	6 (5.60)	0.331
Insulin treatment	19 (59.37)	115 (64.97)	67 (62.61)	0.804
Insulin (IU/day ±SD)	41.63 ±28.29	44.55 ±27.81	53.5 ±27.46	0.025
Statins	24 (75)	109 (61.58)	57 (53.27)	0.074
Fibrates	1 (3.12)	4 (2.25)	12 (11.21)	0.004

Statistical significance: p < 0.05; BMI – body mass index, DM – diabetes mellitus, FBG – fasting blood glucose, LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, TG – triglycerides, TSH – thyroid stimulating hormone, APRI – AST to platelet ratio index, NFS – NAFLD fibrosis score, FIB-4 – Fibrosis-4 index, DPP4i – dipeptidyl peptidase inhibitors, SGLT2i – sodium glucose cotransporter 2 inhibitors, GLP-1RA – glucagon like peptide 1 receptor agonist

Table 2. Demographic, laboratory, and clinical characteristics of type 2 diabetes mellitus patients with hepatosteatosis on ultrasound. Comparative analysis of parameters according to NAFLD Fibrosis Score (NFS) and FIB-4 score

Parameter	FIB-4 score (mean ±SD)		*P*-value	NFS score (mean ±SD)			*P*-value
	FIB-4 < 1.3 *n* = 222	FIB-4 ⩾ 1.3 *n* = 64		NFS < −1.455 *n* = 86	−1.455 ⩽ NFS < 0.675 *n* = 201	NFS ⩾ 0.675 *n* = 29	
Age (years)	57.72 ±8.95	65.26 ±6.78	< 0.001	55.52 ±7.53	61.09 ±8.76	65.28 ±10.01	< 0.001
Male, *n* (%)	88 (39.63)	49 (76.56)	0.041	35 (40.69)	92 (45.77)	10 (34.48)	0.437
BMI (kg/m^2)	32.03 ±5.17	30.84 ±4.50	0.087	29.85 ±4.56	31.80 ±4.64	36.25 ±5.71	< 0.001
DM duration (years)	14.04 ±6.29	16.1 ±7.92	0.050	12.52 ±5.89	15.51 ±7.17	15.03 ±6.25	0.001
FBG (mg/dl)	158.13 ±46.64	155.88 ±55.05	0.319	161.53 ±54.51	154.59 ±47.49	165.14 ±44.20	0.160
HbA_{1c} (%)	7.94 ±1.22	7.93 ±1.33	0.595	8.09 ±1.22	7.81 ±1.27	8.34 ±1.14	0.004
Total cholesterol (mg/dl)	198.55 ±42.72	203.19 ±56.78	0.918	199.58 ±47.62	201.79 ±47.91	188.14 ±41.39	0.631
LDL-C (mg/dl)	114.41 ±34.49	122.15 ±46.91	0.438	115.34 ±36.76	118.79 ±40.27	107.25 ±33.66	0.534
Non-HDL-C (mg/dl)	151.19 ±42.02	155.57 ±53.86	0.890	153 ±47.10	153.51 ±45.95	143.52 ±41.46	0.848
TG (mg/dl)	188.57 ±124.67	164.05 ±83.06	0.255	190.4 ±135.54	179.08 ±108.52	169.48 ±81.79	0.936
APRI	0.18 ±0.07	0.35 ±0.30	< 0.001	0.18 ±0.10	0.24 ±0.19	0.36 ±0.31	< 0.001

Statistical significance: p < 0.05; DM – diabetes mellitus, BMI – body mass index, FBG – fasting blood glucose, LDL-C – low-density lipoprotein cholesterol, non-HDL-C – non-high density lipoprotein cholesterol, TG – triglycerides, APRI – AST to platelet ratio index, NFS – NAFLD fibrosis score, FIB-4 – Fibrosis-4 index

Table 3. Factors affecting hepatic steatosis in regression analysis

Groups according to USG findings		B	S.E.	Exp(B)	*P*-value	95% CI for Exp(B)	
						Lower	Upper
Mild hepatosteatosis	Intercept	−6.564	2.646		0.013		
	Age	0.054	0.028	1.056	0.051	1.000	1.115
	Diabetes duration	0.020	0.035	1.020	0.571	0.952	1.092
	BMI	0.160	0.055	1.174	0.004	1.054	1.307
	NFS	−0.524	0.197	0.592	0.008	0.402	0.871
	HbA_{1c}	−0.147	0.169	0.863	0.384	0.619	1.202
	LDL-C	0.002	0.005	1.002	0.692	0.992	1.013
	Triglyceride	0.004	0.003	1.004	0.236	0.997	1.011
	Gender	−0.308	0.426	0.735	0.469	0.319	1.693
Moderate to severe hepatosteatosis	Intercept	−8.085	2.854		0.005		
	Age	0.031	0.030	1.032	0.297	0.973	1.094
	Diabetes duration	−0.012	0.039	0.988	0.759	0.916	1.066
	BMI	0.241	0.059	1.273	0.000	1.135	1.427
	NFS	−0.356	0.209	0.700	0.088	0.465	1.055
	HbA_{1c}	−0.114	0.180	0.892	0.527	0.627	1.270
	LDL-C	−0.001	0.006	0.999	0.813	0.987	1.010
	Triglyceride	0.008	0.004	1.008	0.019	1.001	1.015
	Gender	−0.698	0.466	0.498	0.134	0.199	1.241

Statistical significance: p < 0.05; BMI – body mass index, FBG – fasting blood glucose, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein cholesterol, NFS – NAFLD fibrosis score

Logistic regression analysis is reported in Table 3. BMI and NFS were significant variables for mild hepatosteatosis ($p < 0.05$). The increase in BMI increases the mild hepatosteatosis status 1.174 times compared to the cases without hepatosteatosis (OR = 1.174, $p = 0.004$). An increase in NFS reduces the incidence of mild hepatosteatosis 1.69 times compared to cases without hepatosteatosis. BMI and serum triglyceride were found to be significant variables for moderate to severe hepatosteatosis status. The increase in BMI levels increases the moderate to severe hepatosteatosis status 1.27 times compared to the cases without hepatosteatosis (OR = 1.273, $p < 0.001$). The increase in serum triglyceride levels increases the status of having moderate to severe hepatosteatosis 1.008 times compared to the cases without hepatosteatosis (OR = 1.008, $p = 0.019$).

Discussion

In our study, 89.8% of the T2DM patients had fatty liver according to ultrasound, which suggests the importance of investigating the factors affecting fatty liver in our country. While 25% of the general population has NAFLD, 50% to 70% of T2DM patients have NAFLD, and its severity tends to increase, including fibrosis [11]. The prevalence of NAFLD detected using USG in patients with T2DM was reported to be between 29.6% [12] and 87.1% [13]. The overall prevalence of NAFLD in Turkey in the period 2014-2016 was reported as 48.3% and found to be associated with the presence of diabetes [14]. However, there are no data on the recent prevalence of NAFLD in T2DM patients in Turkey. In our study, the relative increase in frequency of NAFLD in T2DM patients according to the past studies worldwide may be accounted for by the differences between patient populations such as ethnic/genetic characteristics, age, BMI, triglyceride level, and glycemic control.

Current EASL guidelines regarding NAFLD management suggest that non-invasive scores are acceptable diagnostic tools for both the risk identification and progression of NAFLD among individuals with increased metabolic risk [3]. A common point of non-invasive scoring systems is high negative predictive but poor positive predictive values [15]. In the present study, APRI score was increased in moderate to severe hepatosteatosis among noninvasive hepatic fibrosis score systems. The diagnostic accuracy of non-invasive tests differs among various studies. In a study by Amernia *et al.* [16] APRI score was found to be a better predictor of advanced fibrosis on FibroScan than FIB-4 score. In another study that compared the negative predictive factors (NPV) and area under the receiver operating curve (AUROC) of noninvasive fibrosis tools in NAFLD, 89.9% and 0.80 for APRI, 95.7% and 0.88 for FIB-4, 93.0% and 0.86 for NFS values were reported [17]. In the study conducted by Pan *et al.* [18], which included 442 patients with and without diabetes, both the NFS and APRI score were found to be high in patients with hepatosteatosis. APRI score < 1 is the recommended cut-off point for advanced fibrosis in NAFLD patients [6]. Although APRI scores of our patients were below < 1, NAFLD patients with high FIB-4 and NFS scores had higher APRI scores in our study that those in the literature. On the other hand, we observed similar NFS and FIB-4 scores regardless of hepatosteatosis stages according to ultrasound. Since age and BMI are parameters of NFS, the older age of mild NAFLD patients (61.12 ±9.19 vs. 58.51 ±8.56 respectively, $p = 0.041$) and higher BMI values of moderate to severe NAFLD patients (31.15 ±4.87 vs. 33.32 ±5.0, $p < 0.001$) may have interfered with the results of our study. Likewise, the older age of mild NAFLD patients than moderate to severe NAFLD patients may have resulted in similar FIB-4 scores.

The pathogenesis of NAFLD is linked to endocrine derangements but is complex and multifactorial [19]. In addition to the differences in insulin sensitivity and leptin levels between genders, female sex is characterized by sex-specific browning of white adipose tissue and has advantages due to the ability to convert fatty acids to ketone body rather than very low-density lipoprotein-triacylglycerol [19]. In the study conducted by Hossain *et al.* [20], higher prevalence of NAFLD and moderate and severe hepatic fibrosis were found in men than in women. Our study showed that both men and women have hepatosteatosis in similar rates according to the ultrasound assessment. However, the male proportion is higher in patients with FIB-4 ≥ 1.3. While some studies have shown increased prevalence of NAFLD in male gender [21, 22], others have associated increased NAFLD prevalence with increasing age in both sexes [23, 24]. One possible pathogenetic mechanism underlying the aging and NAFLD relation is suggested to be the attenuated effects of male sexual hormones in males and the decline in the protective effect of estrogen in older females [23, 25].

It has been asserted that NAFLD contributes to T2DM development through hepatic and peripheral insulin resistance. Pathophysiological aspects of the bidirectional relationship between NAFLD and insulin resistance suggest that increased steatosis leads to worse glycemic control or *vice versa* [3]. In addition, oxidative stress which influences the lifespan of erythrocytes is another blamed mechanism for the HbA_{1c}

and NAFLD interaction [26]. In the current study, the HbA_{1c} levels of the patients with increased NFS were higher than those of patients with a low NFS score, which supports previous knowledge. On the other hand, despite similar glycemic regulation, an increase in insulin dose was observed as the degree of hepatosteatosis increased. This means that patients with moderate to severe hepatosteatosis require higher insulin unit doses per day to achieve the same glycemic regulation as patients with mild hepatosteatosis, which may be related to increased insulin resistance in NAFLD. Previous studies have suggested the beneficial effect of pioglitazone on NAFLD in both diabetic and non-diabetics [1]. Bril *et al.* [27] observed better reduction of liver fibrosis and improved insulin sensitivity in T2DM patients than in prediabetes. However, the use of pioglitazone was not common in our study group; its causes need to be investigated further. In addition, SGLT-2 inhibitors are posited as potential candidates for the treatment of NAFLD by reducing hepatic fat content [28]. In our study, it was observed that the use of SGLT-2 inhibitors was increased in patients with both mild and advanced NAFLD. Future long-term studies on T2DM with NAFLD are needed to clarify the role of SGLT-2 inhibitors in the management of fatty liver.

Among non-invasive liver fibrosis scores, NFS is associated with mild hepatosteatosis but not with moderate to severe hepatosteatosis. While NFS and BMI values are associated with mild hepatosteatosis, BMI and triglyceride values were found to be independent risk factors for moderate to severe hepatosteatosis. We demonstrated that both triglyceride and BMI increase have an impact on the degree of hepatosteatosis. In a study by Leite *et al.* [29], any grade of NAFLD in USG was found to be associated with obesity and hypertriglyceridemia in T2DM patients. Similarly, Sima *et al.* [13] observed BMI, abdominal circumference and serum triglyceride as predictive for NAFLD in T2DM patients. An important limitation of the non-invasive scores such as FIB-4 and NFS is related to their rule-in and rule-out cutoff points that leave up to 50% of the patients in a gray area [29]. In addition, although the NFS score has been independently validated in populations of various ethnicities, BMI and diabetes status [29], Qadri *et al.* [30] demonstrated that the specificity of standard cut-offs of NFS began sharply declining with BMI over 30 kg/m^2. Furthermore, separate cut-offs for lean-overweight, obese and morbidly obese patients were suggested to prevent false positive classifications in patients with high BMI [30]. On the other hand, the FIB-4 score is suggested as an accurate predicter of advanced fibrosis in NAFLD in all BMI stages in the general population [15]. In this study, participants with moderate to severe hepatosteatosis had a higher BMI, which may limit the interpretation of the results. Although abdominal ultrasound examination is recommended to evaluate fatty liver, sensitivity decreases in mild steatosis and patients with morbid obesity. Our study population did not include morbid obese patients; however, we may have underestimated the presence of hepatosteatosis in patients with mild hepatosteatosis.

Conclusions

In our study, the frequency of fatty liver diagnosed by USG in patients with T2DM was 89.7%. An important result was that the NFS, developed for the prediction of fibrosis in NAFLD, could be a guide for the estimation of mild hepatosteatosis. In addition, moderate to severe hepatosteatosis on ultrasound was found to be related to BMI and triglyceride level rather than NFS. Finally, the high rate of NAFLD in T2DM patients in our country supports the guidelines for NAFLD screening recommendations for T2DM patients.

Disclosure

The authors declare no conflict of interest.

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