ORIGINAL ARTICLE

Investigation of cardiovascular risk factors in diabetic and nondiabetic patients with nonalcoholic fatty liver disease

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Background: The current study aims to assess cardiovascular risk factors (CVRFs) among diabetic versus nondiabetic nonalcoholic fatty liver disease (NAFLD) patients. NAFLD is the most common hepatic disorder worldwide which is directly associated with diverse CVRFs such as type 2 diabetes mellitus (T2DM) and metabolic syndrome (MS). **Materials and Methods:** The current cross-sectional population-based study has been conducted on 1031 NAFLD patients. After excluding 340 prediabetes patients, the NAFLD patients were divided into T2DM and normal blood glucose (NBG). Then, CVRFs were compared between the two groups. **Results:** Out of 691 NAFLD cases included in the study, 337 (48.8%) patients had T2DM. In the T2DM and NBG groups, the body mass index (BMI) was 31.2 ± 4.6 and 29.9 ± 4.3 kg/m2, respectively (P = 0.001). The waist circumference was 102.2 ± 10.2 and 97.6 ± 10.6 cm, respectively (P < 0.001). The systolic blood pressure was 123.3 ± 15.6 and 119.6 ± 13.6 mmHg, respectively (P = 0.043). The triglyceride levels were 191.9 ± 104.7 and 176.5 ± 89.6 mg/dL, respectively (P = 0.042). Generally, these factors were significantly higher among the diabetic patients. Besides, cardiovascular disease (CVD), hypertension, and MS were statistically more prevalent in NAFLD patients with T2DM ($P < 0.001$) than nondiabetic NAFLD patients. In multiple logistic regression models, the odds ratio of CVD, hypertension, and MS was 2.18, 2.12, and 6.63 for patients with T2DM compared with NBG, respectively. Adjustment was made for age, sex, BMI, smoking, and physical activity. **Conclusion:** CVRFs were higher in NAFLD patients with T2DM than NAFLD patients with NBG.

Key words: Cardiovascular diseases, diabetes mellitus, nonalcoholic fatty liver disease

How to cite this article: Barati M, Teimouri A, Feizi A, Iraj B, Karimifar M. Investigation of cardiovascular risk factors in diabetic and nondiabetic patients with nonalcoholic fatty liver disease. J Res Med Sci 2024;29:51.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) refers to a condition in which, in the absence of excessive alcohol consumption, more than 5% of the liver weight is saturated with fat[1] and pharmacological, viral, autoimmune, and hereditary causes of hepatic steatosis are ruled out.[2]

Nonalcoholic steatohepatitis (NASH) is an invasive form of NAFLD that can progress to cirrhosis and hepatocellular carcinoma and is rapidly becoming a major cause of liver failure and liver transplantation.[3] NAFLD is the most common liver disease worldwide.[4] Its prevalence in high-income countries among adult population is 25%–30%[5] and reaches 50%–75% in type 2 diabetes mellitus (T2DM) patients and 80%–90% in obese people.[6] The highest prevalence is detected in the Middle East and South America.[7] In a systematic review in Iran, the prevalence of NAFLD was estimated at 33.9%.[8] The prevalence of NAFLD in Isfahan was 39.3%.[9] Normal liver enzymes do not rule out

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_830_23

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Submitted: 20-Dec-2023; **Revised:** 02-Feb-2024; **Accepted:** 21-Feb-2024; **Published:** 02-Aug-2024

necrosis, inflammation, and fibrotic changes in the liver, and up to 70% of patients with NAFLD may have normal enzymes.[1] The preferred modality for the diagnosis of NAFLD is ultrasound, which has the advantages of easy access and low cost.[10]

Epidemiological evidence suggests that NAFLD not only affects the liver but also increases the risk of extrahepatic diseases such as T2DM, metabolic syndrome (MS), dyslipidemia, hypertension, and cardiovascular disease (CVD).[11] A reciprocal association links NAFLD to T2DM and MS.[12] Although in NAFLD, the risk of T2DM is not as high as impaired fasting glucose (IFG), NAFLD can increase the risk of developing IFG to T2DM.[13]

The grade of hepatic steatosis is also associated with the risk of developing T2DM in the future.[11] Compared to patients with simple steatosis, those with NASH and hepatic fibrosis appear to have a higher chance of developing T2DM and CVD.[12] On the other hand, the coexistence of NAFLD and T2DM significantly increases the risk of disease progression to NASH and cirrhosis.[14] According to the results of a 150-month follow-up, T2DM doubles overall mortality and death rates associated with liver diseases in patients with NAFLD.[15]

The most common cause of death in patients with NAFLD is cardiovascular causes,[10] and components of MS, especially T2DM, are strong predictors of mortality rate associated with cardiac diseases in patients with NAFLD.[16] Studies show that the risk of cardiovascular problems in people with NAFLD and T2DM is almost doubled.[17]

This study aimed to determine the prevalence of T2DM in patients with NAFLD referred to the Fatty Liver Clinic of Isfahan Endocrine and Metabolism Research Center and to compare cardiovascular risk factors (CVRFs) in NAFLD patients with T2DM and NAFLD patients with normal blood glucose (NBG).

MATERIALS AND METHODS

This research is a retrospective cross-sectional study. To collect the required information, the records of all patients with NAFLD referred to the Fatty Liver Disease Division of the Endocrine and Metabolic Disorders Research Center Affiliated with Isfahan University of Medical Sciences have been reviewed. The inclusion criteria included all patients with non-alcoholic fatty liver disease. Patients were considered as non-alcoholic fatty liver disease if they had two separate ultrasounds indicating liver steatosis and the absence of concurrent chronic liver diseases such as viral or autoimmune hepatitis, excessive alcohol consumption, and other causes of liver steatosis such as chronic use of hepatotoxic drugs (glucocorticoids, sodium valproate, methotrexate, amiodarone and tamoxifen, etc). These data were obtained by taking the history of the patients and performing some tests such as checking viral markers of hepatitis. Type 1 diabetes mellitus, indeterminate diabetes status, and prediabetes have been considered exclusion criteria. According to the American Diabetes Association guideline, the diagnostic criteria for diabetes are fasting plasma glucose (FPG) ≥126 mg/dL or having symptoms of hyperglycemia and random plasma glucose ≥200 mg/dL or HbA1c ≥6.5% or plasma glucose ≥200 mg/dL 2 h after taking 75 g of glucose. Furthermore, if there are no signs of hyperglycemia, FPG and HbA1c will be checked again.[18] In this study, those who had fulfilled the criteria, or had mentioned diabetes in their past medical history, or used antidiabetic medication, were considered diabetic patients. Patients with a history of myocardial infarction, unstable angina, angina pectoris, coronary artery stenosis or coronary artery bypass graft surgery, percutaneous coronary intervention, heart failure, or hospitalization for heart disease as CVD were considered.

Out of a total of 1200 cases reviewed, 169 cases were excluded. Of the remaining 1031 patients, 354 had NBG, 337 had T2DM, and 340 had prediabetes. The overall prevalence of T2DM in this study was 32.7%, and finally, out of 1200 cases, 691 cases (354 NBG patients and 337 patients with T2DM) were included in the study [Figure 1].

Information including past medical and drug history, age, sex, height, weight, waist circumference, hip circumference, wrist circumference, systolic and diastolic blood pressure, lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride [TG]), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and grade of hepatic steatosis were extracted from the files. Taking antihypertensive medication, self-reported medical history of high blood pressure, and a registered systolic blood pressure ≥140 mmHg or diastolic ≥ 90 mmHg was considered hypertension.[18] The grade of hepatic steatosis was determined using ultrasound reports available in files, and those for whom at least two ultrasounds showed an equal amount of hepatic contrast were classified into one of the three categories of mild, moderate, and severe steatosis. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2), and BMI <25 kg/m^2 was considered normal, 25–29.99 kg/m^2 as overweight, 30–34.99 kg/m^2 as obesity Class 1, 35–39.99 kg/m^2 as obesity Class 2, and ≥40 kg/m^2 as obesity Class 3.[19] Waist-to-hip ratio > 0.9 in women and >1 in men was considered abnormal, and those who had 3 or more of the following criteria were considered to have MS: (1) waist circumference >102 cm

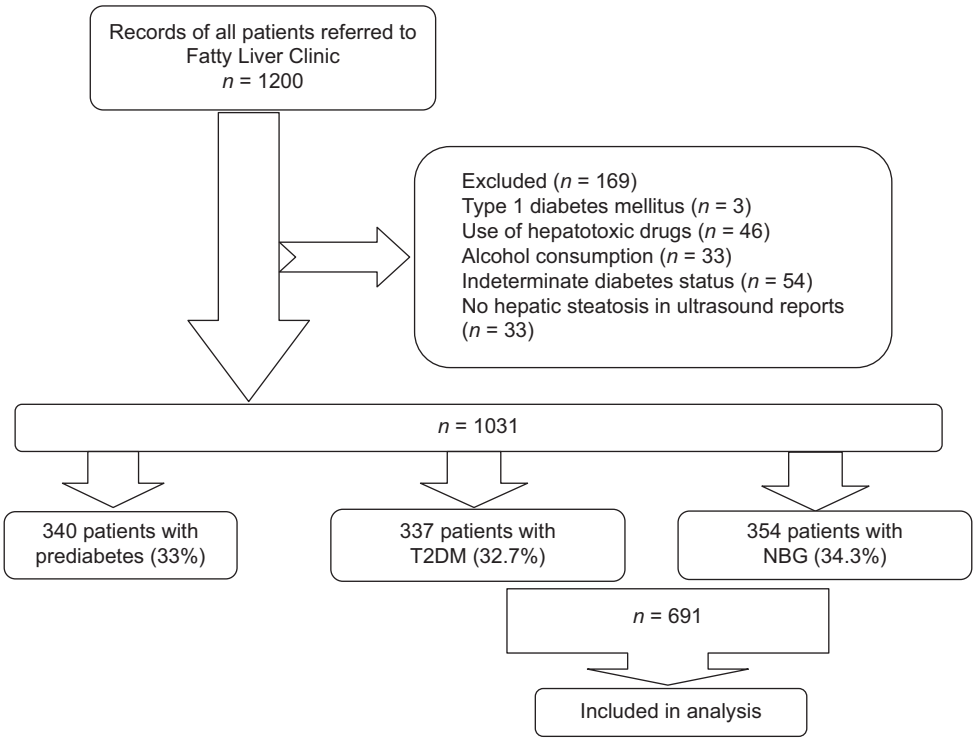

Figure 1: The flow diagram of patient selection and study design. T2DM = Type 2 diabetes mellitus; NBG = Normal blood glucose

for males and >88 cm for females, (2) TG ≥150 mg/dL, (3) FPG ≥100 mg/dL, (4) blood pressure ≥130/85 mmHg, and (5) HDL cholesterol <40 mg/dL for males and <50 mg/dL for females.[19]

In this study, the frequency of T2DM based on basic demographic and clinical characteristics of NAFLD patients such as age, sex, grade of hepatic steatosis, BMI, and waist-to-hip ratio was calculated at first. Then, for comparing diabetic and nondiabetic patients, the files were divided into two groups: NAFLD with T2DM (n = 337) and NAFLD with NBG (n = 354). Age, BMI, waist circumference, hip circumference, wrist circumference, systolic and diastolic blood pressure, lipid profile, AST, ALT, and also the frequency and the risk of CVD, hypertension, and MS were compared between the two groups.

The Ethics Committee of Isfahan University of Medical Sciences approved the current study (code: IR.MUI.MED.REC.1399.272).

Statistical analysis

Data analysis was performed using version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) of SPSS software. Numerical variables were reported as mean and standard deviation and nonnumerical variables were reported as number and percentage. Comparison of numerical variables at the levels of nonnumerical variables was performed by a two-sample independent t-test. Chi-squared test was used for the comparison of qualitative variables. Multiple binary logistic regressions in crude and adjusted models were used to evaluate the risk of (odds ratio [OR]) CVD, hypertension, and MS in T2DM NAFLD patients compared to NBG NAFLD patients. P <0.05 was considered statistically significant.

RESULTS

The patients included in the study were 691 NAFLD patients who had NBG and type 2 diabetes, and prediabetes patients were excluded [Figure 1]. Out of 691 patients with NAFLD, 297 (43%) were male and 394 (57%) were female and the mean age was 47.94 ± 11.72. Among the 691 patients participating in the study, 337 patients (48.8%) had type 2 diabetes. While 325 of them (96.4%) were the known cases of T2DM, 12 patients (3.6%) turned out to be the new cases of T2DM. The frequency of T2DM was remarkably higher in women than men. With increasing age and BMI, the prevalence of T2DM increased significantly. The frequency of T2DM in patients with moderate or severe hepatic steatosis was higher than in patients with mild steatosis, and the difference was remarkable. The frequency of T2DM was significantly higher in people with abnormal waist-to-hip ratio than those with normal waist-to-hip ratio [Table 1].

The mean age of the T2DM group was 53.1 ± 8.9, and in the NBG group, it was 43.0 ± 11.9 and the difference was significant (P < 0.001). In physical examination parameters,

there was no significant difference in diastolic blood pressure, hip circumference, and wrist circumference between the two groups. However, BMI, waist circumference, and systolic blood pressure in the T2DM group were significantly higher than the NBG group. In laboratory findings AST, ALT, and HDL were not remarkably different between the two groups. TG in the T2DM group was significantly higher than the NBG group, but total cholesterol and LDL were lower in the T2DM group, and the difference was significant. It should be noted that in the results above, it is not considered whether patients were taking medication or not [Table 2].

Table 1: Basic demographic and clinical characteristics of studied nonalcoholic fatty liver disease patients according to type 2 diabetes mellitus status

Variables	T2DM group (*n*=337; 48.8%), *n* (%)	NBG group (*n*=354; 51.2%), *n* (%)	*P**
Sex			
Man	113 (38)	184 (62)	<0.001
Woman	224 (56.9)	170 (43.1)	
Age (years)			
≤30	3 (5.1)	56 (94.9)	<0.001
31–40	28 (22.6)	96 (77.4)	
41–50	74 (42.5)	100 (57.5)	
51–60	169 (69.8)	73 (30.2)	
>60	59 (68.6)	27 (31.4)	
BMI (kg/m^2)			
<25	20 (37.7)	33 (62.3)	0.001
25–29.99	116 (43)	154 (57)	
30–34.99	134 (52.8)	120 (47.2)	
35–39.99	43 (57.3)	32 (42.7)	
≥40	15 (62.5)	9 (37.5)	
Waist-to-hip ratio			
Normal	130 (33.6)	257 (66.4)	<0.001
Abnormal[a]	196 (69)	88 (31)	
Hepatic steatosis grade[b]			
Mild	100 (38)	163 (62)	<0.001
Moderate	196 (55.7)	156 (44.3)	
Severe	41 (53.9)	35 (46.1)	

*Resulted from Chi-squared test, [a]Waist-to-hip ratio >0.9 in women and >1 in men was considered abnormal, [b]The hepatic steatosis grade was determined on two separate occasions based on the ultrasound report. BMI=Body mass index; NBG=Normal blood glucose; *n*=Number of patients; T2DM=Type 2 diabetes mellitus

Table 2: Cardiometabolic risk factors in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease patients with normal blood glucose

Variables	T2DM group	NBG group	*P**
BMI (kg/m^2)	31.2±4.6	29.9±4.3	0.001
Waist circumference (cm)	102.2±10.2	97.6±10.6	<0.001
Hip circumference (cm)	105.1±8.4	105.5±7.9	0.532
Wrist circumference (cm)	17.1±1.2	17.1±1.3	0.872
SBP (mmHg)	123.3±15.6	119.6±13.6	0.043
DBP (mmHg)	79.6±8.4	80±9.3	0.683
TG (mg/dL)	191.9±104.7	176.5±89.6	0.042
Total cholesterol (mg/dL)	183.9±42.9	196±39.4	<0.001
HDL (mg/dL)	43.2±11.4	44.1±10.6	0.286
LDL (mg/dL)	103.5±36.3	115±32.7	<0.001
AST (U/L)	33.2±17.2	31.7±17.8	0.296
ALT (U/L)	44.1±24	44.9±28.4	0.719

*Resulted from independent samples *t*-test. Data are presented as mean±SD. ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; BMI=Body mass index; DBP=Diastolic blood pressure; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; NBG=Normal blood glucose; SBP=Systolic blood pressure; TG=Triglyceride; T2DM=Type 2 diabetes mellitus; SD=Standard deviation

CVD, hypertension, and MS in the T2DM group were significantly more prevalent than the NBG group. In addition, our findings revealed an increased significant risk of CVD, hypertension, and MS (All OR >1; $P < 0.001$ in crude model) among NAFLD patients with T2DM compared to those with NBG. Moreover, even after adjusting confounding factors such as age, sex, BMI, smoking, and physical activity, the results remained significant [Table 3].

DISCUSSION

In the present study, the frequency of NAFLD was higher in women. The frequency of type 2 diabetes increased in people with abnormal waist-to-hip ratio as well as increasing age and increasing BMI. In lipid profile, TG in the T2DM group was significantly higher than the NBG group, but total cholesterol and LDL were significantly lower in the T2DM group, and HDL was not remarkably different between the two groups. In type 2 diabetes patients, CVD, hypertension, and MS were significantly more than in the NBG group.

NAFLD is the most common chronic liver disease affecting a quarter of the adult population worldwide.[4] In a recent meta-analysis of 86 studies, the global prevalence of NAFLD was estimated at 25.24%,[20] and based on the results of other meta-analyses, its prevalence was approximately doubled (54%–59.67%) in T2DM patients.[21] This study examined the frequency of T2DM in patients with NAFLD, which was 32.7% in the total population of 1031 patients and is similar to the results obtained in the study of Wong *et al*. in Hong Kong, performed on 73 NAFLD patients where the frequency was 33%.[22] However, in a study conducted in the Philippines on a population of 134 people much smaller than our population, the prevalence was 60% and was higher than the current study.[23] Furthermore, in another case–control study conducted by Fan *et al*. in China in the case group of 358 people with NAFLD, the prevalence of T2DM was reported to be 14.8%, which was less than our study.[24] Some studies suggest that NAFLD may increase the risk of T2DM as well as prediabetes.[13,25] The results of a follow-up showed that 78% of patients with NAFLD may develop T2DM or impaired glucose tolerance.[26]

According to the results of a systematic review article, NAFLD can predict the risk of T2DM, regardless of age and BMI.[27] Mantovani *et al*. stated that NAFLD doubles the risk

Table 3: Frequency and risk of cardiovascular disease, hypertension, and metabolic syndrome in nonalcoholic fatty liver disease patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease patients with normal blood glucose

Variables	T2DM group, *n* (%)	NBG group, *n* (%)	*P*	Unadjusted OR (95% CI for OR)	AOR (95% CI for OR)*
CVD	60 (17.8)	20 (5.6)	<0.001	3.9 (2.16–7.03)	2.18 (1.16–4.10)
Hypertension	173 (51.3)	85 (24)	<0.001	3.72 (2.59–5.33)	2.12 (1.42–3.17)
MS	231 (68.8)	86 (24.4)	<0.001	6.93 (4.82–9.96)	6.63 (4.34–10.11)

*Adjustment was made for age, sex, BMI, smoking, and physical activity. CVD=Cardiovascular disease; MS=Metabolic syndrome; OR=Odds ratio; NBG=Normal blood glucose; T2DM=Type 2 diabetes mellitus; BMI=Body mass index; CI=Confidence interval; AOR=Adjusted OR

of developing T2DM, and it seems that, as the severity of liver disease increases, the risk of developing T2DM will also grow.[28] The results of our study show that the prevalence of T2DM in patients with NAFLD increases with age and BMI, and the frequency of T2DM is higher in moderate or severe steatosis than in mild steatosis. However, since our study is a cross-sectional study and the duration of T2DM and NAFLD in patients and their precedence and latency are not specified, it is not possible to say for sure whether NAFLD and its grade of steatosis increased the risk of developing T2DM or not.

In our study, 43% of all patients with NAFLD were men and 57% were women, and the frequency of women was higher than men. These results differ from the study by Bacon *et al*.[29] in which the frequency of males was 58% and the frequency of females was 42%, and this could be due to racial, geographical, and sampling method differences.

In a cross-sectional study from Leite *et al*. in which NAFLD was also diagnosed and graded by ultrasound, it was observed that in people with T2DM who also had NAFLD, the distribution of steatosis severity was 34.2% mild, 53.8% moderate, and 12% severe.[30] These results are consistent with the grade of steatosis obtained in our study (29.7% mild, 58.2% moderate, and 12.1% severe).

T2DM increases mortality in patients with NAFLD.[31] CVDs are the most important causes of death in NAFLD, which are mostly caused by metabolic changes associated with NAFLD. For this reason, it is emphasized that when we encounter patients with NAFLD, screening for T2DM and MS is essential.[32] According to a meta-analysis by Younossi *et al*., it is concluded that compared to those with only T2DM, patients with both T2DM and NAFLD are at higher risk for developing hypertension, dyslipidemia, CVD, and peripheral and cerebrovascular diseases.[20] Furthermore, an observational study showed that patients with NAFLD longer than T2DM had a higher prevalence of coronary artery disease and hypertension than those with T2DM longer than NAFLD.[33] In the study we performed, the frequency and the risk of CVD, hypertension, and MS were significantly higher in NAFLD patients with T2DM than those with NBG.

A cross-sectional study conducted by Vanjiappan *et al*. on a population of 300 people with T2DM concluded that between the group of NAFLD with T2DM and the group of T2DM without NAFLD, there was no difference in AST, ALT, TG, LDL, and HDL. However, BMI was significantly higher in the group with both NAFLD and T2DM.[34] In another study, ALT, TG, and BMI were higher in the group with both NAFLD and T2DM than the group with just T2DM, and the difference was significant. However, AST, LDL, HDL, and Total cholesterol were not significantly different between the two groups.[30] Zhang *et al*. found that in the group of NAFLD with T2DM, BMI, TG, total cholesterol, LDL, and ALT were significantly higher than the group with only T2DM. However, there was no significant difference between group of NAFLD with T2DM and group with only T2DM in AST, HDL, systolic and diastolic blood pressure and mean age.[35] In the patients we studied, there was a significant difference in mean age, BMI, waist circumference, systolic blood pressure, TG, LDL, and total cholesterol between NAFLD patients with T2DM and NAFLD patients with NBG; thus, total cholesterol and LDL were higher in NBG group and other variables were higher in the other group. It seems that total cholesterol and LDL in the group with T2DM are lower due to the use of glucose and lipid-lowering medication and the detection of dyslipidemia following the T2DM diagnosis. Furthermore, these patients are being regularly checked by their physician for their blood pressure, glucose, and lipids. In addition, the LDL treatment goal in patients with T2DM is lower than NBG patients, and a more rigid treatment is performed in T2DM patients, which can also cause lower LDL in this group. Hip circumference, wrist circumference, diastolic blood pressure, AST, ALT, and HDL were not significantly different between the two groups.

In our study, the waist-to-hip ratio was abnormal in 25.5% of the NAFLD group with NBG, and in the NAFLD group with T2DM, it reached 60.1%. At the same time, in the NBG population, 90.5% of the subjects were overweight or obese. Based on these findings, we conclude that most people in the NBG group had generalized obesity.

One of the limitations of our study was being retrospective. On the other hand, patients were receiving treatment before being referred to fatty liver clinic and therefore it was not possible to determine the mean of lipids and liver enzymes

before starting to take medication. One of the strengths of our study was the large number of patients, and we can claim that this population can be a representative of the entire NAFLD community in this area.

CONCLUSION

In this study, nearly a third of the population of patients with NAFLD had T2DM. With increasing age and BMI, the prevalence of T2DM in NAFLD patients increased. The frequency of CVD, hypertension, and MS in patients with T2DM was higher than NBG patients. In multiple logistic regression models, the OR of CVD, hypertension, and MS in NAFLD patients with T2DM was higher than NAFLD patients with NBG. As the patients were from a limited geographical area, further studies are necessary to confirm these results. In the present single-center study, CVRFs were investigated in patients with NAFLD. We recommended comparing the risk factors of CVD in a multicenter study by including people without NAFLD and NAFLD patients. However, the pathogenesis of NAFLD is still not well understood. So far, the role of factors such as overweight, obesity, adiponectin, insulin resistance, gut microbiota, and genetic predisposition in the pathogenesis of fatty liver has been suggested.[36,37] It is recommended that future studies be conducted on this population in order to identify the pathogenesis of NAFLD.

Acknowledgments

The cooperation Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences is hereby appreciated.

Authors' contribution

1. MB: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or reviewing it critically for important intellectual content; AND final approval of the version to be published
2. AT: Drafting the work or reviewing it critically for important intellectual content; AND final approval of the version to be published
3. AF: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND final approval of the version to be published
4. BI: Drafting the work or reviewing it critically for important intellectual content; AND final approval of the version to be published
5. MK: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND drafting the work or reviewing it critically for important intellectual content; AND final approval of the version to be published; AND agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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