ORIGINAL ARTICLE

Indirect insulin resistance markers are associated with nonalcoholic fatty liver disease in type 1 diabetes

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KEY WORDS

insulin resistance, liver steatosis, type 1 diabetes

EDITORIAL

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ABSTRACT

INTRODUCTION Insulin resistance (IR) in type 1 diabetes mellitus (T1DM) is associated with increased insulin dose requirements, poor glycemic control, and elevated risk of chronic complications. IR increases lipid synthesis and hepatic lipid content. Disruption in hepatic lipid accumulation and export leads to liver steatosis resulting in nonalcoholic liver disease (NAFLD).

OBJECTIVES The aim of the study was to explore the relationship between indirect IR markers and NAFLD in T1DM.

PATIENTS AND METHODS We analyzed 151 patients with T1DM (59 men, 92 women), with a median (interquartile range [IQR]) age of 40 (33–47) years and a median (IQR) diabetes duration of 19 (13–21) years. The median (IQR) value of glycated hemoglobin (HbA_{1c}) was 7.5% (6.8%–8.%; 58 [51–66] mmol/mol). The following indirect IR markers were evaluated: estimated glucose distribution rate (eGDR), visceral adiposity index (VAI), and the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C). Fatty infiltration of the liver was quantified using transient elastography. Presence of NAFLD was defined as a controlled attenuation parameter value of 238 dB/m or greater.

RESULTS NAFLD was observed in 65 patients (43%). The participants with NAFLD were less insulin-sensitive (eGDR, 8.93 [6.39–9.97] vs 9.94 [8.09–11.13] mg/kg/min; $P = 0.001$; VAI, 1.52 [1.2–2.64] vs 1.34 [0.92–1.74]; $P = 0.014$; TG/HDL-C ratio, 1.35 [0.95–2.11] vs 1.11 [0.77–1.6]; $P = 0.02$) and were characterized by higher HbA_{1c} values (7.75% [7.2%–8.4%] vs 7.3% [6.5%–8.1%]; 61 [55–68] vs 56 [48–65] mmol/mol; $P = 0.02$) than the patients without the disease. In a multivariable regression analysis adjusted for sex, diabetes duration, and HbA_{1c} level, indirect IR markers were independently associated with NAFLD (eGDR: odds ratio [OR], 0.86; 95% CI, 0.77–0.97; $P = 0.01$; VAI: OR, 1.61; 95% CI, 1.05–2.49; $P = 0.03$, TG/HDL-C ratio: OR, 1.88; 95% CI, 1.11–3.18; $P = 0.02$).

CONCLUSIONS In T1DM, NAFLD is more likely to be found in individuals with lower insulin sensitivity.

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INTRODUCTION Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by destruction of β cells and absolute insulin deficiency. Insulin resistance (IR) is a state in which 1) higher-than-normal insulin concentrations are required to achieve a normal metabolic response or 2) normal insulin concentrations fail to achieve the metabolic response.[1] In T1DM, exogenous insulin supplementation is adjusted to a patient's insulin requirement. Despite insulin treatment tailored to individual needs, IR might still develop in T1DM. IR is linked to the following clinical factors: increased waist-to-hip ratio (WHR), hypertension, family history of type 2 diabetes

WHAT'S NEW?

Individuals with type 1 diabetes (T1DM) typically present as young, lean patients. However, in the course of the disease, alongside a growing demand for insulin, especially when accompanied by unhealthy lifestyle, they might gain body weight and their insulin sensitivity might decrease. T1DM patients with an unfavorable metabolic profile might be characterized by increased liver fat content. Our study shows an association between decreased insulin sensitivity, as described by indirect insulin resistance (IR) markers, and nonalcoholic fatty liver disease (NAFLD) in T1DM. It describes the prevalence of NAFLD in a Polish population of patients with T1DM, explores insulin sensitivity in individuals with and without NAFLD, and shows an association of indirect IR markers with liver steatosis, independently of sex, diabetes duration, and metabolic control.

mellitus (T2DM), and an increased glycated hemoglobin (HbA_{1c}) level. The mechanism that leads to IR is based on excessive hepatic glucose production, impaired suppression of hepatic glucose production, and reduced skeletal muscle glucose transport and blood flow.[2]

Individuals with T1DM treated with intensive functional insulin therapy are trained in self-administration and dosage adjustment of exogenous insulin. Physiologically, insulin is secreted into the portal vein, where it achieves its highest concentration. The liver clears between 40% and up to 80% of the portal insulin during the first-pass transit, creating a significant gradient between the portal and systemic circulation.[3] In contrast, subcutaneous insulin injections result in relative peripheral hyperinsulinemia and hepatic hypoinsulinemia.[4] Consequently, peripheral glucose uptake and muscle glycogen synthesis are higher, but the suppression of liver glucose production and liver glycogen synthesis are lower, which explains the mechanism through which exogenous insulin triggers IR in T1DM. An additional risk factor for IR in T1DM might be possible weight gain after initiation of the insulin therapy.[4] Moreover, constant weigh gain caused and accompanied by unhealthy lifestyle may lead to so-called double diabetes, that is, coexistence of a T1DM phenotype and the burden of IR in a person initially diagnosed with T1DM.

IR alters lipid metabolism via the mechanism of lipotoxicity caused by excessive lipolysis, adipogenesis, and IR of the adipose tissue.[5] Therefore, IR is both the cause and the result of lipotoxicity. The imbalance in lipid metabolism leads to organ dysfunction, with liver being one of them. Excessive lipolysis results in free fatty acid flux into the liver, causing steatosis and lipotoxic effects, which are the key factors for the development of nonalcoholic fatty liver disease (NAFLD).

NAFLD is associated with metabolic syndrome (MetS).[6] To underline the pathogenesis of fatty liver disease and focus on clinical characteristics of patients at risk, a new definition, namely metabolic dysfunction–associated liver disease (MAFLD) has been proposed.[7] In the flowchart for the MAFLD diagnosis, the backbone of the 3 criteria (overweight or obesity, T2DM, or at least 2 metabolic abnormalities in lean / normal-weight individuals) is IR. The gold standard for measuring IR is the hyperinsulinemic-euglycemic clamp. However, this method is invasive as well as cost- and time-consuming. Therefore, in clinical settings, it is easier to replace it with indirect IR markers. The most popular IR estimation methods, such as the homeostatic model assessment (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), include insulinemia and glucose concentrations in the calculation formula, and therefore are inadequate in people treated with exogenous insulin. Estimated glucose distribution rate (eGDR), visceral adiposity index (VAI), and the trigliceryde to high-density lipoprotein cholesterol ratio (TG/HDL-C) are easily applicable, noninvasive IR markers, and their validity in comparison with the hyperinsulinemic-euglycemic clamp has been proven in previous studies.[2,8-10]

Increased risk of cardiovascular disease is still a challenge in terms of preventing long-term complications of T1DM.[11] It has been shown that the prevalence of subclinical atherosclerosis as well as cardiovascular complications (coronary artery disease, cardiovascular events, cerebrovascular disease, peripheral vascular disease) is higher in T1DM patients with NAFLD.[12-16] However, the independent contribution of NAFLD to the development of cardiovascular disease in T1DM is yet to be established. IR leads to an increased risk of both NAFLD and cardiovascular disease. Thus, improving insulin sensitivity, which is the principal component of NAFLD management,[17] could also result in decreased cardiovascular risk for patients with T1DM.

We hypothesized that insulin-resistant individuals with T1DM were characterized by a greater amount of hepatic fat content. Therefore, the aim of the study was to explore the relationship between indirect IR markers and NAFLD in T1DM.

PATIENTS AND METHODS **Patients** During the year 2017, a total of 151 individuals with T1DM (59 men and 92 women) treated at the Department of Internal Medicine and Diabetology at the Poznan University of Medical Sciences in Poland and the Department of Internal Medicine and Nephrodiabetology at the Medical University of Lodz in Poland were recruited to the study. The recruitment took place during regular outpatient visits or scheduled hospitalizations for the assessment of chronic diabetes complications or patient reeducation. The participants were over 18 years old and had at least a 10-year history of the disease. Excluded were individuals with positive serology for viral hepatitis and / or chronic liver disease and / or those with a daily alcohol consumption greater than or equal to 30 g for men and 20 g for women.[18] All participants gave their written informed consent before

TABLE 1 Clinical characteristics of the study population

Variable		Value
Sex	Male	59 (39)
	Female	92 (61)
Age, y		40 (33–47)
Diabetes duration, y		19 (13–21)
Daily insulin dose, U		42 (34–57.2)
Smoking		27 (18)
Body weight, kg		73 (63–85)
BMI, kg/m^2		24.5 (21.8–28.2)
WHR		0.84 (0.78–0.88)
SBP, mm Hg		129 (120–143)
DBP, mm Hg		79 (74–85)
HbA_{1c}, %; mmol/mol		7.5 (6.8–8.2); 58 (51–66)
hs-CRP, mg/l		0.81 (0.64–1.33)
Creatinine, mg/dl		0.86 (0.77–0.99)
eGFR (CKD-EPI), ml/min/1.73 m^2		101(89–110)
TC, mg/dl		181 (164–202)
LDL-C, mg/dl		98 (80–117)
HDL-C, mg/dl		65 (57–78)
TG, mg/dl		84 (63–109)
ALT, U/l		18 (13–23)
AST, U/l		18 (15–22)
eGDR, mg/kg/min		9.41 (7.3–10.8)
VAI		1.43 (1.04–2.04)
TG/HDL-C ratio		1.20 (0.88–1.72)
CAP, dB/m		235 (207–271)
Stiffness, kPa		4.6 (3.8–5.4)

Data are shown as number (percentage) or median (interquartile range).

SI conversion factors: to convert hs-CRP to nmol/l, multiply by 9.524; creatinine to µmol/l, by 88.4, TC, HDL-C, and LDL-C to mmol/l, by 0.0259; TG to mmol/l, by 0.0113; ALT and AST to µkat/l, by 0.0167.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; eGDR, estimated glucose distribution rate; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglicerydes, VAI, visceral adiposity index; WHR, waist-to-hip ratio

enrolment. The study was approved by the Medical Ethical Committee of Poznan University of Medical Sciences (1080/17), and was carried out in accordance with the principles of the Declaration of Helsinki.

Data collection and anthropometric measurements Data on sex, age, diabetes duration, medical history, medications used, alcohol intake, and smoking status were collected via a questionnaire. Anthropometric and blood pressure measurements were recorded at the time of admission to the hospital. Blood pressure was measured after a 10-minute rest, in a sitting position. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and WHR as the ratio of waist circumference to hip circumference.

Biochemical analysis Blood samples were collected after overnight fasting using the S-Monovette blood collection system (Sarstedt, Nümbrecht, Germany). The HbA_{1c} level was measured using the competitive turbidimetric inhibition immunoassay (Cobas 6000, Roche Diagnostics, Basel, Switzerland). Serum levels of total cholesterol, low-density lipoprotein cholesterol, HDL-C, and TG were measured using the enzymatic colorimetric technique with the Cobas 6000 device. The high-sensitivity C-reactive protein concentration in serum was measured by the highly-sensitive microparticle turbidimetric immunoassay. Creatinine levels were measured using the kinetic method. The estimated glomerular filtration rate was calculated with the 2021 Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).[19] Alanine aminotransferase and aspartate aminotransferase levels in serum were measured using commercially available enzymatic methods (Roche Diagnostics, Basel, Switzerland).

Indirect markers of insulin resistance We evaluated indirect IR markers using the following equations: 1) eGDR = 24.31 – (12.22 × WHR) – (3.29 × arterial hypertension 0/1) – (0.57 × HbA_{1c}); 2) VAI = (waist circumference/39.68 + [1.88 × BMI]) × [TG/1.03] × [1.31/HDL-C]) for men or VAI = (waist circumference/36.58 + [1.89 × BMI]) × [TG/0.81] × [1.52/HDL-C]) for women; and 3) TG/HDL-C = serum TG (mg/dl) / HDL-C level (mg/dl).

Daily insulin dose representing a patient's requirement for exogenous insulin was expressed in units (U) and calculated as a mean daily sum of basal and prandial insulin.

Liver steatosis and fibrosis assessment Transient elastography (TE) was performed to assess liver steatosis and fibrosis. The measurements were taken by experienced operators using a FibroScan device (Echosens, Paris, France). The patients were examined with either a 3.5-MHz standard M probe or, when appropriate, with a 2.5-MHz XL probe. TE results for controlled attenuation parameter (CAP), representing liver steatosis, were expressed in decibels per meter (dB/m), and for stiffness, representing fibrosis, in kilopascals (kPa). At least 10 valid measurements and a CAP value with an interquartile range (IQR) of 0 to 40 dB/m had to be obtained to allow for further analysis. NAFLD was defined as hepatic steatosis described by CAP of 238 dB/m or greater in the absence of other causes of chronic liver disease.[20]

Statistical analysis Normality of data distribution was tested using the Kolmogorov–Smirov test with the Lilliefors correction. Data are presented as median with IQR for continuous variables or number and percentage for categorical variables. To compare the groups according to the presence of NAFLD, the Mann–Whitney test or the χ^2 test was used. Correlations between clinical parameters, indirect IR markers, and CAP

TABLE 2 Characteristics of the study patients according to the presence of nonalcoholic fatty liver disease[a]

Parameter	No NAFLD (n = 86)	NAFLD (n = 65)	*P* value
Male sex	30 (20)	29 (19)	0.15
Age, y	38 (28–44)	43 (38–52)	<0.001
Diabetes duration, y	18 (11–20)	20 (17–21)	0.009
Daily insulin dose, U	36.5 (31.4–48)	50.2 (39–63)	<0.001
Smoking	13 (9)	14 (9)	0.21
Body weight, kg	66.5 (58.1–74.2)	83.5 (73–99.1)	<0.001
BMI, kg/m^2	22.8 (20.2–24.8)	28.2 (24.9–30.3)	<0.001
WHR	0.82 (0.75–0.87)	0.86 (0.82–0.95)	0.001
SBP, mm Hg	126 (117–136)	134 (124–145)	0.006
DBP, mm Hg	79 (74–85)	80 (75–85)	0.72
HbA_{1c}, %; mmol/mol	7.3 (6.5–8.1); 56 (48–65)	7.75 (7.2–8.4); 61 (55–68)	0.02
hs-CRP, mg/l	0.73 (0.61–1.1)	0.93 (0.69–3.15)	0.004
Creatinine, mg/dl	0.82 (0.76–0.94)	0.88 (0.79–1)	0.14
eGFR (CKD-EPI), ml/min/1.73 m^2	104 (95–111)	98 (86–110)	0.16
TC, mg/dl	177 (161–195)	185 (166–211)	0.08
LDL-C, mg/dl	94 (76–113)	102 (86–124)	0.045
HDL-C, mg/dl	69 (60–81)	62 (55–74)	0.04
TG, mg/dl	80 (61–101)	91 (67–114)	0.04
ALT, U/l	17 (13–21)	19 (15.5–26)	0.02
AST, U/l	18 (15–22)	18 (15–22)	0.84
eGDR, mg/kg/min	9.94 (8.09–11.13)	8.93 (6.39–9.97)	0.001
VAI	1.34 (0.92–1.74)	1.52 (1.2–2.64)	0.01
TG/HDL-C ratio	1.11 (0.77–1.6)	1.35 (0.95–2.11)	0.02
CAP, dB/m	212 (195–225)	279 (257–309)	<0.001
Stiffness, kPa	4.45 (3.9–4.3)	4.7 (3.7–5.8)	0.32

Data are shown as number (percentage) or median (interquartile range). Variables were compared using the Mann-Whitney test, except for sex (χ^2 test). Differences were considered significant at P <0.05.

a Presence of NAFLD was defined as CAP ≥238 dB/m.

SI conversion factors: see TABLE 1

Abbreviations: NAFLD, nonalcoholic fatty liver disease; others, see TABLE 1

were assessed with the Spearman test (Spearman correlation coefficient, Rs). Subsequently, the parameters associated with steatosis were estimated using multivariable logistic regression analysis. Each model focused on a different indirect IR marker and was adjusted for sex, diabetes duration, and HbA_{1c} level.

Statistical analyses were performed using Statistica 12 (StatSoft, Kraków, Poland). *P* values lower than 0.05 were considered significant.

RESULTS

Anthropometric and clinical characteristics of the study population

Clinical characteristics of the study population are shown in TABLE 1. The median (IQR) age of the patients was 40 (33–47) years, and the median (IQR) duration of diabetes was 19 (13–21) years. The median (IQR) value of HbA_{1c} was 7.5% (6.8%–8.2%; 58 [51–66] mmol/mol). Serum levels of liver enzymes were within normal ranges. The median (IQR) CAP value was 235 (207–271) dB/m, and median (IQR) stiffness was 4.6 (3.8–5.4) kPa. NAFLD was found in 65 patients (43%).

Patient characteristics according to the presence of nonalcoholic fatty liver disease

The patients with NAFLD were older (43 [38–52] vs 38 [28–44] years; P<0.001) and had a longer history of diabetes (20 [17–21] vs 18 [11–20] years; P = 0.009) than the individuals without the disease. Both daily insulin dose and HbA_{1c} values were higher in the patients with NAFLD: 50.2 (39–63) vs 36.5 (31.4–48) U; P <0.001 and 7.75% (7.2%–8.4%) vs 7.3% (6.5%–8.1%; 9.8 [8.9–10.8] vs 9 [7.8–10.3] mmol/l, P = 0.02), respectively. The patients with NAFLD were characterized by clinical signs of IR—they had higher BMI (28.2 [24.9–30.3] vs 22.8 [20.2–24.8] kg/m^2; P <0.001) and greater WHR (0.86 [0.82–0.95] vs 0.82 [0.75–0.87]; P = 0.001) than the individuals without NAFLD. Based on the indirect IR markers, the patients with NAFLD were less insulin-sensitive, as shown by lower eGDR (8.93 [6.39–9.97] vs 9.94 [8.09–11.13] mg/kg/min; P = 0.001), higher VAI (1.52 [1.2–2.64] vs 1.34 [0.92–1.74]; P = 0.01), and higher TG/HDL-C ratio (1.35 [0.95–2.11] vs 1.11 [0.77–1.6]; P = 0.02) in this group. A detailed comparison of both groups is presented in TABLE 2.

Parameters associated with liver steatosis

All the analyzed indirect IR markers correlated with CAP: eGDR, Rs = –0.27; P = 0.001; VAI, Rs = 0.28; P = 0.002; TG/HDL-C ratio, Rs = 0.26; P = 0.003. We also observed a significant correlation between CAP and diabetes duration (Rs = 0.21; P = 0.01), HbA_{1c} values (Rs = 0.21; P = 0.01), BMI (Rs = 0.71; P <0.001), and WHR (Rs = 0.36; P <0.001) (TABLE 3).

In multivariable regression analysis (TABLE 4), we built 3 models adjusted for sex, diabetes duration, and HbA_{1c} and showed an association between the indirect IR markers and NAFLD (odds ratio [OR], 0.86; 95% CI, 0.77–0.97; P = 0.01; OR, 1.61; 95% CI, 1.05–2.49; P = 0.03; and OR, 1.88; 95% CI, 1.11–3.18; P = 0.02 for eGDR, VAI, and TG/HDL-C ratio, respectively).

DISCUSSION

In the present study, we showed that NAFLD can develop in individuals with T1DM, and its prevalence (around 40%, as determined by TE) was comparable with that reported in other studies,[21] as well as with data from analyses using ultrasound imaging for the diagnosis.[15,22] The most important finding of this study is that individuals with T1DM and NAFLD are less insulin-sensitive, and the association between indirect IR markers and steatosis is independent of sex, diabetes duration, and HbA_{1c} values.

Prevalence of nonalcoholic fatty liver disease in type 1 diabetes

Fatty liver is characterized by accumulation of excess fat (mainly TG) in the liver. The most benign form of the condition is simple

TABLE 3 Correlations between the clinical parameters/indirect insulin resistance markers and the controlled attenuation parameter

Parameter	Rs[a]	*P* value
Age, y	0.25	0.002
Diabetes duration, y	0.21	0.01
Daily insulin dose, U	0.44	<0.001
Body weight, kg	0.68	<0.001
BMI, kg/m^2	0.71	<0.001
WHR	0.36	<0.001
SBP, mm Hg	0.19	0.02
DBP, mm Hg	0.08	0.35
HbA_{1c}, %	0.21	0.01
hs-CRP, mg/l	0.20	0.01
TC, mg/dl	0.11	0.19
LDL-C, mg/dl	0.14	0.11
HDL-C, mg/dl	–0.22	0.02
TG, mg/dl	0.22	0.01
eGDR, mg/kg/min	–0.27	0.001
VAI	0.28	0.002
TG/HDL-C ratio	0.26	0.003

Differences were considered significant at $P < 0.05$.

a Spearman correlation coefficient

TABLE 4 Parameters associated with nonalcoholic fatty liver disease in multivariate regression analysis

Parameter	OR	95% CI	*P* value
Model 1[a] (n = 151)			
Sex (men = 1, women = 0)	0.95	0.2–4.44	0.94
Diabetes duration, y	1.07	1.01–1.13	0.02
eGDR, mg/kg/min	0.86	0.77–0.97	0.01
Model 2 (n = 115)			
Sex (men = 1, women = 0)	0.87	0.38–2	0.75
Diabetes duration, y	1.05	0.98–1.12	0.15
HbA_{1c}, %	1.05	0.75–1.47	0.78
VAI	1.61	1.05–2.49	0.03
Model 3 (n = 124)			
Sex (men = 1, women = 0)	0.97	0.45–2.1	0.94
Diabetes duration, y	1.07	1.00–1.14	0.047
HbA_{1c}, %	1.04	0.75–1.45	0.81
TG/HDL-C ratio	1.88	1.11–3.18	0.02

a HbA_{1c} level was not included in Model 1 as it is part of the eGDR formula.

Abbreviations: see TABLE 1

steatosis, while steatohepatitis and fibrosis may progress to cirrhosis.[23] Based on the alcohol consumption, the abnormalities are classified as alcoholic fatty liver disease (AFLD) or NAFLD.[24,25] NAFLD is the most common liver disease and its prevalence in the general population in the United States and Europe is estimated to be around 20% to 25%.[24,26] In patients with obesity, T2DM, hypertension, and dyslipidemia the prevalence is estimated at around 80% to 90%, 30% to 50%, 50%, and 50% to 90% respectively.[27-29]

In the present study, using TE, we found that 43% of the patients with T1DM had liver steatosis. This is in line with the results presented by Serdarova et al,[21] who reported NAFLD prevalence of 47% in a group of 115 patients with T1DM. In a study by Targher et al,[15] the prevalence of ultrasound-diagnosed NAFLD in T1DM patients was shown to be 44.4%. This study comprised patients at a similar age to our cohort, and with a comparable duration of diabetes and BMI values. Our study, although using a different diagnostic method, confirms high prevalence of NAFLD in the T1DM population.

Lower insulin sensitivity in the patients with nonalcoholic fatty liver disease NAFLD is frequently associated with components of MetS.[30,31] According to the 2009 Joint Interim Statement,[32] MetS components should meet the following criteria: 1) elevated waist circumference (population- and country-specific definitions), 2) TG level greater than or equal to 150 mg/dl or treatment for hypertriglyceridemia, 3) reduced HDL-C level (<140 mg/dl in men and <50 mg/dl in women) or treatment for reduced HDL-C levels, 4) hypertension (blood pressure ≥130/85 mm Hg) or the use of antihypertensive medication, and 5) elevated fasting glucose level or antihyperglycemic treatment. IR is a pathogenetic factor underlying both NAFLD and MetS.[1] Interestingly, Marchesini et al[33] showed that IR itself, regardless of T1DM, overweight, or obesity, is associated with NAFLD. The authors emphasized that even normal-weight and euglycemic individuals could develop NAFLD, possibly solely due to reduced insulin sensitivity and hypertriglyceridemia. In the present study, to show the relationship between liver steatosis and IR, we used indirect IR parameters that include MetS components in their equations, such as waist circumference, WHR, BMI, TG, HDL-C, and hypertension. Therefore, we could not distinguish the coexistence of MetS from pure IR or reduced insulin sensitivity. We assumed, in line with the traditional understanding, that (in contrast to T2DM) T1DM does not typically coexist with MetS. We hypothesized that MetS in our cohort of patients with T1DM could have developed as a result of reduced insulin sensitivity, which in itself was a sequel of exogenous insulin administration. Extending this thought process further, NAFLD in these patients was could have been caused not by MetS itself, but rather developed concurrently with MetS as a result of reduced insulin sensitivity. However, the cross-sectional character of our study prevented us from drawing conclusions to prove the causative mechanism. We observed that the group with NAFLD was characterized by lower insulin sensitivity: lower eGDR, higher VAI, and higher TG/HDL-C ratio.

Data on indirect IR markers in T1DM are still scarce. We lack clear cutoff values to classify patients with T1DM as either insulin-sensitive or insulin-resistant. Previous studies on different IR statuses and their relationship with

clinical parameters used arbitrary divisions into quartiles or tertiles of eGDR values.[8,34,35] Chillarón et al[8] defined eGDR levels in T1DM patients according to the presence of MetS, and showed lower eGDR values (greater IR) in the group with MetS (mean [SD], 6.19 [1.5] vs 9.93 [1.6] mg/kg/min). In the receiver operating characteristic analysis, they determined a cutoff level below 8.77 mg/kg/min for MetS diagnosis.[8] In a study by Epstein et al,[34] which compared the types and incidence of vascular complications in multiethnic populations, the highest levels of eGDR in the third tetrile (the most insulin sensitive) were defined as levels greater than 7.75 mg/kg/min. Nyström et al[35] classified patients as normal insulin-sensitive if eGDR was greater than or equal to 8 mg/kg/min and intermediate--to-low insulin-sensitive if eGDR values were below 8 mg/kg/min, and showed that the latter group had a shorter expected survival, as compared with the general population. In our study, the group with NAFLD was characterized by lower eGDR levels (less insulin-sensitive), whereas the group without the disease had higher eGDR levels (more insulin-sensitive), with median levels of 8.93 mg/kg/min and 9.94 mg/kg/min, respectively. These values are higher than those reported in the abovementioned studies. We can only speculate that metabolic changes, such as steatosis, occur relatively early in the course of altered insulin sensitivity, yet steatosis is paired with reduced insulin sensitivity.

Data on VAI and the TG/HDL-C ratio as indirect IR markers in T1DM are lacking. To our knowledge, the only study in a T1DM population that directly compared VAI values and the TG/HDL-C ratio with GDR measured directly using the hyperinsulinemic-euglycemic clamp was conducted by Uruska et al.[10] The authors showed that the group with IR, defined as GDR values below 4 mg/kg/min, was characterized by VAI and TG/HDL-C values of 2.61 and 1.6, respectively. In the group without IR and with GDR values of 4 mg/kg/min or greater, the median VAI was 1.56 and the median TG/HDL-C ratio was 1.05. We reported lower median values of VAI and the TG/HDL-C ratio (1.43 and 1.2, respectively). In relation to the hepatic fat content, the group with NAFLD, regarded as more insulin-resistant, had a median VAI of 1.52 and a median TG/HDL-C ratio of 1.35, whereas the group without NAFLD, regarded as insulin--sensitive, had median VAI and TG/HDL-C values of 1.34 and 1.11, respectively.

Assuming that NAFLD is a disease that develops in the context of IR or primarily decreased insulin sensitivity, based on the TG/HDL-C ratio, VAI, and eGDR levels, we can conclude that at the time point when liver steatosis is diagnosed, only alterations in insulin sensitivity are present, and not true IR. We can only speculate that decreased insulin sensitivity primarily induces liver steatosis, which is a further cause of IR development. However, based on this study, we were not able to show the causative nature of this relation.

Association between insulin resistance markers and nonalcoholic fatty liver disease As suggested above, IR might lead to NAFLD in T1DM independently of MetS components. In the nondiabetic population, the risk for NAFLD increases along with the rising level of HbA_{1c},[36] also independently of obesity and other MetS components.[37] Therefore, in the course of diabetes and persistent metabolic derangement, duration of the disease might be a possible factor influencing hepatic fat accumulation. Another point worth noting is a higher prevalence of NAFLD in men than in women.[37] However, after menopause, women become more likely to develop the disease than men.[38] In our study group, the majority of patients were women. To rule out the possible confounding influence of sex, diabetes duration, and HbA_{1c} values, these variables were included in regression models. The regression analysis demonstrated that all 3 indirect IR markers were associated with liver steatosis, consistently and independently of sex, diabetes, and HbA_{1c}. This a clinically relevant finding, showing that reduced insulin sensitivity itself coexists with liver metabolic alterations.

Study limitations The cross-sectional design of the study limited our ability to draw conclusions about the temporal relationship between IR and NAFLD. Secondly, we could not compare TE results with those of liver biopsy, which is the gold standard to confirm liver steatosis and distinguish it from more severe stages of NAFLD.[18] We relied solely on TE in assessing liver steatosis, encouraged by a proven correlation of CAP value with fat accumulation in the liver demonstrated by liver biopsy.[39] Lastly, we did not include a separate analysis of MetS components in the study group. We were not able to distinguish the coexistence of MetS from pure IR or reduced insulin sensitivity since the indirect IR parameters used in the study include the MetS components in their equations.

Conclusions The present study showed that NAFLD might coexist with T1DM, especially in patients with lower insulin sensitivity. Indirect IR markers could be easily implemented in everyday clinical practice as a tool to assess the risk for incident NAFLD in individual patients.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT AG-W collected, analyzed, and interpreted the data, and wrote the manuscript; AU collected the data, assisted with the statistical analysis, contributed to the discussion, and edited the manuscript, ES-G collected and analyzed the data, and reviewed and edited the manuscript; AA collected and analyzed the data, contributed to the study design, and reviewed and edited the manuscript; MJ collected and analyzed the data, and reviewed and edited the manuscript; LC contributed to the study design, and reviewed, and edited the manuscript, DZ-Z contributed to the study design, reviewed, and edited the manuscript; she is also the guarantor of this work and, as such, takes responsibility for the work as a whole.

CONFLICT OF INTEREST None declared.

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