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Prevalence of non-alcoholic fatty liver disease (NAFLD) and its association with surrogate markers of insulin resistance in patients with type 1 diabetes

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ABSTRACT

Aims: Assess prevalence of hepatic steatosis (HS) and of fibrosis in an unselected population of patients with type 1 diabetes. Describe their clinical profile and explore the association between insulin resistance and NAFLD as secondary objectives.

Methods: We prospectively assessed NAFLD by transient elastography in adult outpatients with type 1 diabetes. Patients were eligible if they did not have any known secondary cause of liver disease. NAFLD was defined as HS with or without fibrosis/cirrhosis. Associations between estimated glucose disposal rate (eGDR) and metabolic syndrome, as surrogate markers of insulin resistance, and NAFLD were explored using multivariate logistic regression models, adjusting for age, sex and diabetes duration.

Results: We enrolled 150 consecutive subjects (age 47 ± 14 years, male 55%, diabetes duration 25 ± 14 years, median BMI 25 kg/m^2). NAFLD prevalence was 20% (n = 30). Thirty patients (20%) had HS. Five patients (3.3%) had HS with fibrosis. eGDR and metabolic syndrome were statistically significantly associated with the presence of NAFLD (OR 0.62, 95% CI 0.49–0.77, OR 7.62, 95% CI 2.95–19.77).

Conclusions: NAFLD prevalence in patients with type 1 diabetes is considerable, mainly restricted to isolated HS, while fibrosis is rare. Insulin resistance is associated with NAFLD in patients with type 1 diabetes.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum ranging from the relatively benign isolated hepatic steatosis (HS), to the more harmful stages of non-alcoholic steatohepatitis (NASH), hepatic fibrosis and cirrhosis. NAFLD, by definition, can be diagnosed only in the absence of other causes of liver disease.[1] The clinical burden of NAFLD is high, explained by the development of liver-related complications and, to an even bigger extent, by its association with cardiovascular morbidity and mortality.[2–4].

Global prevalence rates of NAFLD in the general population are estimated at 25%, for an important part consisting of patients with obesity and type 2 diabetes, a population in which NAFLD prevalence is consistently reported to be approximately twofold, and who often suffer from more advanced NAFLD.[2,5] Conversely, in patients with type 1 diabetes a wide variance of prevalence rates ranging from 0% to 53% have been reported and meta-analysis has shown a pooled prevalence of 19.3%.[6] Data on advanced NAFLD stages in patients with type 1 diabetes are scarce.[7–9].

To better understand NAFLD prevalence in patients with type 1 diabetes and to put it in perspective, it is of great interest to learn more about the determinants of NAFLD in this population. Insulin resistance is a key factor in the development and progression of NAFLD.[10] Metabolic syndrome, obesity, type 2 diabetes, and NAFLD are mutually associated disorders, with insulin resistance as the linking pin.[11] Also in patients with type 1 diabetes insulin resistance is a prominent feature,

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HS, hepatic steatosis; eGDR, estimated glucose disposal rate; NASH, non-alcoholic steatohepatitis; TE, transient elastography; UMC Utrecht, University Medical Center Utrecht; WC, waist circumference; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; LADA, latent autoimmune diabetes in adults; LFC, liver fat content.

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and is closely connected to the presence of the metabolic syndrome. [12,13] As the rising obesity prevalence in patients with type 1 diabetes will presumably come with an increase in insulin resistance, it is conceivable that NAFLD prevalence will follow this trend.[14] Nonetheless, the association between insulin resistance and NAFLD especially in patients with type 1 diabetes is to date ambiguous.[15–18].

Previous NAFLD prevalence estimates in patients with type 1 diabetes were highly dependent on the specific diagnostic modality and NAFLD definition used.[6] Moreover, earlier NAFLD studies are limited by applying preselection to the study participants based on certain anthropometric and laboratory characteristics, or by only including patients with historically available imaging data.[6] To our knowledge, data on prospective assessment of HS as well as fibrosis with transient elastography (TE) as single diagnostic method without applying any preselection are lacking. Therefore, our primary objective was to assess prevalence of liver steatosis and of fibrosis by TE in non-preselected patients with type 1 diabetes. Secondary aims were to describe their clinical profile and to explore the associations between surrogate markers of insulin resistance and NAFLD.

2. Materials and methods

This cross-sectional study was conducted at the Department of Diabetology of the University Medical Center Utrecht (UMC Utrecht), the Netherlands, a secondary and tertiary care center for diabetes. In the Netherlands, all type 1 diabetes care is concentrated in hospitals. The UMC Utrecht both serves the local community and acts as a referral center. Patients were enrolled from September 2019 to December 2019. The study consisted of one study visit, without further follow-up.

2.1. Participants

All consecutive patients with type 1 diabetes regularly visiting the outpatient diabetes clinic were prospectively screened and considered for eligibility until the number of 150 subjects was reached.

Inclusion criteria were type 1 diabetes, diabetes duration of at least 1 year, and age of 18 years or older. Type 1 diabetes was defined by the use of insulin, in combination with either the presence of anti-GAD or anti-islet cell auto-antibodies, and/or a clearly documented diagnosis of type 1 diabetes by internist or referring pediatrician, hereby also following the ADA diagnostic criteria.[19] Exclusion criteria were a history of known secondary causes of hepatic steatosis or – fibrosis - i.e. autoimmune or viral hepatitis, Wilson's disease, haemochromatosis, alfa-1-antitrypsin deficiency, total parenteral nutrition, or former or current excessive alcohol consumption - as required by international guidelines.[1] Excessive alcohol consumption was defined as $>$ 21 standard drinks per week in men and $>$ 14 standard drinks per week in women.[1] Furthermore, there was a number of exclusion criteria regarding the safety of TE (pregnancy, pacemaker or implantable cardioverter defibrillator) and regarding possibly false TE-measurements (ascites, liver congestion (right heart failure), extrahepatic cholestasis or intrahepatic mass). The study was approved by the medical ethics committee of UMC Utrecht. Written consent has been obtained from each patient after full explanation of the purpose and nature of all procedures used.

2.2. Data collection and definitions

The main study endpoint was the prevalence of HS and of fibrosis assessed by TE. Secondary endpoints were the clinical profile of patients with and without NAFLD and the association between surrogate markers of insulin resistance and NAFLD. All patients underwent a detailed medical history, physical examination, laboratory tests and TE. Interview, physical examination and TE were performed by one researcher.

2.2.1. Medical history

Patients were interviewed about their medical history, diabetes duration, insulin therapy, physical activity, diet, alcohol use, diabetes complications (retinopathy, nephropathy, neuropathy, cardiovascular disease), and medication use. When necessary, information was reviewed by checking the electronic medical record. Nephropathy was defined as present or former eGFR $<$ 60 ml/min and/or albuminuria in the absence of other readily available diagnosis than diabetes.

2.2.2. Physical examination

Weight and height were obtained and BMI was calculated. Waist circumference (WC) was measured at the highest point of the iliac crest, according to the NIH recommendation.[20] Blood pressure was measured with the patient sitting on the bedside, once at the left and once at the right hand side, and was repeated twice at the arm with the initial highest blood pressure. The average of these three measurements was used for the analysis.

2.2.3. Laboratory examination

HbA1c, creatinine, eGFR, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and platelet count were determined at the outpatient laboratory of the UMC Utrecht, using standard procedures. Blood tests were taken in the non-fasting state.

2.2.4. Transient elastography

TE was performed by one trained researcher (MV) using FibroScan (Echosense, FibroScan 502). No preselection was applied. Patients had to fast during the three hours before TE.[21] Hepatic steatosis was assessed by controlled attenuation parameter (CAP) and hepatic fibrosis was assessed by liver stiffness measurement (LSM). Patients were supine with their right arm placed under their head. The probe was placed in the intercostal space of approximately the 10th to 12th rib in the mid-axillary line. Either the M- or XL-probe was used according to the software's recommendation. TE was considered successful if at least 10 valid measurements were obtained and reliable if the interquartile range from the median of LSM was $\leq$ 30%.[22]

To grade steatosis and fibrosis severity, CAP and LSM scores were further divided with cutoffs from a landmark study, that has recently been used in patients with type 2 diabetes: S0 $<$ 274 dB/m, S1 274–289 dB/m, S2 290–301 dB/m, S3 $\geq$ 302 dB/m and F0/F1 $<$ 8.2 kPa, F2 8.2–9.6 kPa, F3 9.7–13.5 kPa, F4 $\geq$ 13.6 kPa [23–25].

NAFLD was defined as either isolated HS, or a combination of HS with fibrosis or cirrhosis. So patients with a CAP score $\geq$ 274 either with or without an LSM $\geq$ 8.2 were considered as having NAFLD. Severity of steatosis ranged from S0 (no steatosis) to S3 (severe steatosis). Severity of fibrosis ranged from F0/F1 (no fibrosis) to F4 (cirrhosis). Stage F3 or higher was considered advanced fibrosis.

2.2.5. Surrogate markers of insulin resistance

Insulin resistance was determined using the formula of the estimated glucose disposal rate (eGDR): eGDR (mg/kg/min) = 21.158 + (−0.09*WC (cm)) + (−3.407*hypertension) + (−0.551*HbA1c (%)). [26,27] Hypertension was defined as present if blood pressure was $>$ 140/90 mmHg and/or the patient was receiving antihypertensive medication (0 = absent, 1 = present). Lower eGDR values reflect higher insulin resistance.

Metabolic syndrome was defined according to an adapted version of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. The presence of three or more of the following elements constitutes a diagnosis of metabolic syndrome: (1) elevated waist circumference (men $\geq$ 102 cm, women $\geq$ 88 cm), (2) elevated blood pressure ($\geq$ 130 mmHg systolic or $\geq$ 85 mmHg diastolic) and/or receiving drug treatment for elevated blood pressure, (3) elevated HbA1c ($>$ 7.0% or $>$ 53 mmol/mol), (4) elevated triglycerides ($\geq$ 1.70

mmol/L) and/or receiving lipid lowering medication (fibrate or nicotinic acid), (5) reduced high density lipoprotein levels (< 1.03 mmol/L in men and < 1.30 mmol/L in women) and/or receiving lipid lowering medication (fibrate or nicotinic acid).[28,29]

2.3. Study size

Previous studies in patients with type 1 diabetes report a variety of NAFLD prevalence estimates ranging from 0% to 53%.[6] For our prevalence estimate we aimed for a level of confidence of 95% and a precision of 5–10%. Therefore, with an expected NAFLD proportion of approximately 30%, we aimed to recruit 150 patients.[30] Regarding the exploratory character of our secondary objectives, we needed five to ten NAFLD endpoints for each determinant we would like to test. So, with a putative prevalence of 30%, this group size would also allow for the secondary analyses.

2.4. Statistical methods

Analyses were performed using SPSS software version 25.0.0.2. Data are mean ± SD, median [IQR], or frequencies (percentage), when appropriate. Included and excluded patients, and patients with and without NAFLD were compared with independent samples *T*-test for normally distributed variables, Mann-Whitney-*U* test for skewed variables, and Chi-square test or Fisher's exact test for categorical variables. The prevalence of NAFLD was presented according to BMI categories to explore the association between increased adiposity and NAFLD. Multivariate binary logistic regression analyses were performed to explore associations between the different surrogate markers of insulin resistance and NAFLD as dichotomous dependent variable, adjusting for age, sex, and diabetes duration. BMI was not included in these multivariate analyses, because the highly correlated variable WC is already a component of the eGDR formula and the metabolic syndrome criteria. Results were expressed as odds ratio's (OR) with a 95% CI. Covariates with a *p*-value < 0.05 were considered independently associated with NAFLD. Interaction analyses were performed to investigate possible

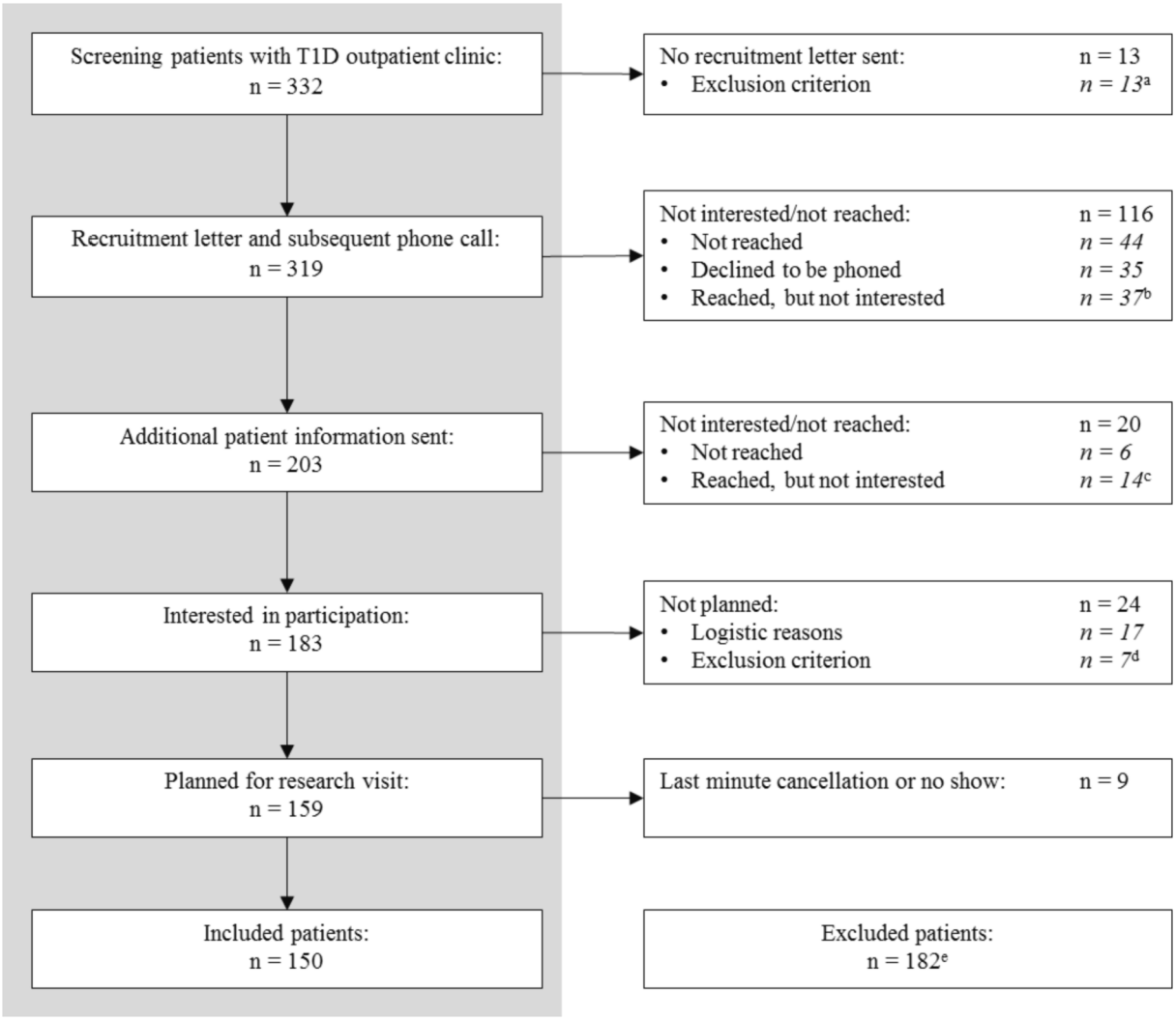

Fig. 1. Flowchart of study recruitment process. T1D, type 1 diabetes
[a] peritoneal dialysis (n = 1), alcohol abuse (n = 2), T1D since < 1 yr (n = 2), diabetes type unclear (n = 1), history of hepatitis, primary biliary cirrhosis or primary sclerosing cholangitis (n = 6), implantable cardioverter defibrillator (n = 1). [b] recovery from heart operation (n = 1), many hospital visits (n = 6), travel time (n = 1), hospital admission (n = 1), not feeling well (n = 1), no time (n = 11), no explanation (n = 8), logistic combination other appointments not possible (n = 4), fear of interference with sensor (n = 1), fear of finding liver problems (n = 1), never participating in research (n = 1), impaired cognitive functioning (n = 1). [c] fear of hospital (n = 1), many hospital visits (n = 4), not interested (n = 2), too complicated, (n = 1), no time (n = 3), fear of finding liver problems (n = 1), logistic reasons (n = 1), too much effort (n = 1). [d] excessive alcohol use (n = 5), not possible to fast (n = 1), T1D since < 1 yr (n = 1). [e] data were available from 179 of 182 excluded patients; 3 patients objected to use of their medical records for research purpose.

effect modification of age and sex on the association between surrogate markers of insulin resistance and NAFLD. *P*-values of the interaction terms were reported and considered significant when < 0.05.

We performed sensitivity analyses on our primary and secondary endpoints using CAP cutoffs as proposed by Karlas et al. in a recent individual patient data meta-analysis: S0 < 248 dB/m, S1 248–267 dB/m, S2 268–279 dB/m, S3 ≥ 280 dB/m. We expected that the population characteristics, in terms of age and BMI-distribution, as well as the steatosis prevalence and distribution of Karlas et al. would match the characteristics of our type 1 diabetes population more than those of Eddowes et al.[23,31] Furthermore, these cutoffs were used in a recent large population study on NAFLD prevalence in young adults in the United Kingdom.[32] As a second step, Karlas et al. suggest abiding by their CAP cutoffs, but deducting 10 dB/m from the CAP value for diabetes patients and deducting/adding 4.4 dB/m for each unit of BMI above/below 25 kg/m^2 over the range of 20–30 kg/m^2. To account for possible other diabetes disease progression in patients with latent autoimmune diabetes in adults (LADA) compared to juvenile type 1 diabetes, we performed sensitivity analysis excluding patients with LADA.

3. Results

3.1. Participants

The study recruitment process is shown in Fig. 1. All patients with type 1 diabetes visiting the outpatient clinic between September 2019 and December 2019 were considered for eligibility (n = 332). Eventually 150 patients with type 1 diabetes were included in the study and 182 patients were not.

Baseline characteristics are shown in Table 1. Mean age was 46.5 ± 13.5 years and mean diabetes duration was 25.3 ± 13.7 years. Eighty two patients (54.7%) were male. Median BMI was 25.0 kg/m^2 [22.7–28.2]. Mean waist circumference was 93.8 ± 13.3 cm. Mean systolic blood pressure was 132 ± 16 mmHg, mean diastolic blood pressure was 82 ± 8 mmHg, and 54 patients (36%) were using antihypertensive medication. Median HbA1c was 60 mmol/mol [55–67]. Metabolic syndrome was present in 38.9% of patients (n = 58). Median eGDR was 6.94 mg/kg/min [4.64–8.93]. Microvascular complications of retinopathy, nephropathy, and neuropathy were seen in 51 (34.0%), 19 (12.7%), and 43 patients (28.7%) respectively. Macrovascular complications were seen in 12 patients (8.0%).

There were no significant differences between in- and excluded patients for age, diabetes duration, HbA1c, and BMI (Table S1). Significantly more women were excluded compared to men.

3.2. NAFLD prevalence in type 1 diabetes

Prevalence of NAFLD was 20% (n = 30), with steatosis stage S1 in 4.0% of patients (n = 6), S2 in 3.3% (n = 5), and S3 in 12.7% (n = 19). Ten patients (6.7%) had fibrosis. Fibrosis stage F2 was seen in 4.7% of patients (n = 7), F3 in 2.0% (n = 3), and F4 in 0.0% (n = 0). Five patients (3.3%) with fibrosis also had steatosis and could be considered having NAFLD fibrosis. Five patients had fibrosis without HS (F2 n = 4, F3 n = 1). Two patients with F2 without HS did have a low eGDR (4.87, 6.33 mg/kg/min). Two patients with F2 without HS and the patient with F3 without HS did have a relatively high eGDR (10.59, 9.32, 8.78 mg/kg/min). Prevalence of NAFLD did not differ significantly between male and female patients (21.9% vs 17.6%, *p*-value 0.512).

Table 1
Baseline characteristics of total group of patients with type 1 diabetes and groups stratified by absence or presence of NAFLD.

	All patients (n = 150)	NAFLD− (n = 120)	NAFLD+ (n = 30)	*p*-value
Age, years	46.5 ± 13.5	45.5 ± 13.9	50.4 ± 10.8	0.043
Sex male, n (%)	82 (54.7)	64 (53.3)	18 (60.0)	0.512
Diabetes duration, years	25.3 ± 13.7	24.9 ± 14.1	26.9 ± 12.2	0.437
Insulin use, U/24h	42.0 [34.7–56.3]	43.7 ± 16.3	58.1 ± 24.8	0.005
Insulin use, U/kg/24h	0.54 [0.46–0.66]	0.56 ± 0.17	0.65 ± 0.27	0.100
Other diabetes medication*	15 (10.0)	7 (5.8)	8 (26.7)	0.003
CSII, n (%)	86 (57.3)	73 (60.8)	13 (43.3)	0.083
FGM or CGM, n (%)	67 (44.7)	56 (46.7)	11 (36.7)	0.324
Alcohol, U/week	2.5 [0–7]	3 [0–8]	0 [0–5]	0.016
BMI, kg/m^2	25.0 [22.7–28.2]	24.4 [22.2–27.1]	28.3 [25.6–30.3]	<0.001
Waist circumference, cm	93.8 ± 13.3	90.6 ± 11.4	106.6 ± 12.7	<0.001
HbA1c, %	7.6 [7.2–8.3]	7.5 [7.1–8.2]	7.9 [7.5–8.4]	0.019
HbA1c, mmol/mol	60 [55–67]	59 [54–66]	63 [58–68]	0.019
ALT, U/L	19 [15–26]	19 [15–24]	23 [16–29]	0.118
AST, U/L	19 [16–25]	20 [16–25]	19 [16–23]	0.452
ALP, U/L	76 [63–90]	72 [62–88]	87 [76–114]	0.001
GGT, U/L	16 [13–25]	15 [12–20]	21 [16–33]	0.002
Total cholesterol, mmol/L	4.46 ± 0.97	4.47 ± 0.86	4.45 ± 1.31	0.944
Triglycerides, mmol/L	1.00 [0.70–1.35]	0.90 [0.70–1.20]	1.35 [1.10–2.20]	<0.001
HDL cholesterol, mmol/L	1.61 [1.29–1.87]	1.63 [1.35–1.88]	1.37 [1.07–1.74]	0.011
LDL cholesterol, mmol/L	2.30 [1.90–2.80]	2.40 [1.90–2.70]	2.25 [1.50–3.05]	0.687
Blood pressure, mmHg				
Systolic	132 ± 16	131 ± 15	136 ± 18	0.153
Diastolic	82 ± 8	81 ± 8	83 ± 8	0.298
Use antihypertensive drugs, n (%)	54 (36.0)	36 (30.0)	18 (60.0)	0.002
Use lipid lowering drugs, n (%)	49 (32.7)	35 (29.2)	14 (46.7)	0.068
Metabolic syndrome NCEP ATPIII, n (%)	58 (38.9)	35 (29.4)	23 (76.6)	<0.001
eGDR (mg/kg/min)	6.94 [4.64–8.93]	7.58 [5.54–9.33]	4.01 [3.14–7.32]	<0.001
Retinopathy, n (%)	51 (34.0)	33 (27.5)	18 (60.0)	0.001
Nephropathy, n (%)	19 (12.7)	9 (7.5)	10 (33.3)	0.001
Neuropathy, n (%)	43 (28.7)	28 (23.3)	15 (50.0)	0.004
Cardiovascular disease, n (%)	12 (8.0)	9 (7.5)	3 (10.0)	0.707

n (%), mean ± SD, median [IQR].
NAFLD, non-alcoholic fatty liver disease; NAFLD−, patients without NAFLD; NAFLD+, patients with NAFLD; CSII, continuous subcutaneous insulin infusion; FGM, flash glucose monitoring; CGM, continuous glucose monitoring; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; eGDR, estimated glucose disposal rate.
* metformin n = 11, SGLT2-inhibitor n = 3, GLP-1 agonist, n = 1, combination metformin and SGLT2-inhibitor n = 1.

Table 2
NAFLD prevalence and distribution of NAFLD stages in 150 patients with type 1 diabetes, total group and stratified by BMI.

Patients with type 1 diabetes (n = 150)		BMI** < 25 kg/m^2 (n = 76)	BMI 25–30 kg/m^2 (n = 54)	BMI > 30 kg/m^2 (n = 19)
NAFLD+	30 (20.0)	5 (6.6)	16 (29.6)	8 (42.1)
NAFLD−	120 (80.0)	71 (93.4)	38 (70.4)	11 (57.9)
Steatosis	30 (20.0)	5 (6.6)	16 (29.6)	8 (42.1)
CAP, dB/m	231 ± 53			
S0	120 (80.0)	71 (93.4)	38 (70.4)	11 (75.9)
S1	6 (4.0)	1 (1.3)	4 (7.4)	1 (5.3)
S2	5 (3.3)	0 (0.0)	2 (3.7)	3 (15.8)
S3	19 (12.7)	4 (5.3)	10 (18.5)	4 (21.1)
Fibrosis	10 (6.7)	5 (6.6)	3 (5.6)	1 (5.3)
LSM, kPa	5.0 [3.7–6.2]			
F0/F1	140 (93.3)	71 (93.4)	51 (94.4)	18 (94.7)
F2*	7 (4.7)	4 (5.3)	2 (3.7)	1 (5.3)
F3*	3 (2.0)	1 (1.3)	1 (1.9)	0 (0.0)
F4*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n (%), mean ± SD, median [IQR].
NAFLD, non-alcoholic fatty liver disease; NAFLD+, patients with NAFLD; NAFLD−, patients without NAFLD; CAP, controlled attenuation parameter; LSM, liver stiffness measurement.
* S0F2 (n = 4), S0F3 (n = 1), S1F2 (n = 1), S2F2 (n = 1), S3F2 (n = 1), S3F3 (n = 2).
** BMI missing in 1 patient.

3.3. Association surrogate markers of insulin resistance and NAFLD in type 1 diabetes

eGDR was independently associated with the presence of NAFLD in multivariate logistic regression analysis, after adjustment for age, sex, and diabetes duration (OR 0.62, 95% CI 0.49–0.77, p-value < 0.001). This association was not modified by age (p-value interaction term = 0.997) and was modified by sex (p-value interaction term = 0.032, OR men 0.45, 95% CI 0.29–0.69, OR women 0.76, 95% CI 0.57–0.99). Presence of metabolic syndrome according to the adapted NCEP ATPIII criteria was independently associated with the presence of NAFLD (OR 7.62, 95% CI 2.95–19.77, p-value < 0.001). This association was not modified by age and sex (p-value interaction term 0.522 and 0.132). NAFLD prevalence and steatosis severity did increase across BMI categories (Table 2). Five lean patients had HS (S1 n = 1, S3 n = 4). Three patients, despite their normal BMI, did have a low eGDR (4.44, 4.08, 3.34 mg/kg/min), due to the combination of a high WC, presence of hypertension and relatively high HbA1c. Two did have a relatively high eGDR (8.20, 9.71 (S1) mg/kg/min) and had no clear explanation for the development of NAFLD.

3.4. Sensitivity analyses

Applying the cutoffs from Karlas et al. the prevalence of NAFLD was higher at 34%. Adapting the CAP values taking into account the diabetes status and BMI, resulted in lower CAP values in 80% of patients. Applying the cutoffs from Karlas et al. to these adapted CAP values yielded a NAFLD prevalence rate of 28.0%, still higher than the original prevalence by the Eddowes et al. cutoffs (Table S2). The independent association between surrogate markers of insulin resistance (eGDR, metabolic syndrome) and the presence of NAFLD remained significant (data not shown). Leaving out patients with LADA did slightly lower the NAFLD prevalence rate to 18.8% (Table S2), but did not change the independent association between surrogate markers of insulin resistance and the presence of NAFLD (data not shown).

4. Discussion

The prevalence of non-alcoholic fatty liver disease (NAFLD) in unselected patients with type 1 diabetes, as measured by transient elastography (TE), is considerable at 20%, mainly consisting of isolated hepatic steatosis (HS), and comprising a small proportion of NAFLD fibrosis of 3.3%. Insulin resistance was independently associated with the presence of NAFLD in our population of patients with type 1 diabetes.

The NAFLD prevalence rate we report, appears to be higher than those formerly reported in liver biopsy and MRI studies.[6] One study using liver biopsy reported a NAFLD prevalence of 19.3% in 57 patients.[8] In that study there was a high a priori suspicion of liver disease probably increasing the prevalence of HS. Six additional studies assessed liver fat content (LFC) by MRI techniques.[15,16,33–36] Three defined NAFLD as an LFC of more than 5.5%, which is comparable to a CAP stage of S1 or higher, and reported prevalence rates ranging from 0.0 to 8.8%.[33–35] Three reported LFC as continuous measure and found significantly lower LFC in groups of less than 20 patients compared to age- and BMI matched controls.[15,16,36] All three studies reported quite low LFC values in patients as well as in the control populations. These large discrepancies of NAFLD prevalence in MRI studies compared to ours may be explained by differences in study population, sample size and patient selection, as well as by measurement techniques. In general, our participants were older and had a longer diabetes duration. Furthermore, the largest MRI study involved a post hoc analysis on MRI data of people that were already included in an insulin development study, and may therefore not reflect the typical type 1 diabetes population.[35] Not surprisingly, our sensitivity analysis applying cutoffs and adapted CAP values as proposed by Karlas et al. yielded an even higher prevalence of NAFLD, since patients more easily reached the cutoff for HS grade S1.

The low NAFLD fibrosis rate we found, is comparable to those reported in previous TE-studies in patients with type 1 diabetes. In a study reporting an extrapolated prevalence rate of advanced fibrosis, based on TE in a preselected population with a high suspicion of fibrosis as derived from the Fib-4 score, the prevalence was only 1.8%.[9] This low prevalence as assessed by TE has been corroborated in a population of 145 patients with type 1 diabetes admitted to the hospital (2.1%).[7].

The present study is the first to find an independent association between insulin resistance, as measured by the eGDR, and the presence of NAFLD in type 1 diabetes. An increase in eGDR (i.e. less insulin resistance), comes with a lower odds for developing NAFLD. Three previous studies explored the relationship between insulin resistance and NAFLD in type 1 diabetes. One study using the eGDR in a preselected population could not find any correlation between insulin resistance and liver fat assessed by MRI, even though their NAFLD prevalence was substantial at 30%.[18] The overall mean value of eGDR in that study was remarkably low, which suggests that not the average type 1 diabetes population was evaluated. Two other studies quantified LFC by MRI and determined insulin sensitivity with the euglycemic-hyperinsulinemic clamp.[15,16] The first study did not find any correlation between insulin resistance and LFC.[15] The other reported a correlation between insulin resistance and LFC in the group including both patients with type 1 diabetes and healthy controls, but did not find an independent association between insulin resistance and LFC in regression analysis in patients with type 1 diabetes separately.[16] Both studies were limited by a very small sample size and therefore the generalizability of their results was limited. The conflicting results regarding the association between insulin resistance and NAFLD between our study and the other studies may seem surprising, especially since eGDR has been validated with the clamp technique.[26] The differences may be related to group size, method of assessment of NAFLD and patient selection procedures.

Regarding the future, results from this study suggest that NAFLD is an emerging complication of type 1 diabetes as it is in type 2 diabetes, with a definite relationship with insulin resistance. With the tendency of increasing body weight, BMI and visceral adiposity in type 1 diabetes

and consequently increasing insulin resistance, NAFLD will potentially become an untoward phenomenon in type 1 diabetes with possibly similar long term consequences as in type 2 diabetes.[5,14].

In interpreting the results, some strengths and limitations of the study are to be taken into account. Strengths of this study include the method of patient recruitment and the sample size, which enabled us to determine NAFLD prevalence and its association with insulin resistance in the average type 1 diabetes population. One limitation of our study is the relatively limited age range, not including the very young and very old. Furthermore, half of the patients were not included in the study. Although most relevant clinical characteristics were comparable between included and non-included patients, relatively more women were excluded compared to men. We do not think this substantially affected the NAFLD prevalence estimate. The distribution of male and female patients was similar in other type 1 diabetes NAFLD prevalence studies and in our population there was no statistically significant difference between NAFLD prevalence in male and female patients.[7,9,34,35] Also the association between insulin resistance and NAFLD was statistically significant in both sexes. The gold standard to assess insulin resistance is the euglycemic hyperinsulinemic clamp. However, this test is invasive and time consuming and therefore not feasible to perform in a large population. Although the eGDR is validated against the euglycemic hyperinsulinemic clamp, it should be considered a crude measurement of insulin resistance. Lastly, some patients may have been misclassified as NAFLD. The history of secondary causes of hepatic steatosis does not exclude subjects with unknown chronic/subclinical viral hepatitis and the self-reported alcohol intake may be inaccurate.

In conclusion, NAFLD prevalence in patients with type 1 diabetes is considerable, mainly restricted to isolated hepatic steatosis, while fibrosis is rare. Insulin resistance is associated with NAFLD in patients with type 1 diabetes.

CRediT authorship contribution statement

MV and HV conceived of the study. All authors contributed to the study design. MV performed the data collection and statistical analysis and drafted the manuscript. HV, JW, FEM and KK provided critical revision. All authors read, provided feedback and approved the final version of the manuscript. MV is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109827.

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