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Original article

Non-alcoholic fatty liver disease: identical etiologic factors in patients with type 1 and type 2 diabetes

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ABSTRACT

Aims: To compare NAFLD prevalence, distribution and its etiologic determinants in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D).
Methods: In this cross-sectional study, NAFLD was evaluated by transient elastography in adult outpatients with T1D and T2D. NAFLD was defined as hepatic steatosis with or without fibrosis. Associations between insulin resistance related factors and NAFLD and advanced fibrosis (≥ F3) were explored in T1D and T2D separately, using multivariate logistic regression models. Interaction analysis was performed to compare the associations in patients with T1D and T2D.
Results: One hundred and fifty patients with T1D (mean age 47 years, male 55%, mean diabetes duration 25 years, median BMI 25 kg/m^2) and 100 patients with T2D (median age 67 years, male 56%, median diabetes duration 17 years, mean BMI 30 kg/m^2) were included. NAFLD prevalence was 20% in patients with T1D and 76% in patients with T2D. Advanced fibrosis prevalence was 2.0% in patients with T1D and 22% in patients with T2D. In both patients with T1D and T2D, waist circumference, BMI and metabolic syndrome were positively associated, and estimated insulin sensitivity was negatively associated with the presence of NAFLD, adjusted for age, sex and diabetes duration. There was no effect modification by diabetes type for any of these associations.
Conclusions: Despite differences in population characteristics and pathophysiology between T1D and T2D, insulin resistance related factors are similarly associated with NAFLD in both groups.

1. Introduction

Alongside the obesity-epidemic, non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide, with an estimated prevalence of 25% in the general population [1]. NAFLD is a spectrum of liver disease, encompassing isolated hepatic steatosis (HS) and non-alcoholic steatohepatitis, which may progress to fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD has a high clinical and economic burden, as it is currently the most common indication for liver transplantation, comes with an increased risk of hepatocellular carcinoma, and is associated with cardiovascular disease, and mortality [1,2]. Development of advanced fibrosis is the most important predictor of future intra- and extrahepatic NAFLD outcomes [3].

Insulin resistance has a central role in NAFLD pathogenesis [4]. Hence, patients with type 2 diabetes (T2D) and/or obesity are at an increased risk of developing NAFLD and progression to fibrosis and cirrhosis. In the T2D population NAFLD prevalence is 56%, with evidence of advanced fibrosis in up to 15% of patients [5,6]. Insulin resistance is also a prominent feature of patients with type 1 diabetes (T1D) [7]. Nonetheless, prevalence of NAFLD in patients with T1D is estimated at only 19% and advanced fibrosis is rare [8].

The difference in NAFLD prevalence and severity between both types of diabetes warrants further investigation on possible dissimilarities in the pathogenesis of NAFLD in T1D and T2D. The aim of this study is to

Abbreviations: NAFLD, non-alcoholic fatty liver disease; HS, hepatic steatosis; T2D, type 2 diabetes; T1D, type 1 diabetes; UMC Utrecht, University Medical Center Utrecht; TE, transient elastography; BMI, body mass index; WC, waist circumference; TG, triglycerides; eGDR, estimated glucose disposal rate; SEARCH eIS, SEARCH estimated insulin sensitivity; CVD, cardiovascular disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; LFC, liver fat content.

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evaluate and compare NAFLD prevalence, distribution and its etiologic determinants in patients with T1D and T2D.

2. Materials and methods

This cross-sectional study was conducted at the outpatient diabetology and gastroenterology clinic of University Medical Center Utrecht (UMC Utrecht), the Netherlands. For patients with T1D, all diabetes care is concentrated in hospitals. For patients with T2D secondary and tertiary care is provided if needed.

2.1. Participants

All patients with T1D visiting the outpatient clinic between September 2019 and December 2019 were screened for eligibility. Patients with T2D were considered for eligibility if they were previously registered in the Dutch Diabetes Pearl clinical and biobank cohort and were still visiting the outpatient diabetes clinic of UMC Utrecht between November 2017 and December 2019 [9]. The study was approved by the medical ethics committee of UMC Utrecht. Written consent was obtained from each patient.

2.2. Eligibility criteria

Inclusion criteria were either T1D or T2D, diabetes duration $\geq$ 1 year, and age $\geq$ 18 years. T1D was defined by the use of insulin, in combination with either the presence of anti-GAD or anti-islet cell autoantibodies, and/or a clearly documented diagnosis of T1D. T2D was defined as a clearly documented diagnosis of T2D, and by use of either oral glucose lowering medication and/or use of insulin, according to the latest ADA-definition.

Exclusion criteria were a history of other causes of HS and/or fibrosis, including former or current excessive alcohol consumption (men > 21 standard drinks per week, women > 14 standard drinks per week [10]). Exclusion criteria regarding the safety and reliability of transient elastography (TE) were: known pregnancy, use of a pacemaker or an implantable cardioverter defibrillator and the presence of ascites, liver congestion, extrahepatic cholestasis or an intrahepatic mass.

2.3. Data collection and measurements

For all patients, the study consisted of one study visit for TE. All patients with T1D also underwent a detailed medical history, physical examination, and laboratory tests. For patients with T2D, information on medical history, insulin use and laboratory test results were obtained from the electronic health record.

Weight and height were obtained and body mass index (BMI) was calculated. Measurement of waist circumference (WC) between the level of the lowest rib and the top of the iliac crest (WHO recommendation) was added to the protocol from October 2019. Before this date, WC was measured at the level of the iliac crest in patients with T1D, and was not yet measured in patients with T2D. 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.

Laboratory tests were performed following standard procedures. HbA1c, creatinine, eGFR (CKD-EPI formula), total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (TG), liver enzymes and platelet count were determined.

To assess insulin resistance two different formulas were used, that do not rely on preserved insulin secretion and can be used in insulin-treated and non-insulin treated patients. Currently, there is no insulin sensitivity formula validated in both adult T1D and T2D patients. Therefore we calculated the estimated glucose disposal rate (eGDR), which was validated in adult patients with T1D, as well as the SEARCH estimated insulin sensitivity (SEARCH eIS), which was validated in youth patients with both T1D and T2D. The eGDR (mg/kg/min) was calculated as follows: 21.158 + (−0.09*WC (cm)) + (−3.407*hypertension) + (−0.551*HbA1c (%)) [11,12]. In this formula, hypertension was defined as present if blood pressure was >140/90 mmHg and/or the patient was receiving antihypertensive medication. The SEARCH eIS (mg/kg/min) was calculated as follows: exp (4.64725 – 0.02032 (WC (cm)) – 0.09779 (HbA1c (%)) – 0.00235 (TG (mg/dl))) [13]. Lower eGDR and SEARCH eIS 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 [14,15]. Nephropathy was defined as elevated urine albumin excretion (>30 mg/g) and/or reduced estimated glomerular filtration rate (eGFR <60 ml/min per 1.73m^2). Cardiovascular disease (CVD) was defined as either coronary artery disease, stroke or peripheral arterial disease.

2.4. Transient elastography and NAFLD definition

TE was performed by three trained researchers (MV, FEM and SB) using FibroScan (Echosense, FibroScan 502). Patients had to fast during the three hours before TE. 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 the 10th to 12th rib in the midaxillary 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%.

CAP cutoff values from a recent landmark study were used, applying equal cutoffs for M- and XL-probe: 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 [16]. NAFLD was defined as the presence of hepatic steatosis ($\geq$ S1), either with or without fibrosis. Advanced fibrosis was defined as $\geq$ F3.

2.5. Statistical analysis

Analyses were performed using SPSS software version 26.0.0.1. Data are presented as mean ± SD, median [IQR], or frequencies (percentage), when appropriate.

Missing values were imputed by multiple imputation, using logistic regression models for categorical variables, and linear regression models in combination with predictive mean matching for continuous variables. In total 5 multiple imputed datasets were created for both the T1D group and T2D group. Primary analyses were performed with the imputed datasets. Pooled results were reported. In patients with T1D missing values were imputed for daily insulin requirement dose (0.7%), liver enzymes and lipids (0.7%), platelets (2.7%), weight (0.7%), WC (36.7%), and blood pressure (0.7%). In patients with T2D missing values were imputed for HbA1c (9.0%), liver enzymes (11.0–17.0%), lipids (23.0–25.0%), platelets (7.0%), WC (25.0%) and microvascular complications (3.0–5.0%). WC measured at the level of the iliac crest was available in all patients with T1D, but in none of the patients with T2D.

Comparisons between binary groups were performed 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.

To assess the association between potential etiologic determinants and the presence of NAFLD, logistic regression analyses were performed separately in patients with T1D and patients with T2D. Included variables encompassed factors related to insulin resistance and were selected on the basis of literature research: eGDR, SEARCH eIS, WC, BMI, metabolic syndrome, TG, HDL-cholesterol, HbA1c and insulin requirement dose. One model was created per variable, adjusting for the potential confounders age, sex and diabetes duration. Subsequently, the

models were additionally adjusted for use of acetylsalicylic acid and statin use in light of their well-known protective effect on liver disease [17,18]. These models were also applied within HS patients to evaluate factors potentially associated with advanced fibrosis. Odds ratio's (OR) and 95% confidence intervals (95% CI) were reported.

To assess whether potential etiological factors have different relations with the endpoint under investigation in patients with either type 1 or 2 diabetes, interaction analyses were performed by repeating the analyses in patients with T1D and T2D combined, adding diabetes type as a covariate and an interaction term of diabetes type with the variable of interest. Diabetes type was considered a significant effect modifier if the *p*-value of the interaction term was < 0.05.Furthermore we performed a complete case analysis for the logistic regression analysis.

3. Results

3.1. Participants and characteristics

In total, 332 patients with T1D and 364 patients with T2D were screened for eligibility, of which 150 patients with T1D and 100 with T2D were included (Fig. S1). Baseline characteristics of both patient groups are given in Table 1.

Of patients with T1D, 82 (55%) were male, mean age was 47 years and mean diabetes duration was 25 years. Of patients with T2D, 56 (56%) were male, median age was 67 years and median diabetes duration was 17 years. Sixty-one patients (61%) with T2D were using insulin. Patients with T1D had lower WC, BMI, TG levels and higher eGDR, SEARCH eIS and HDL-cholesterol levels compared to those with T2D. Patients with T1D less frequently had metabolic syndrome. Diabetes regulation as measured by HbA1c was slightly better in the T2D group, while daily insulin requirement dose was considerably higher.

Table 1
Baseline characteristics of patients with T1D and patients with T2D.

	Type 1 diabetes	Type 2 diabetes	*p*-value
	(*n* = 150)	(*n* = 100)	
Age, years	46.5 ± 13.5	67.0 [58.3–73.0]	<0.001
Sex male	82 (54.7)	56 (56.0)	ns
Diabetes duration, years	25.3 ± 13.7	17.0 [13.0–22.0]	<0.001
Insulin use, U/24h*	42.0 [34.8–56.2]	61.0 [38.0–97.0]	<0.001
Insulin use, U/kg/24h*	0.54 [0.46–0.66]	0.67 [0.44–0.93]	0.025
Alcohol, U/week	2.5 [0–7]	1 [0–2]	0.008
BMI, kg/m^2	25.0 [22.7–28.3]	30.2 ± 6.4	<0.001
Waist circumference, cm	90.5 ± 13.4	106.7 ± 16.3	< 0.001
HbA1c, mmol/mol	60 [55–67]	58 ± 11	0.003
ALT, U/L	19 [15–26]	23 [19–34]	<0.001
AST, U/L	19 [16–25]	22 [18–27]	0.032
ALP, U/L	76 [63–89]	82 ± 20	ns
GGT, U/L	16 [13–25]	29 [20–47]	<0.001
Platelets, x10^9/L	258 ± 65	258 ± 75	ns
Total cholesterol, mmol/L	4.47 ± 0.97	4.37 ± 1.18	ns
Triglycerides, mmol/L	1.00 [0.70–1.36]	2.30 ± 1.44	<0.001
HDL cholesterol, mmol/L	1.61 [1.28–1.86]	1.30 ± 0.47	<0.001
LDL cholesterol, mmol/L	2.35 [1.90–2.80]	2.18 ± 0.93	0.029
Blood pressure, mmHg			
Systolic	131 ± 16	-	-
Diastolic	82 ± 8	-	-
Use antihypertensive drugs	54 (36.0)	78 (78.0)	<0.001
Use lipid lowering drugs	49 (32.7)	77 (77.0)	<0.001
Use acetylsalicylic acid	12 (8.0)	27 (27.0)	<0.001
Metabolic syndrome	50 (33.5)	73 (73.0)	<0.001
eGDR, mg/kg/min	7.23 [4.83–9.23]	4.82 ± 2.17	<0.001
SEARCH eIS, mg/kg/min	6.50 ± 2.19	4.01 [2.47–5.19]	<0.001
Retinopathy	51 (34.0)	23 (23.0)	ns
Nephropathy	19 (12.7)	31 (31.0)	<0.001
Neuropathy	43 (28.7)	24 (24.0)	ns
Cardiovascular disease	12 (8.0)	36 (36.0)	<0.001

n (%), mean ± SD, median [IQR]
BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; eGDR, estimated glucose disposal rate; SEARCH eIS, SEARCH estimated insulin sensitivity.
* *n* = 61 (61.0%) in patients with T2D.

3.2. NAFLD prevalence and distribution in T1D and T2D

NAFLD prevalence was 20% in patients with T1D and 76% in patients with T2D. Of patients with T1D the majority did not have any steatosis, whereas in patients with T2D the majority had severe steatosis (Fig. 1). In the total T1D group, advanced fibrosis was seen in only 2.0% (*n* = 3). Of patients with T1D and concomitant HS, 6.7% (*n* = 2/30) had advanced fibrosis. Twenty-two percent (*n* = 22) of patients with T2D had advanced fibrosis. Advanced fibrosis was present in 26.3% (*n* = 20/76) of patients with T2D and concomitant HS.

3.3. Factors associated with NAFLD in T1D and T2D

In patients with T1D and T2D similar differences were observed when comparing patients with and without NAFLD (Table S1). Patients with NAFLD had a higher BMI, WC, and TG, more frequently had metabolic syndrome, and were more insulin resistant, as measured by eGDR and SEARCH eIS. Daily insulin use per kilogram bodyweight did not differ between both groups. In the T1D group, patients with NAFLD were older, with higher HbA1c and lower serum HDL cholesterol than those without NAFLD. In patients with T1D, prevalence of NAFLD was roughly half in patients with moderate alcohol use (n = 11/86) as compared to abstinent patients and rare alcohol users (n = 19/64), while these prevalence rates were comparable in patients with T2D (n = 21/26 vs n = 55/74) (data not shown).

3.4. Association between insulin resistance related variables and NAFLD in T1D and T2D

Fig. 2 shows the association between insulin resistance related variables and NAFLD in patients with T1D and T2D separately with *p*-values of the interaction terms. In both patient groups, WC, BMI and metabolic syndrome were positively associated, and eGDR and SEARCH eIS were negatively associated with the presence of NAFLD. In patients with T1D, higher TG levels and lower levels of HDL-cholesterol had a significantly higher odds of having NAFLD, while in patients with T2D these associations were not significant. Daily insulin use per kilogram bodyweight and HbA1c were significantly associated with NAFLD only in patients with T1D. Additional adjustment for use of acetylsalicylic acid and lipid lowering medication did not change these results. There was no effect modification by diabetes type for any of the associations between determinants and NAFLD, except for TG.

3.5. Insulin resistance related factors associated with advanced fibrosis in T1D and T2D

Differences in patient characteristics according to the presence or absence of advanced fibrosis in patients with HS, showed the same pattern as comparing patients with and without NAFLD (Table S2). In patients with T1D and T2D, patients with advanced fibrosis had a higher BMI and WC, more often had metabolic syndrome, and had a lower estimated insulin sensitivity than patients without advanced fibrosis. In patients with T2D and concomitant HS, logistic regression analysis showed an independent positive relationship between WC, CAP score and advanced fibrosis (Table S3). Higher SEARCH eIS was associated with lower odds of having advanced fibrosis, whereas BMI, eGDR, TG, and metabolic syndrome were not significantly associated with advanced fibrosis. Due to the small number of patients with advanced fibrosis in T1D, it was not possible to perform logistic regression analysis in this group, precluding a comparison between associations of etiologic determinants and advanced fibrosis in patients with T1D and T2D.

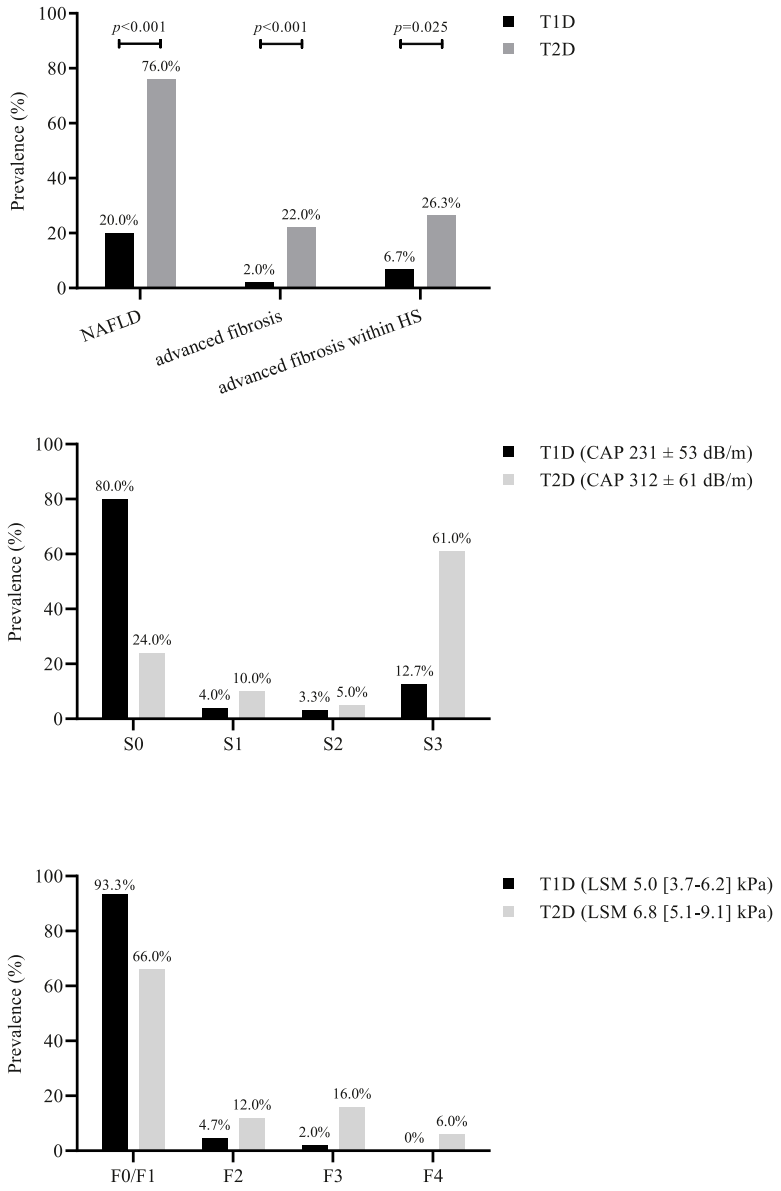

Fig. 1. Prevalence and distribution of NAFLD in patients with T1D and patients with T2D.
NAFLD, non-alcoholic fatty liver disease; T1D, type 1 diabetes; T2D, type 2 diabetes; HS, hepatic steatosis; CAP, controlled attenuation parameter; LSM, liver stiffness measurement.

3.6. Other analysis

Complete case analysis for the logistic regression analysis yielded similar results as those with the imputed data (Table S4).

4. Discussion

This study underscores the difference in NAFLD prevalence and distribution between patients with T1D and T2D. Of importance, the associations between insulin resistance related factors and NAFLD are identical in patients with T1D and T2D, suggesting similar etiology.

NAFLD prevalence in patients with T2D was approximately three fold higher than in patients with T1D. This finding is in line with meta-analyses, reporting a NAFLD prevalence of 56% in patients with T2D and of 19.3% in patients with T1D [6,8]. Also, we found that NAFLD as assessed by TE was more severe in T2D than in T1D, with most patients with T2D having severe HS and one out of five having advanced fibrosis. Two recent TE-studies in patients with T2D reported a slightly lower prevalence of HS than ours [5,19]. Distribution of severity grades of HS was similar to the ones we found [5,19]. TE-measured prevalence of advanced fibrosis in T2D was 9% and 15%, as compared to 22% in our study [5,19]. There are no previous adult TE-studies in patients with T1D assessing prevalence and severity of HS. In previous reports on patients with T1D and HS, assessment of HS severity with ultrasound, MRI or liver biopsy revealed only grade 1 steatosis in most patients, while in our study grade 3 steatosis was most common [20–23]. Advanced fibrosis was rare, which is in line with previous TE-findings in patients with T1D [24,25].

Notably, despite differences in patient characteristics and pathophysiology between T1D and T2D, similar etiologic factors were associated with NAFLD in both populations in the current study. Insulin resistance, as characterized by elevated BMI, high WC, presence of metabolic syndrome and atherogenic lipid profile, low eGDR and low SEARCH eIS, seem to be equally important in explaining the presence of NAFLD in T1D and T2D.

Until now, only one study specifically aimed to compare the clinical phenotype of NAFLD in patients with T1D and (insulin-naïve and insulin-treated) T2D [26]. In line with our results, BMI, bodyweight and

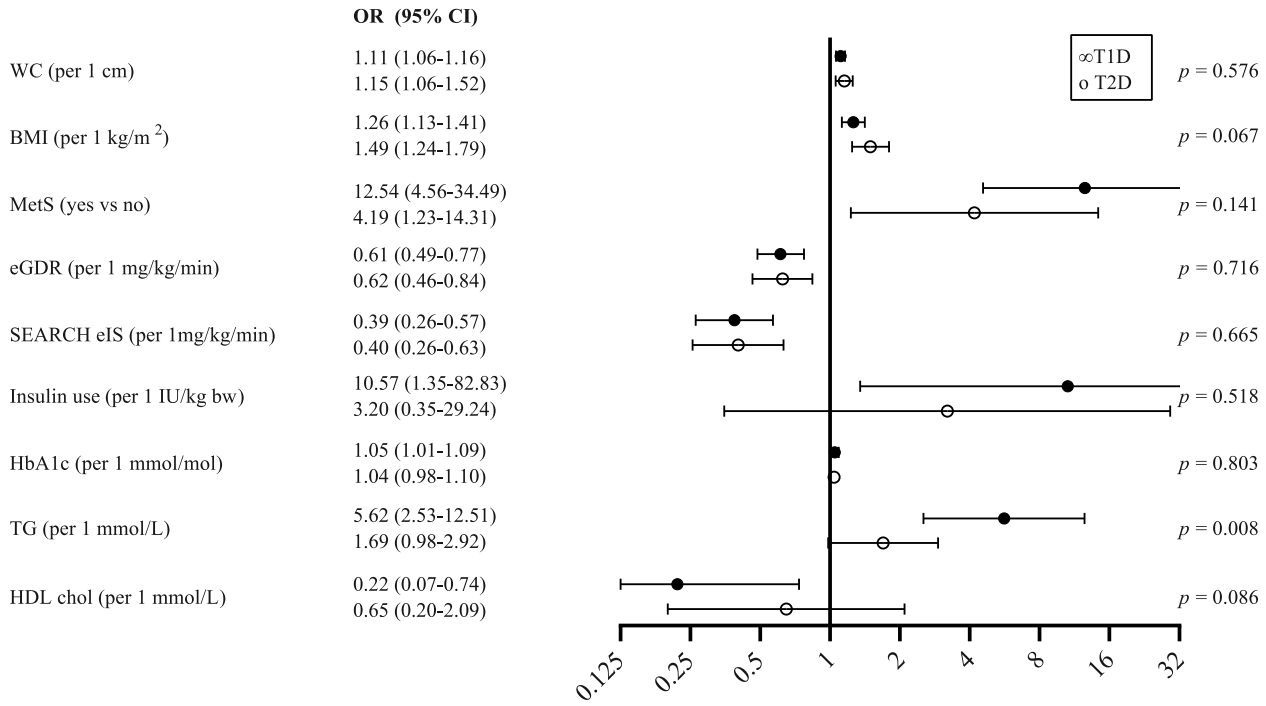

Fig. 2. Association between insulin resistance related determinants and NAFLD, adjusted for age, sex, and diabetes duration in patients with T1D and patients with T2D.
WC, waist circumference; BMI, body mass index; MetS, metabolic syndrome; eGDR, estimated glucose disposal rate; SEARCH eIS, SEARCH estimated insulin sensitivity; bw, bodyweight; TG, triglycerides; HDL chol, high density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval; T1D, type 1 diabetes; T2D, type 2 diabetes.
p represents the *p*-value of the interaction term.

triglyceride levels were higher in patients with than without NAFLD in all three populations [26]. Also, correlations of BMI and triglyceride level with liver fat content (LFC) were statistically significant in all three groups [26]. These findings support the crucial role of insulin resistance in the pathogenesis of NAFLD in both T1D and T2D. Another study found a significant correlation between BMI and LFC and triglycerides and LFC in both T1D and T2D as well [27]. In contrast, a previous study in patients with newly diagnosed diabetes, reported a significant association between BMI and NAFLD in T2D, but not in T1D [28]. This could be explained by the long silent phase of T2D that is not present in T1D.

It is important to identify patients at risk for progression of NAFLD in clinical practice, because advanced fibrosis is associated with an increased risk of both hepatic and cardiovascular complications [1,3]. In the current study, in patients with T2D and HS, higher WC and TG levels and lower SEARCH eIS were all associated with increased risk of advanced fibrosis. This supports the concept that adipose tissue dysfunction, via insulin resistance and chronic systemic low-grade inflammation, is an important contributing factor for development of advanced fibrosis [17]. In our group of patients with T1D and HS, similar differences were observed between patients with and without advanced fibrosis, as compared to patients with T2D and HS. No further statistical tests regarding severity of fibrosis were performed in the T1D group, because of the relatively low prevalence of advanced fibrosis.

Our findings indicate that insulin resistance is crucial in development and progression of NAFLD, irrespective of diabetes type. This might implicate that, alongside the obesity epidemic, NAFLD will become more prevalent in T1D and might increasingly resemble the NAFLD phenotype of T2D. Recent evidence is contradictory in this respect. One study reported an association between visceral adipose tissue and NAFLD in patients with T1D, in line with our findings [29]. Another study, however, reported lower LFC in overweight patients with T1D as compared to age-, BMI- and gender matched controls without diabetes. [30]

Our study provides a detailed comparison of factors associated with NAFLD and advanced fibrosis in patients with both T1D and T2D and is the first to assess whether the strength of the associations is affected by diabetes type. Data on both steatosis and fibrosis assessed by TE were prospectively collected in both patient groups. Limitations of the study include the relatively small sample size of patients with T2D. Furthermore, imputed data were used for one third of waist circumference measurements in both populations. Repeating the analysis in patients with T1D with WC measurements at the level of the iliac crest, available in all 150 patients, did not change the results, neither did complete case analysis. Also, the cross-sectional study design does not allow any conclusions on, but does support, causality. Finally, we used TE for diagnosing NAFLD, instead of the gold standards liver biopsy or magnetic resonance imaging.

In conclusion, despite differences in population characteristics and endocrine pathophysiology between T1D and T2D, insulin resistance related factors are similarly associated with NAFLD in both patient groups. In our opinion, NAFLD should be considered a similar disease in patients with T1D and T2D.

5. Other information

5.1. Contribution statement

MV, FEM, SB, HV, and KvE conceived of the study. All authors contributed to the study design. MV, FEM and SB performed the data collection. MV and FEM performed the statistical analysis and drafted the manuscript. HV, KvE, JW, SB, 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.

6. Data availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Disclosures

The authors declare they have no conflict of interest.

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Supplementary materials

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