Cardiovascular Diabetology

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Increased prevalence and risk of atherosclerotic cardiovascular disease in individuals with Type 1 diabetes and metabolic dysfunction-associated steatotic liver disease

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Abstract

Objective This study aimed to investigate the correlation between metabolic dysfunction-associated steatotic liver disease (MASLD) and atherosclerotic cardiovascular disease (ASCVD) in individuals with type 1 diabetes (T1D).

Methods Adults with T1D ($n=659$) were consecutively screened for liver steatosis via abdominal ultrasound. The presence of macrovascular disease (including coronary artery disease [CAD], peripheral artery disease [PAD], or ischaemic stroke [CVA, cerebrovascular accident]) was identified via electronic medical records. The 5- and 10-year risks of fatal/nonfatal ASCVD were assessed via the Steno Type 1 Risk Engine. Insulin resistance was assessed via the estimated glucose disposal rate (eGDR).

Results The MASLD prevalence was 16.8%. The prevalence of composite ASCVD (18.9 vs. 6.8%, $p<0.001$), CAD (9.9 vs. 4.7%, $p=0.031$), PAD (9.0 vs. 2.2%, $p<0.001$) and CVA (6.3 vs. 1.1%, $p=0.002$) was greater in people with MASLD. The 5-year (7.8 [2.1–14.4] vs. 4.8 [1.6–12.0]%, $p=0.034$) and 10-year (15.0 [4.1–26.8] vs. 9.4 [3.1–22.5]%, $p=0.035$) risks of ASCVD were greater in those with MASLD. MASLD was associated with prevalent ASCVD (adjusted OR 4.26, 95% CI 1.79–10.11, $p<0.001$), independent of age, sex, diabetes duration, smoking, statin use, LDL-cholesterol, the glomerular filtration rate, albuminuria, and metabolic syndrome.

Conclusion MASLD is associated with both an increased prevalence of ASCVD and an increased calculated risk of fatal/nonfatal ASCVD in people with T1D.

Keywords Atherosclerotic cardiovascular disease, Insulin resistance, MASLD, Metabolic syndrome, Type 1 diabetes

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Research insights

What is currently known about this topic?

Type 1 diabetes is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), despite attaining optimal glycaemic control. Metabolic comorbidities might contribute to this ASCVD risk.

What is the key research question?

Is metabolic dysfunction-associated steatotic liver disease (MASLD) an ASCVD risk factor in people with type 1 diabetes?

What is new?

This study is the first to both link prevalence of atherosclerotic ASCVD with MASLD, and to link risk of fatal/non-fatal ASCVD with MASLD.

How might this study influence clinical practice?

MASLD guidelines have recommended to screen for MASLD in certain populations, but have explicitly mentioned lack of evidence in people with type 1 diabetes. This study provides insights that can lead to improved management strategies for people with type 1 diabetes.

Background

The phenotype of "double diabetes" consisting of autoimmune-mediated insulin deficiency combined with insulin resistance (IR)/metabolic syndrome (MetS) is increasingly prevalent, likely due to the increasing rate of overweight in people with type 1 diabetes (T1D) [1, 2]. IR is closely linked to metabolic dysfunction-associated steatotic liver disease (MASLD), which is a subtype of steatotic liver disease (SLD), formerly referred to as non-alcoholic fatty liver disease (NAFLD) [3]. SLD is an overarching term of conditions hallmarked by liver steatosis, encompassing not only MASLD, but also metALD (MASLD with moderate alcohol consumption), alcohol-related liver disease (ALD), and other causes of steatosis not inflicted by metabolism- or alcohol-related aetiologies [4]. In the general population, MASLD is considered an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) [3–7].

People with T1D have a lower but still notable NAFLD prevalence (12–20%) compared to prevalence rates observed in the general population (38%) [8–11]. A recently updated meta-analysis demonstrated a MASLD prevalence of 22% in people with T1D, based on the reinterpretation of NAFLD data as MASLD [12]. NAFLD has been linked to ASCVD in people with T1D, although the findings are limited by methodological inconsistencies such as selection bias, publication bias and the use of unvalidated non-invasive tests [13–16]. As ASCVD is the leading cause of death in individuals with T1D, identifying at-risk individuals is crucial since cardiovascular mortality persists despite optimal glycaemic control [17–19]. The aims of this study are to provide MASLD prevalence data and to investigate the correlation between MASLD and both prevalent and future ASCVD risk in people with T1D.

Methods

Study design & population

This cross-sectional study analysed ASCVD prevalence and the calculated future cardiovascular risk in a T1D cohort with/without MASLD. Prospective consecutive screening for liver steatosis was conducted between 2018 and 2023 at Antwerp University Hospital, Belgium (NCT04664036). All outpatient adults (≥ 18 years old) with T1D (American Diabetes Association definition) attending the diabetes clinic of our tertiary care centre were invited to participate, using folders, by telephone and by active recruitment during clinical visits [20]. The only exclusion criteria were pregnancy and substantial residual beta-cell function (C-peptide > 0.2 nmol/L). A target sample of minimally 50% of the 987 outpatients was set to reduce selection bias and to obtain an adequate representative sample of the outpatient population. The study protocol was in accordance with the modified Declaration of Helsinki and approved by the local Ethics Committee (18/32/361). All participants provided informed consent. The manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [21].

Data collection

Demographics, diabetes duration, medication use, including total insulin dose (TDI), exercise habits using the International Physical Activity Questionnaire short form, alcohol consumption, smoking status, and comorbidities were ascertained through electronic medical records, [22]. Total daily insulin (TDI) was available in 557 of 659 subjects. Missing data were due to absence of insulin pump readings in the medical files or the use of insulin-to-carbohydrate ratios without clarification of total prandial doses. Clinical assessments included anthropometry, including BMI and waist circumference (WC), systolic (SBP) and diastolic (DBP) blood pressure, via an automated sphygmomanometer (lowest value from a minimum of three measurements), laboratory tests for HbA1c (using high-performance liquid chromatography), creatinine levels and estimated glomerular filtration rate (eGFR, using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), total

cholesterol, high-density and low-density lipoprotein (HDL, LDL), triglycerides (TG), alanine and aspartate aminotransferase (ALT, AST), gamma-glutamyl transferase (GGT), and platelet count, and a screening panel for secondary liver disease, including viral hepatitis (hepatitis B surface antigen, hepatitis B core antigen antibodies, hepatitis C antibodies, alpha-1 antitrypsin assay, copper, ceruloplasmin and IgG. Twenty-four-hour urine collections were performed to determine the albumin excretion rate. Data on 24 h urine collections were present in 594 of 659 cases (10% missing) due to technical errors or failure to submit urine collections. IR was quantified via the eGDR (estimated glucose disposal rate, mg/kg/min) = 21.158 + (− 0.09 * WC (cm)) + (− 3.407 * hypertension) + (− 0.551 * HbA1c (%)) [23]. The hypertension criterion for the eGDR was SBP/DPB > 140/90 mmHg or the use of antihypertensive treatment. The presence of MetS was based on the modified 2005 revised National Cholesterol Education Program Adult Treatment Panel III criteria (since all individuals already met the criterion of hyperglycaemia), and thus required the presence of two of the following four criteria: elevated WC (≥ 102 cm in men and ≥ 88 cm in women), hypertriglyceridaemia (≥ 1.7 mmol/l or ≥ 150 mg/dl), low HDL cholesterol level (< 1.03 mmol/l or < 40 mg/dl in men and < 1.3 mmol/l or < 50 mg/dl in women), high blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or pharmacological treatment) [24].

Liver steatosis and fibrosis evaluation, definition of MASLD

Liver steatosis was assessed via ultrasound and vibration-controlled transient elastography (VCTE) via the FibroScan© 502 device (Echosens, Paris, France), which was supervised by a single experienced and Echosens-certified physician (JM). The full details of the used ultrasonographic and VCTE quality criteria are described elsewhere [9]. VCTE data were present in 605 of 659 cases. Missing data were due to technical issues such as failure to obtain measurements or measurements not reaching quality restrictions. The controlled attenuation parameter as a steatosis marker (CAP™) and liver stiffness measurement (LSM) as a non-invasive marker of fibrosis were obtained from VCTE. We used an LSM < 8.0 kPa to rule out significant fibrosis (≥ F2 fibrosis) [25]. The FIB-4 score was calculated to estimate the risk of liver fibrosis [26]. MASLD is defined as the presence of liver steatosis with at least one metabolic risk factor: (1) BMI ≥ 25 kg/m^2 or WC > 94/80 cm for males/females, (2) SBP/DBP ≥ 130/85 mmHg or antihypertensive treatment, (3) hypertriglyceridaemia ≥ 150 mg/dL/1.70 mmol/L or triglyceride-lowering treatment, and (4) HDL ≤ 40/50 mg/dL (1.0/1.3 mmol/L) for males/females, in the absence of excessive alcohol consumption, as proposed by the recently published guidelines [3, 4]. The fifth cardiometabolic risk factor, hyperglycaemia, was discarded as a criterion in this study since we studied people with T1D. The absence of excessive alcohol intake (< 20 g/day in women, < 30 g/day in men) and the absence of secondary liver disease (viral hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, drug-induced disease) were needed to differentiate MASLD from the other conditions that are encompassed by SLD; *i.e.*, we studied MASLD as a single aetiology of steatosis.

Cardiovascular and renal assessment

Microvascular (nephropathy, retinopathy) and macrovascular complications were evaluated. Chronic kidney disease (CKD) was defined as an eGFR < 60 mL/min/1.73 m^2 and/or albuminuria (albumin excretion rate > 30 mg/24 h) [27]. Retinopathy was evaluated via fundoscopy and scored positive if the abnormalities observed were more than simple background alterations (mild non-proliferative changes and absence of macular disease) or when laser intervention was needed [28]. Fundoscopy data were present in 636 of 659 cases. Missing data were due to failure to attend the ophthalmologist or unavailability of written reports. Prevalent ASCVD was defined as the presence of a history of coronary artery disease (CAD), ischaemic stroke (cerebrovascular accident (CVA)) or peripheral arterial disease (PAD). CAD was defined as myocardial infarction, coronary artery catheterization revealing significant (> 70%) stenosis requiring coronary revascularization, or documented ischaemic heart disease. CVA was defined as ischaemic stroke, carotid endarterectomy or transient ischaemic attack. Peripheral arterial disease (PAD) was defined as one or more significant (> 70%) peripheral arterial stenotic lesions and/or occlusions at one or more sites (i.e., femoral, popliteal and tibial arteries), diagnosed by duplex ultrasonography or angiography requiring revascularization, or diabetic foot ulcers requiring amputation.

The 5- and 10-year risks of fatal/nonfatal ASCVD comprising CAD, PAD, CVA and heart failure were calculated via the Steno Type 1 Risk Engine [29] on the basis of clinical data from the electronic health records of 4,306 individuals with T1D treated at Steno Diabetes Centre Copenhagen in combination with data from the Danish National Patient Register and Cause of Death Register. The engine was then validated in 2,118 individuals with T1D from Denmark. The calculator is based on age, sex, diabetes duration, SBP, LDL, HbA1c, albuminuria, eGFR, smoking status, and exercise. People with a history of ASCVD were excluded from the ASCVD risk analysis since the Steno Type 1 Risk Engine is applicable only to people without prior ASCVD.

Statistical analysis

Continuous variables are summarized as the means ± standard deviations or medians [interquartile

ranges]. Comparisons between groups were performed using Student's t tests, Mann–Whitney U tests, or chi-square/Fisher's exact tests as appropriate. We used one-way analysis of variance (ANOVA) to compare means across multiple groups. Post-hoc least significant difference (LSD) tests were used to adjust for multiple comparisons. The independence of associations of MASLD and other variables with the dependent variable (ASCVD) was assessed by univariable and multivariable logistic regression and expressed as odds ratios (OR) and 95% confidence intervals (CI). As mentioned above, in these analyses, ASCVD was considered a composite endpoint of any significant event of CAD, CVA or PAD. We performed unadjusted univariable logistic regression models, and forced-entry adjusted logistic regression models. Covariates included in these adjusted multivariable regression models were selected as potential confounding factors based on their significance in univariable regression analyses or based on their clinical plausibility (Suppl. Table 2). Model 1 included age and sex. Model 2 included age, sex and diabetes duration. Model 3 included age, sex, diabetes duration, smoking status, LDL, the use of lipid-lowering medication, and HbA1c. Model 4a was composed of model 3 plus Mets as a categorical variable, model 4b was composed of model 3 plus eGDR, but minus HbA1c (collinearity with eGDR). Model 5 was composed of model 3 plus WC, SBP, HDL, TG and lipid-lowering medication. Model 6 was composed of model 3 plus eGFR and albuminuria as a categorical variable. To evaluate the effect of smoking on the prevalence of ASCVD, ex-smokers and active smokers were combined and dichotomously compared to people who never smoked. To compare the predictive models built with MASLD on one hand, and with MetS on the other hand, the Akaike information criterion (AIC) was calculated and compared as a means for model selection. A difference in AIC > 2 (ΔAIC) is indicative of a statistical superiority in predictive accuracy [30]. A two-sided p value < 0.05 was considered significant in all analyses. To accommodate for significant (> 2% of variable) missing data (TDI, VCTE, albuminuria and fundoscopy results), we used Little's MCAR (missing completely at random) test [31]. Albuminuria and fundoscopy missing data were, according to Little's test missing completely at random, but TDI and VCTE data were not. Further analysis of missing data by using regression analysis and dichotomizing missingness of TDI/VCTE data, showed that missing data on TDI were inversely associated only with age, and missing data on VCTE were associated with BMI. No absence of data was associated with MASLD nor with ASCVD. Since this study is an exploratory descriptive study, we opted to use pairwise deletion in all correlation analyses [31]. All the statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 28.0 (IBM Corp., Armonk, N.Y., USA). Images were generated via GraphPad Prism software (GraphPad software, Boston, MA, USA).

Results

Study group characteristics

A total of 659 individuals with T1D (67% of outpatients) were screened and included (Fig. 1). The median age was 47 [31–60] years, and the mean diabetes duration was 26 ± 14 years. The median HbA1c was 7.4 [6.8–8.0]% or 57 [51–64] mmol/mol, the median eGDR was 6.02 [4.71–8.33] mg/kg/min, and the median TDI was 0.57 [0.45–0.76] IU/kg/24 h. BMI showed a left-skewed distribution due to outliers, with a median of 25.3 [22.7–28.6] kg/m^2, while obesity was present in 18.1% of individuals, and overweight was present in 35.7%. ASCVD was present in 8.8% (n = 58) of subjects. The details are listed in Table 1.

Steatosis (ultrasound) was detected in 17.9% (n = 118) of the patients, with 16.8% meeting the MASLD criteria (94.1% of all steatosis patients). The mixed aetiologies included metALD (0.8%) and MASLD combined with other liver diseases (0.6%). MASLD-NAFLD overlap was 100% in our cohort (Fig. 1). The mean CAP™ was 228 ± 56 dB/m, and the median LSM was 4.80 [4.00–5.90] kPa. An elevated LSM indicative of potentially significant (> F2) fibrosis was observed in 3.8% (n = 23) of the patients.

MASLD characteristics

MASLD subjects had a higher BMI, higher obesity prevalence, and more MetS components, including truncal adiposity, hypertension, and dyslipidaemia (Table 1). These subjects had lower eGDR, indicating lower insulin sensitivity, higher ALT and GGT levels and higher LSM values. ASCVD prevalence was significantly greater in people with MASLD (18.9 vs. 6.8%, p < 0.001), CAD (9.9 vs. 4.7%, p = 0.031), PAD (9.0 vs. 2.2%, p < 0.001) and CVA (6.3 vs. 1.1%, p = 0.002) (Fig. 2).

MASLD and MetS

Within the complete cohort, 11.7% (n = 77) of subjects featured both MASLD and MetS (M+MetS+), 18.1% (n = 119) met the criteria for MetS without featuring MASLD (M-MetS+), 5.2% (n = 34) met the criteria for MASLD without meeting the criteria for MetS (M + MetS-), and 65.1% (n = 429) featured neither MASLD nor MetS (M-MetS-). ASCVD prevalence was highest (23.4%) in the M+MetS+ group, reached 16.0% in the M-MetS + group, 8.8% in the M + MetS- group and 4.2% in the M-MetS- group. No significant difference in ASCVD was found in the subjects with MetS on the basis of the presence vs. the absence of MASLD (23.4% vs. 16.0%, p = 0.195).

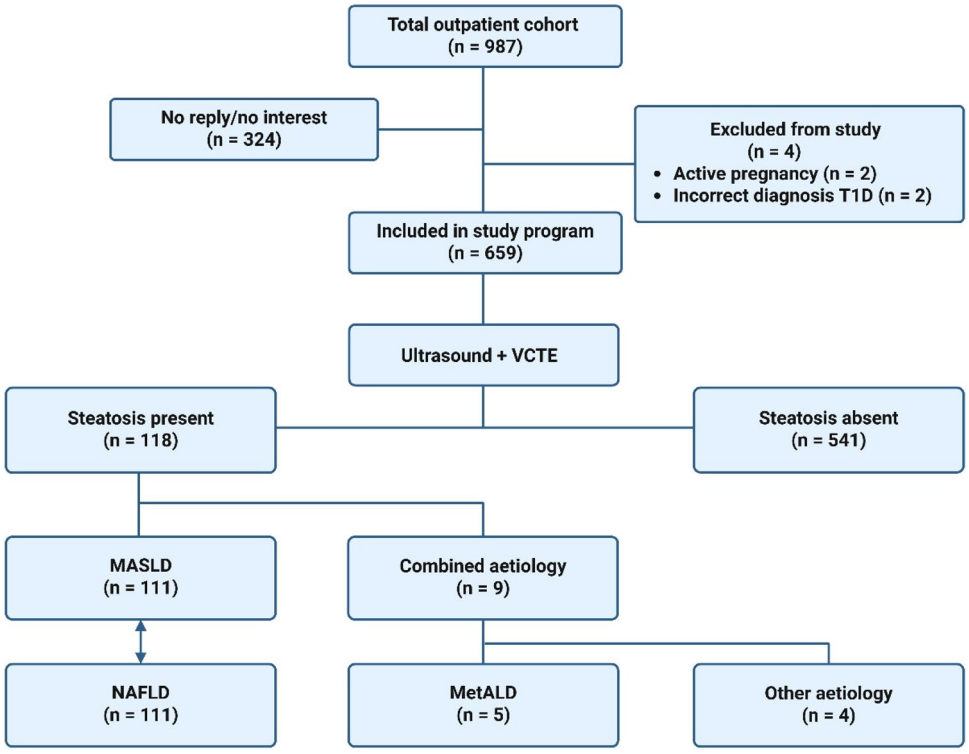

Fig. 1 Study flowchart and distribution of steatotic liver disease subtypes across the cohort. T1D: type 1 diabetes, VCTE: vibration-controlled transient elastography, MASLD: metabolic dysfunction-associated steatotic liver disease, NAFLD: non-alcoholic fatty liver disease, metALD: MASLD with moderate alcohol consumption

Stratification by ASCVD presence

Patients with ASCVD were older, had a longer diabetes duration, higher BMI, worse renal function, and higher SBP ($p < 0.001$). They had more MASLD (36.2 vs. 15.0%, $p < 0.001$) and MetS (63.8 vs. 26.5%, $p < 0.001$) and a lower eGDR (4.74 vs. 6.16 mg/kg/min, $p < 0.001$). LSM values and significant fibrosis rates did not differ, although FIB-4 was higher ($p < 0.001$) (Suppl. Table 1).

Correlation analysis

Univariable logistic regression revealed that MASLD was strongly associated with ASCVD (OR 3.22, 95% CI 1.80–5.76; $p < 0.001$). eGDR (OR 0.64, 95% CI 0.55–0.75, $p < 0.001$) and MetS (OR 4.90, 95% CI 2.78–8.62, $p < 0.001$) were also associated with ASCVD but not LSM (as a continuous variable or dichotomized with a cut-off of 8.0 kPa). In multivariable logistic regression, we found that MASLD, age, eGFR, LDL and total cholesterol, statin use, and microalbuminuria were associated with established ASCVD, whereas MetS and eGDR were not. After multiple adjustments, odds for ASCVD were fourfold in those with MASLD (adjusted OR 4.27, 95% CI 1.80–10.14, $p = 0.001$). Among the multivariable models, MASLD (AIC = 89) outperformed MetS (AIC = 103) for ASCVD prediction (ΔAIC = 14), emphasizing MASLD's predictive superiority (Suppl. Table 2).

Steno type 1 risk engine: predicted risk of ASCVD

Excluding patients with established ASCVD, the five- and 10-year risks of future ASCVD in our cohort ($n = 598$) were 5.2 [1.6–12.5]% and 10.2 [3.3–23.4]%, respectively. ASCVD risks ≥ 5% were observed in 50.4% (5 years) and 63.6% (10 years), whereas risks ≥ 10% were observed in 30.8% (5 years) and 50.1% (10 years) of adults with T1D. People with MASLD had greater predicted risk (5-year: 7.8% vs. 4.8%, $p = 0.034$; 10-year: 15.0% vs. 9.4%, $p = 0.035$) (Table 1).

Subgroup analysis revealed greater risks in M+MetS+ individuals than in M + MetS- individuals (5-year: 10.8 vs. 6.0%, p = 0.020; 10-year: 19.7 vs. 11.4%, $p = 0.008$), but the predicted risk in the M-MetS + group was even greater (5-year: 15.2 ± 14.3%, $p = 0.003$; 10-year: 26.1 ± 20.5%, $p = 0.008$) (Fig. 3).

Analysis of the individuals components of the Steno Type 1 Risk Engine showed that the greater risk in the M-MetS + group compared to the M + MetS- group can be attributed to older age (53 ± 15 vs. 39 ± 14 years, $p < 0.001$), longer diabetes duration (32 ± 14 vs. 20 ± 12 years, $p < 0.001$), lower eGFR (93 ± 14 vs. 109 ± 15 ml/min/1.73m^2, $p < 0.001$), and higher SBP (144 ± 20 vs. 131 ± 16 mm Hg, $p = 0.001$), while no difference was observed in sex, HbA1c, LDL, active smoking, nor albuminuria. The greater risk in the M-MetS + group

Table 1 Cohort characteristics + stratification between MASLD/non-MASLD

	Overall cohort	MASLD	No MASLD	*p* value
n (%)	659	111 (16.8)	548 (83.2)	
Age, years	47 [31–60]	50 [34–61]	47 [30–59]	0.298
Male sex, n (%)	364 (55.2)	67 (60.4)	297 (54.2)	0.234
Active smoking, n (%)	68 (10.3)	18 (16.2)	50 (9.1)	0.025
Diabetes duration, years	26 ± 14	26 ± 15	26 ± 14	0.851
TDI, U/kg/24 h[§]	0.56 [0.45–0.76]	0.69 [0.50–0.91]	0.55 [0.44–0.72]	< 0.001
Biguanide use, n (%)	52 (7.9)	18 (16.2)	34 (6.2)	< 0.001
GLP-1 RA use, n (%)	18 (2.7)	6 (5.4)	12 (2.2)	0.100
BMI, kg/m^2	25.3 [22.7–28.6]	30.4 [27.9–32.9]	24.6 [22.3–27.1]	< 0.001
Obesity, n (%)	119 (18.1)	62 (55.9)	57 (10.4)	< 0.001
WC, cm	94.8 ± 13.3	107.4 ± 12.3	92.0 ± 12.3	< 0.001
Males	86.4 ± 14.1	104.1 ± 14.3	83.3 ± 11.6	< 0.001
Females				
BP, mm Hg	134 ± 17	138 ± 16	133 ± 17	0.006
Systolic	79 ± 9	80 ± 9	78 ± 9	0.093
Diastolic				
Antihypertensive drug use, n (%)	252 (38.5)	54 (49.1)	198 (36.4)	0.013
ACE-inhibition, n (%)	211 (32.4)	44 (40.4)	167 (30.8)	0.052
Hypertension, n (%)	373 (56.6)	76 (69.7)	297 (54.0)	0.002
MetS, n (%)	196 (29.7)	77 (69.4)	119 (21.7)	< 0.001
Creatinine, mg/dL	0.76 [0.67–0.86]	0.77 [0.67–0.88]	0.76 [0.66–0.86]	0.729
eGFR, mL/min/1.73m^2	104 [91–119]	101 [90–116]	104 [91–119]	0.401
HbA1c, %	7.4 [6.8–8.0]	7.6 [7.0–8.2]	7.4 [6.7–7.9]	0.013
HbA1c, mmol/mol	57 [51–64]	60 [53–66]	57 [50–63]	0.013
AST, IU/L	21 [17–27]	23 [18–27]	21 [17–26]	0.076
ALT, IU/L	22 [16–29]	26 [19–35]	21 [16–28]	< 0.001
GGT, IU/L	21 [15–30]	26 [19–43]	20 [14–29]	< 0.001
TG, mg/dL	77 [60—101]	95 [73—138]	74 [57—94]	< 0.001
Tot Chol, mg/dL	172 ± 34	175 ± 34	172 ± 33	0.315
HDL, mg/dL	56 ± 15	50 ± 13	57 ± 15	< 0.001
Males	70 ± 18	62 ± 16	71 ± 18	< 0.001
Females				
LDL, mg/dL	95 [78–115]	99 [82–119]	94 [77–115]	0.076
Statin use, n (%)	281 (42.6)	59 (54.1)	222 (40.4)	0.008
Urinary albuminuria rate, µg/min[+]	3.8 [2.1–8.0]	5.0 [2.4–10.3]	3.5 [2.1–7.9]	0.046
(Micro)albuminuria, n (%)[+]	75 (11.6)	17 (15.9)	58 (10.7)	0.129
CKD, n (%)[+]	97 (15.0)	21 (19.3)	76 (14.1)	0.170
eGDR (mg/kg/min)	6.03 [4.73–8.36]	4.26 [3.19–5.30]	6.34 [5.23–8.86]	< 0.001
CAP™, dB/m*	228 ± 56	285 ± 58	217 ± 50	< 0.001
LSM, kPa*	4.8 [4.0–5.9]	5.4 [4.1–6.6]	4.8 [4.0–5.8]	0.006
LSM ≥ 8.0 kPa, **n** (%)*	27 (4.4)	10 (10.5)	17 (3.3)	0.002
FIB-4 score	0.77 [0.50–1.04]	0.76 [0.50–1.05]	0.77 [0.50–1.16]	0.357
FIB-4 score > 1.3, n (%)	70 (10.6)	7 (6.3)	63 (11.5)	0.106
Retinopathy, n (%)[Δ]	277 (43.1)	53 (49.1)	224 (41.9)	0.168
ASCVD, n (%)	58 (8.8)	21 (18.9)	37 (6.8)	< 0.001
CAD, n (%)	37 (5.6)	11 (9.9)	26 (4.7)	0.031
PAD, n (%)	22 (3.3)	10 (9.0)	12 (2.2)	< 0.001
CVA, n (%)	13 (2.0)	7 (6.3)	6 (1.1)	0.002
5-year ASCVD risk, %	5.2 [1.6–12.5]	7.8 [2.1–14.4]	4.8 [1.6–12.0]	0.034
10-year ASCVD risk, %	10.2 [3.3–23.4]	15.0 [4.1–26.8]	9.4 [3.1–22.5]	0.035
5-year risk ≥ 5%, n (%)	303 (50.4)	52 (57.8)	251 (49.1)	0.130
5-year risk ≥ 10%, n (%)	185 (30.8)	37 (41.1)	148 (29.0)	0.021

Table 1 (continued)

	Overall cohort	MASLD	No MASLD	*p* value
10-year risk ≥ 5%, n (%)	382 (63.6)	64 (71.1)	318 (62.2)	0.107
10-year risk ≥ 10%, n (%)	301 (50.1)	52 (57.8)	249 (48.7)	0.113

The results are presented as the means ± SDs, medians [IQRs] or n (%). Comparisons between groups were performed with independent samples t tests for normally distributed variables, Mann–Whitney U tests for nonnormally distributed variables, and chi–square tests or Fisher's exact tests for categorical variables. MASLD: metabolic dysfunction-associated steatotic liver disease, TDI: total daily dose of insulin, GLP-1 RA: glucagon-like peptide receptor agonist, WC: waist circumference, BP: blood pressure, ACE: angiotensin-converting enzyme, sum of ACE-inhibitors or angiotensin receptor blockers, MetS: metabolic syndrome, eGFR: estimated glomerular filtration rate, HbA1c: haemoglobin A1c, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase, TG: triglyceride, Tot Chol: total cholesterol level, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CKD: chronic kidney disease defined as eGFR < 60 mL/min/1.$^{73\ m2}$ and/or albuminuria (albumin excretion rate > 30 mg/24 h) in the absence of other readily available diagnoses other than diabetes, eGDR: estimated glucose disposal rate, CAP™: controlled attenuation parameter, LSM: liver stiffness measurement, ASCVD: cardiovascular disease defined as a compound of any of the following major cardiovascular events: coronary artery disease (CAD), peripheral arterial disease in need of intervention (PAD), or ischemic cerebrovascular event (CVA). [§]TDI available for 557 subjects. *VCTE available for 605 subjects, [+]24 h urine collection available for 594 subjects, [Δ] fundoscopy data available for 636 subjects

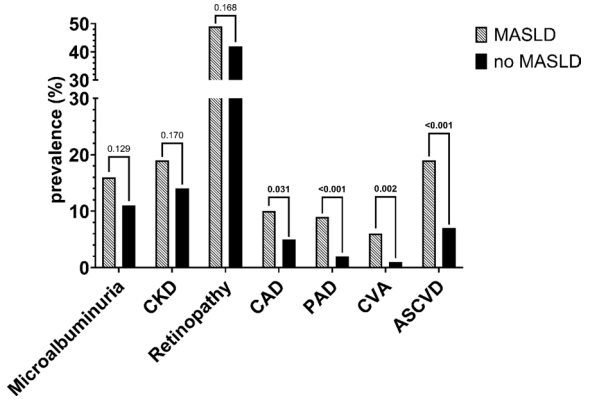

Fig. 2 Distribution of micro- and macrovascular events in people with/without MASLD. The figure shows the distribution of microvascular (microalbuminuria and retinopathy) and macrovascular events. *P* values are shown numerically above each bar graph. *P* values were derived from the chi-square test or Fisher's exact test when appropriate. MASLD: metabolic dysfunction-associated steatotic liver disease, CKD: chronic kidney disease defined as eGFR < 60 mL/min/1.$^{73\ m2}$ and/or albuminuria (albumin excretion rate > 30 mg/24 h) in the absence of other readily available diagnoses other than diabetes, CAD: coronary artery disease, PAD: peripheral arterial disease, CVA: cerebrovascular disease, ASCV: cardiovascular disease

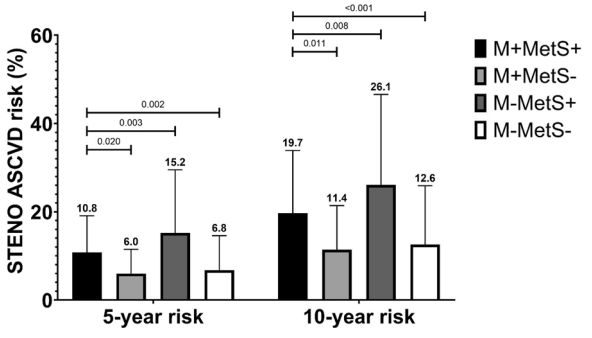

Fig. 3 Subgroup analysis of the Steno Type 1 Risk Engine derived 5- and 10-year risk factors for ASCVD. The figure shows a bar plot of the Steno Type 1 Risk Engine derived 5- and 10-year risks of atherosclerotic cardiovascular disease (ASCVD). *P* values of post hoc comparisons (LSD) are shown above the bar plots. The numbers above the bar plots represent individual risk percentages per subgroup. M+MetS+: MASLD and metabolic syndrome, M+MetS-: MASLD without metabolic syndrome, M-MetS+: metabolic syndrome without MASLD, M-MetS-: no MASLD, no metabolic syndrome

compared to the M+MetS+ could also be attributed to older age (53 ± 15 vs. 47 ± 15 years, $p = 0.034$), longer diabetes duration (32 ± 14 vs. 25 ± 13 years, $p = 0.003$), and lower eGFR (93 ± 24 vs. 102 ± 22 ml/min/1.73m^2, $p = 0.021$) while no difference was observed in sex distribution, HbA1c, LDL, SBP, active smoking, nor albuminuria. However, we also noticed that the rate of regular exercise was higher in the M-MetS + group both compared to the M + MetS- group (19.0 vs. 3.2%, $p = 0.033$) as compared to the M+MetS+ group (19.0 vs 3.5%, $p = 0.005$), potentially attenuating the effect on the calculated risk.

Discussion

Our study demonstrated a 16.8% prevalence of MASLD in adults with T1D, based on ultrasonographic detection of liver steatosis. This finding aligns with a previous report from our study group on NAFLD prevalence in individuals with T1D [9]. It is important for future meta-analyses to note that the cohort described in this study largely overlaps with that of our earlier publication. However, the current cohort is larger and as such should be considered the primary dataset for inclusion in meta-analyses. A recent meta-analysis reported a MASLD prevalence of 22% in T1D overall and 26% based on ultrasound, analysing 13,006 individuals across 23 studies. MASLD was more common in older, more overweight individuals with longer diabetes duration, higher TDI, and more metabolic dysfunction, consistent with our findings. Importantly, quality assessment concluded to a moderate overall risk of bias. Only one study in the meta-analysis used biopsy, the rest relied on non-invasive methods like ultrasound, risk scores, or MRI [12]. We observed a limited proportion (3.8%) with LSM ≥ 8 kPa, indicating potential significant fibrosis. Similarly, the abovementioned meta-analysis showed low fibrosis rates across various non-invasive measures (13.25%), with advanced fibrosis being rare (5.12%), based on 5 studies including ours [12].

We showed that MASLD was significantly associated with prevalent ASCVD (including CAD, PAD, and CVA) in T1D. A 2016 retrospective study showed increased ASCVD risk (adjusted hazard ratio 6.73) in T1D with

NAFLD, despite similar baseline features except for shorter diabetes duration (median 17 years) [14]. Higher NAFLD prevalence in that study (52.4%) likely reflects selection bias. Two additional cohorts from the same group confirmed this association, even after adjusting for common risk factors such as sex, BMI, HbA1c, diabetes duration, lipid profile, albuminuria, smoking and family history of ASCVD [13, 15]. Odds in those two studies were remarkably higher compared to ours (adjusted OR 7.6, 95% CI 3.6–24.0, $p < 0.001$, and 7.36, 95% CI 1.60–34.3, $p < 0.001$ compared to 4.27, 95% CI 1.80–10.14, $p = 0.001$). NAFLD prevalence rates in those two studies were again remarkably higher (44 to 52%). Both these cohorts were similar to ours, with the exception that their HbA1c values were higher on average. Those studies included both non-stenotic and asymptomatic macrovascular disease, whereas we only studied hard endpoints, which might explain their stronger associations.

Importantly, the MASLD-ASCVD association in our study persisted after adjusting for eGDR and MetS. While both were individually associated with ASCVD in univariable analyses, only MASLD remained significant in the final model. When we adjusted the model for common ASCVD risk factors, MASLD showed a stronger predictive association with ASCVD than did a similar model where MASLD was replaced by MetS. Owing to the strong collinearity of MASLD with MetS, we performed further sensitivity analyses, substituting MASLD with liver steatosis, which yielded similar results, reinforcing its independent or additive contribution to ASCVD. Furthermore, a study by Zhang et al. found an association between NAFLD and carotid intima-media thickness, independent of MetS [32]. Serra-planas et al. found similar results showing that carotid intima-media thickness was greater in T1D subjects with NAFLD in 100 adult participants [33]. Evidently, the design of association studies, including ours, does not allow to assess causality, and further research is needed to disentangle both entities.

We also found that individuals with MASLD had higher predicted 5- and 10-year ASCVD risks using the Steno Type 1 Risk Engine [29]. The 5-year risk rose from 5.2% in the cohort to 7.8% in those with MASLD. A study by Shah et al. showed an incidence of ASCVD of 3.7% after 4.6 years of follow-up, which aligns with our results, highlighting the increased risk in individuals with MASLD [34]. At 10-year level, risk increased from 10.2% to 15.0% with MASLD. Paliares et al. compared Steno Type 1 Risk Engine predicted risks with 5- and 10-year follow-up data [35]. Among 435 T1D patients of mixed genetic and ethnic populations (median age 25 years, diabetes median duration 13 years, median BMI 23.5 kg/m^2, median WC 86.0 cm, median HbA1c 8.6%), the 5-year estimated risk versus the observed event rate was 3.4 vs 3.5%, and 6.8 vs. 9.9% at 10-years, respectively. Compared to our cohort, subjects in their study were younger, leaner, and had worse glycaemic control. Mantovani et al. did a large study on MASLD and calculated risk according to the Steno Type 1 Risk Engine, illustrating that 43% of the 1254 subjects had a calculated risk lower than 10% [36]. They did not publish the numerical risk at cohort level, making comparison between our cohorts difficult. The Steno Type 1 Risk Engine is composed of 10 clinical parameters: age, sex, diabetes duration, DBP, LDL, HbA1c, albuminuria, eGFR, smoking, and regular exercise. It does not account for IR-related markers like BMI, WC, TDI, or MASLD, nor for modifiers such as antihypertensive or lipid-lowering therapy. In our cohort, differences in visceral adiposity, TDI, and statin use—known to have pleiotropic effects—may have attenuated the impact of MASLD on predicted risk [37]. By not including these IR-related factors, it remains difficult to disentangle MASLD from MetS. Subgroup analyses showed that those with both MASLD and MetS (M+MetS+) had higher risk than those with MASLD alone (M + MetS-), but lower than MetS alone (M-MetS +). The latter group was significantly older, had a longer diabetes duration, a lower eGFRs and a higher SBP, all age-related factors heavily weighted in the risk calculator. Long-term studies are needed to elucidate the potential independent role of MASLD in cardiovascular risk in T1D.

We found no association between liver fibrosis severity (LSM) and ASCVD. LSM, while non-invasive, cannot determine steatohepatitis and lacks validation in T1D. Evidence linking fibrosis to ASCVD in MASLD exists, but not in T1D due to lack of biopsy data [4, 5]. The guidelines indicate that non-invasive tests can play a role in determining the risk of liver fibrosis, but validation studies are absent in people with T1D [4]. Mantovani and colleagues recently studied the link between MASLD with/without fibrosis based on both non-invasive tests for steatosis (hepatic steatosis index) and fibrosis (FIB-4), both of which have shown discrepancies compared to other tests for their respective results [36]. For instance, our previous epidemiological study provided robust data on non-invasive tests for fibrosis and showed an important discrepancy in prevalence rates based on LSM versus FIB-4, while other studies have shown discrepancy between NAFLD fibrosis score, and FIB-4 in T1D populations [9, 38]. Furthermore, although being a recommended screening tool, there are studies questioning the accuracy of FIB-4 [39–41]. The low prevalence of significant fibrosis in our cohort, and by extension in people with T1D, limits statistical power to evaluate its link to ASCVD.

A major knowledge gap persists regarding the natural history and cardiometabolic effects of MASLD in T1D. Given the already high cardiovascular burden in T1D

[17, 18], even with optimal glycaemic control [42], there is a pressing need to explore underrecognized contributors like MASLD. While the link between MASLD and ASCVD is likely interchangeable with that of NAFLD and ASCVD, confirmation is needed. IR, commonly present in T1D, independently raises ASCVD risk [43]. In people with T1D, IR may increase ASCVD risk on its own [19, 44–46]. The eGDR, derived from the hyperinsulinaemic-euglycaemic clamp, is widely used as a proxy for IR because of the impracticality of the latter gold standard in clinical settings, but its components (hypertension, HbA1c, and WC) may confound ASCVD risk assessment [23]. An important limitation of the eGDR is that the potentially significant effect of IR in younger individuals without hypertension can be underestimated, as they may already feature important IR, but not yet its symptoms. MetS, driven by IR, is linked to ASCVD and may benefit from inclusion of features like inflammation, microalbuminuria, and steatosis [47–49]. The pathophysiological link between IR and NAFLD/MASLD is tied to the role of the liver in glucose homeostasis and insulin clearance. IR increases de novo lipogenesis and fatty acid flux to the liver due to impaired lipolysis inhibition, creating a reciprocal relationship with liver steatosis that amplifies both conditions [50]. Thus, mechanistic and longitudinal studies are needed to disentangle the causal effects of MetS, its components, and MASLD.

Our study has several strengths and limitations. This is a large cohort with minimal exclusion criteria, reducing selection bias. We used a strict definition of ASCVD, focusing on major events and excluding patients with atherosclerosis but no significant stenosis. We assessed future ASCVD risk via the validated Steno Type 1 Risk Engine, although it may underestimate risk in individuals with MASLD because of the increased use of antihypertensive and lipid-lowering agents in that subgroup. Our regression models controlled for MetS/eGDR, supporting an independent association between MASLD and ASCVD. However, due to overlapping parameters, we could not adjust for IR in the Steno model.

Limitations include its cross-sectional design, precluding causal inference, and reliance on ultrasound rather than biopsy for steatosis detection. While ultrasound is validated for moderate-to-severe steatosis, it cannot differentiate from steatohepatitis. Biopsy remains the gold standard but is unsuitable for population screening. Absence of biopsy studies also limits validation of LSM and FIB-4 in T1D. Family history of ASCVD was not collected, limiting adjustment. Finally, changes in lifestyle, metabolic control, or medication use over time may explain the lack of significance for some variables (e.g., smoking) or the lower LDL levels in subjects with ASCVD.

Conclusion

MASLD is common in T1D patients and strongly correlates with established ASCVD and increased future risk. This association appears to be independent of traditional cardiovascular risk factors, including IR. Identifying MASLD in patients with T1D may aid in risk stratification and management. Longitudinal studies are needed to clarify the causal relationship between MASLD and ASCVD.

Abbreviations

AIC	Akaike information criterion
ALD	Alcohol-related liver disease
ALT	Alanine aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CAD	Coronary artery disease
CAP	Controlled attenuation parameter
CI	Confidence interval
CKD	Chronic kidney disease
CVA	Cerebrovascular accident, i.e. ischemic stroke
DBP	Diastolic blood pressure
eGDR	Estimated glucose disposal rate
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
GGT	Gamma-glutamyl transferase
HDL	High-density lipoprotein
IR	Insulin resistance
LDL	Low-density lipoprotein
LSM	Liver stiffness measurement
MASLD	Metabolic dysfunction-associated steatotic liver disease
MetALD	MASLD with moderate alcohol consumption
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
OR	Odds ratio
PAD	Peripheral artery disease
SBP	Systolic blood pressure
SLD	Steatotic liver disease
TDI	Total daily dose of insulin
TG	Triglycerides
T1D	Type 1 diabetes
VCTE	Vibration-controlled transient elastography
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02764-y.

Supplementary Material 1.

Author contributions

JM, JW, EDI, LV, LVG, SF and CDB conceptualized the study. JM interpreted the analyses, visualized the results, searched the literature, and wrote the manuscript. JM, JW, WC, LV, and SF coordinated and supervised the data collection. JM, SF and CDB acquired funding for the analysis. JM and JW designed the statistical analyses. All the authors added to the study plan, interpreted the data, and critically revised the scientific content of the manuscript. All the authors had access to all the data of the study, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work. SF and CDB are the guarantors of this work and, as such, had full access to all the data in the study, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis. JM, SF and CDB had final responsibility for the decision to submit for publication.

Funding
JM received a doctoral grant from the University of Antwerp (BOF, Antigoon ID: 44430) and a research grant from the Belgian Association for the study of the Liver (BASL). SF holds a senior clinical investigator fellowship from the Research Foundation Flanders (FWO) (1802154N).

Data availability
Owing to patient privacy and the extent of patient consent, no individual patient data can be shared with outside investigators. However, collaborative research proposals are welcome. Aggregated data are available upon reasonable request via email to JM (jonathan.mertens@uza.be).

Declarations

Competing interests
The authors declare no competing interests.

Received: 6 March 2025 / Accepted: 29 April 2025
Published online: 29 May 2025

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