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Original article

MASLD, hepatic steatosis and fibrosis are associated with the prevalence of chronic kidney disease and retinopathy in adults with type 1 diabetes mellitus

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ABSTRACT

Aim: We examined whether metabolic dysfunction-associated steatotic liver disease (MASLD) with or without significant fibrosis (assessed by validated non-invasive biomarkers) was associated with an increased risk of prevalent chronic kidney disease (CKD) or diabetic retinopathy in people with type 1 diabetes mellitus (T1DM).
Methods: We performed a retrospective multicenter cross-sectional study involving 1,409 adult outpatients with T1DM, in whom hepatic steatosis index (HSI) and fibrosis (FIB)-4 index were calculated for non-invasively detecting hepatic steatosis (defined by HSI > 36), with or without coexisting significant fibrosis (FIB-4 index ≥ 1.3 or < 1.3). CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or urine albumin/creatinine ratio ≥ 3.0 mg/mmol. The presence of diabetic retinopathy was also recorded in all participants.
Results: Patients with MASLD and significant fibrosis ($n = 93$) had a remarkably higher prevalence of CKD and diabetic retinopathy than their counterparts with MASLD without fibrosis ($n = 578$) and those without steatosis ($n = 738$). After adjustment for sex, diabetes duration, hemoglobin A1c, hypertension, and use of antihypertensive or lipid-lowering medications, patients with SLD and significant fibrosis had a higher risk of prevalent CKD (adjusted-odds ratio 1.76, 95 % confidence interval 1.05–2.96) than those without steatosis. Patients with MASLD without fibrosis had a higher risk of prevalent retinopathy (adjusted-odds ratio 1.49, 95 % CI 1.13–1.46) than those without steatosis.

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; SLD, steatotic liver disease; T1DM, type 1 diabetes mellitus; CKD, chronic kidney disease; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; CKD-EPI, CKD epidemiology collaboration; HSI, hepatic steatosis index; FIB-4, fibrosis-4 index.

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Conclusion: This is the largest cross-sectional study showing that MASLD with and without coexisting significant fibrosis was associated, independently of potential confounders, with an increased risk of prevalent CKD and retinopathy in adults with T1DM.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) (previously termed non-alcoholic fatty liver disease or NAFLD) has become one of the most common chronic liver diseases worldwide, affecting almost ~30 % of the general adult population in many global regions [1], up to ~70 % of individuals with type 2 diabetes mellitus [2], and up to ~30–40 % of adult individuals with type 1 diabetes mellitus (T1DM) [3]. Although there is an almost total concordance between the MASLD and NAFLD definitions (i.e., ~99 % of patients with NAFLD meet MASLD criteria), the newly proposed definition of MASLD better reflects the underlying pathophysiology and cardiometabolic implications of this highly prevalent liver disease [4,5]

In adults of the general population and people with type 2 diabetes mellitus, the global health burden of NAFLD is not only restricted to important liver-related complications (such as cirrhosis, end-stage liver disease, or hepatocellular carcinoma) [6] but also includes major extrahepatic cardiometabolic conditions, such as an increased risk of adverse cardiovascular outcomes and chronic kidney disease (CKD) [7, 8]. In this regard, a comprehensive meta-analysis of 13 observational cohort studies (~1.2 million participants) reported that NAFLD was associated with a ~1.5-fold increased long-term risk of developing CKD stage ≥3, both in patients with and without type 2 diabetes mellitus [9].

Although it is well known that NAFLD creates a considerable health burden in terms of hepatic and extrahepatic complications in patients with type 2 diabetes mellitus [2,3,10–14], to our knowledge, the burden of NAFLD/MASLD in people with T1DM has so far little studied. A prospective cohort study of UK adults with T1DM and type 2 diabetes who had undergone a liver biopsy has reported that those with T1DM had a risk of developing liver-related clinical outcomes (incident cirrhosis and portal hypertension) that was similar to that observed in individuals with type 2 diabetes mellitus, who were matched for age, sex, diabetes duration and other potential confounders [15]. Furthermore, few small single-center studies have examined the association between NAFLD and the risk of major chronic microvascular complications (especially diabetic retinopathy and CKD) in adults with T1DM [16–18].

Therefore, in this multicenter cross-sectional study, we aimed to explore whether MASLD with and without significant fibrosis (determined by validated non-invasive biomarkers) was associated with an increased risk of prevalent CKD and diabetic retinopathy in adults with T1DM.

2. Materials and methods

2.1. Participants

This multicenter cross-sectional study was conducted in 11 Italian diabetes primary care outpatient clinics, all participating sites in the Study Group on Diabetes and Atherosclerosis of the Italian Society of Diabetes. More details about the recruitment methods of the study have been described elsewhere [19]. Briefly, all data were retrospectively retrieved from electronic medical records and patients' charts in each participating center during 2018 and 2019 [19]. The inclusion criteria of the study were adult (age ≥ 18 years) outpatients with known T1DM, according to validated diagnostic criteria [20]. Participants with type 2 diabetes or other specific types of diabetes mellitus (e.g., monogenic diabetes syndromes, cystic fibrosis, or pancreatitis), active cancer, or a prior history of chronic liver diseases or cirrhosis of any etiology were excluded. Participants with a previous history of ischemic heart disease, ischemic stroke, and coronary revascularizations (to avoid including patients at very high risk of CKD) or missing data on platelet counts and serum aminotransferase concentrations were also excluded. After excluding participants who did not meet the inclusion criteria mentioned above, the final sample for analysis consisted of 1409 adults with established T1DM (**Fig. S1; see supplementary materials associated with this article on line**). When we compared patients included in the final analysis to those excluded for missing data on platelet count and serum aminotransferase concentrations, the two patient groups did not significantly differ in demographic characteristics, adiposity measures, glycemic control, and prevalence rates of diabetic retinopathy and CKD (data not shown).

The study protocol was approved by the "*Comitato Etico per la Sperimentazione Clinica della Provincia di Padova*" (code #63,553, October 19th, 2018) and the ethics committee of each participating center [19]. Written informed consent was collected according to the request of each local ethics committee [19].

2.2. Clinical and laboratory data

Extracted electronic data were age, sex, duration of diabetes, body mass index (BMI, measured as kilograms divided by the square of height in meters), blood pressure, and biochemical parameters such as fasting glucose, hemoglobin A1c (HbA1c), lipids, creatinine, platelet count and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transferase [GGT]). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald's equation (except for subjects [$n = 3$] with plasma triglyceride concentrations > 400 mg/dL). Smoking history was dichotomized as current (yes) or no smoker (no or former > 1 year) and physical activity using a cut-point of > 3.5 h/week [19]. Information on hypertension and specific drug treatments, as well as total daily insulin doses and use of antiplatelet and lipid-lowering medications, were also recorded in all participants [19].

2.3. Diagnosis of diabetic retinopathy and CKD

In all participants, the estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) study equation [21]. Abnormal albuminuria was defined as urine albumin-to-creatinine ratio (ACR) ≥ 3.0 mg/mmol [19]. CKD was defined as eGFR < 60 mL/min/1.73 m^2 or abnormal albuminuria [22]. Information on diabetic retinopathy of any degree (mainly diagnosed by fundoscopy) was also recorded using electronic medical records and patients' charts [19].

2.4. Diagnosis of MASLD with or without coexisting liver fibrosis

In 2023, three large pan-national liver associations have proposed a new fatty liver disease nomenclature [4]. Steatotic liver disease was chosen as an overarching term encompassing the various etiologies of steatosis. The name chosen to replace NAFLD was MASLD. In particular, the diagnosis of pure MASLD was based on the evidence of hepatic steatosis (detected either by biopsy, imaging methods, or blood biomarkers/scores) in the presence of type 2 diabetes mellitus, overweight/obesity or other common cardiometabolic risk factors after excluding other competing causes of steatosis [including also a daily alcohol intake > 20 gs (> 140 g/week) for women and > 30 gs (> 210 g/week) for men] [4]. A new category outside pure MASLD, termed metabolic alcohol-associated liver disease (MetALD) was defined to

describe individuals with MASLD who consume moderate amounts of alcohol per week (from 140 to 350 g/week [20–50 g/day] and 210 to 420 g/week [30–60 g/day] for women and men, respectively) [4]. Therefore, in the present study, we excluded participants with a history of chronic liver diseases or cirrhosis of any etiology (as reported above) but preferred not to exclude individuals who consumed moderate amounts of alcohol per week (i.e., 140 to 350 g/week and 210 to 420 g/week for women and men, respectively). None of our participants consumed larger amounts of alcohol per week.

In agreement with two recent studies using this same database [23,24], we used the hepatic steatosis index (HSI) for identifying individuals with a high probability of having hepatic steatosis and the fibrosis (FIB)−4 index for identifying those with an increased likelihood of hepatic fibrosis. We did not calculate the fatty liver index (FLI) because waist circumference measurements were not available in most participants.

The HSI was calculated as follows: HSI = 8 × (ALT/AST ratio) + BMI (+2, if female; +2, if the presence of diabetes) [25]. An HSI value > 36 highly indicated hepatic steatosis, according to a cohort study by Lee et al., who first developed and validated against liver ultrasonography in a cohort of over 10,000 South Korean individuals [25]. In this cohort study, HSI had an area under the receiver-operating curve of 0.812 (95 % confidence interval [CI] 0.801–0.824). At HSI ⟨ 30 or ⟩ 36 values, HSI ruled out hepatic steatosis with a sensitivity of 92.5 % (95 % CI 91.4–93.5 %) or detected steatosis with a specificity of 92.4 % (95 % CI 91.3–93.4 %), respectively [25]. The HSI was also validated against liver ultrasonography in patients with type 2 diabetes [26] and, most importantly, it was also validated against magnetic resonance imaging in a small sample of adults with T1DM, showing a sensitivity of 86 %, specificity of 66 %, positive predictive value of 0.50, and negative predictive value of 0.92 [27]. In a subset of our participants (n = 352, 25 % of total), in whom we had data on liver ultrasonography, we also performed a receiver-operating characteristic curve analysis for predicting hepatic steatosis on ultrasonography according to the HSI, BMI alone, or the ALT-to-AST ratio (**Fig. S2; see supplementary materials associated with this article on line**). The area under the receiver-operating curve (AUROC) for HSI was 0.70 (95 % CI 0.64–0.76), whereas the AUROCs for BMI and the ALT-to-AST ratio were 0.69 (95 % CI 0.63–0.74) and 0.63 (95 % CI 0.57–0.68), respectively. The chi-squared test yielded a P-value < 0.002, thus showing a significant difference among the three AUROCs (principally between the AUROCs for HSI or BMI alone vs. the AUROC for ALT-to-AST ratio).

The FIB-4 index was calculated by using the following equation: FIB-4 index = age × AST (IU/L)/platelet count ($\times 10^9$/L) × $\sqrt{}$ALT (IU/L). The FIB-4 index is one of the most widely used non-invasive biomarkers of advanced liver fibrosis [28]. A FIB-4 cut-off ≥ 1.3 was suggestive of significant fibrosis [29,30]. We did not adopt different age-adjusted cut-offs for the FIB-4 index because the number of participants aged ≥ 65 years was low.

2.5. Statistical analysis

Continuous variables were expressed as means ± SD or medians (interquartile ranges [IQR]), and categorical variables were expressed as proportions. Differences in the main clinical and biochemical characteristics of patients stratified by the presence or absence of MASLD, with or without coexisting significant fibrosis (as non-invasively assessed by HSI and FIB-4 scores) were tested by the one-way ANOVA for normally distributed continuous variables (with adequate post-hoc tests for pairwise comparisons), the Kruskal-Wallis test for non-normally distributed variables, or the chi-squared test for categorical variables. Univariable and multivariable logistic regression analyses were performed to examine the associations between MASLD (with or without coexisting significant fibrosis) and the risk of CKD or diabetic retinopathy. Specifically, we performed unadjusted logistic regression models and three progressive forced-entry adjusted regression models. The first model was adjusted for sex, duration of diabetes and HbA1c (model 1); the second model was additionally adjusted for hypertension (blood pressure ≥ 140/90 mmHg or drug treatment), alcohol intake, and lipid-lowering medication use (model 2); and, finally, the last regression model included the same model 2′s covariates after excluding individuals with moderate alcohol intake (n = 220). Covariates included in these multivariable logistic regression models were chosen as potential confounding factors based on their biological plausibility or statistical associations with CKD and retinopathy in univariable regression analyses. Notably, as age was included in both the FIB-4 index and eGFR (as estimated by the CKD-EPI equation), and BMI was already included in the HSI formula, we decided not to also include age and BMI among covariates of the above-mentioned regression models to reduce possible multicollinearity problems.

All statistical tests were two-sided and a P-value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA software, version 17.0 (STATA, College Station, Texas, USA).

3. Results

3.1. Baseline characteristics

Among the 1409 Italian adult patients with T1DM included in the study (M/F = 768/641; mean [± SD] age 46 ± 15 years; BMI 25.2 ± 4.3 kg/m^2; diabetes duration 22 ± 12 years; HbA1c 7.8 ± 1.2 %; $eGFR_{CKD\text{-}EPI}$ 97.1 ± 20 mL/min/1.73 m^2), 738 (52.4 %) patients had HSI ≤ 36 (i.e., indicative of absent hepatic steatosis), 578 (41 %) had HSI > 36 and FIB-4 index < 1.3 (suggestive of MASLD without significant fibrosis) and 93 (6.6 %) had HSI > 36 and FIB-4 index ≥ 1.3 (suggestive of MASLD with significant fibrosis). All subjects with HSI > 36 had at least one of the five cardiometabolic criteria proposed for the diagnosis of MASLD. Regarding alcohol intake, among the 220 (15.6 % of total) participants who consumed moderate amounts of alcohol daily, 128 (17.3 %) were included among the 738 subjects who did not have steatosis, while the remaining 92 (13.7 %) were included among the 671 subjects who had MASLD with or without liver fibrosis; so in this latter group of 671 patients with MASLD, 579 (86.3 %) had pure MASLD and 92 (13.7 %) had MetALD according to the new fatty liver disease nomenclature. When subjects were stratified by low, intermediate and high HSI values, 128 (9.1 %) participants had HSI < 30, 610 (43.3 %) had intermediate HSI values between 30 and 36, and 671 (47.6 %) subjects had HSI > 36. Among the 93 subjects with HSI > 36 and FIB-4 index ≥ 1.3, about 10 % had FIB-4 index >2.67. Overall, 430 (30.5 %) participants had diabetic retinopathy of any degree and 214 (15.2 %) had CKD defined as $eGFR_{CKD\text{-}EPI}$ < 60 mL/min/1.73 m^2 and/or ACR ≥ 3.0 mg/mmol (184 had abnormal albuminuria alone and 73 had an eGFR < 60 mL/min/1.73 m^2, irrespective of albuminuria); a total of 115 (8.2 %) participants had both diabetic retinopathy and CKD.

The main clinical and biochemical characteristics of participants are summarized in Table 1. Compared to patients without hepatic steatosis or those with MASLD alone (without significant fibrosis), patients with MASLD and significant fibrosis were more likely to be older, overweight/obese, hypertensive, and less likely to be smokers or engaged in regular physical activity. In addition, they also had longer diabetes duration and higher values of blood pressure, HbA1c, serum triglycerides and liver enzymes, as well as lower platelet count, lower LDL-cholesterol, lower $eGFR_{CKD\text{-}EPI}$ and a greater prevalence of abnormal albuminuria than the other two groups. The total daily insulin doses and the proportion of those treated with anti-hypertensive medications (i.e., diuretics, beta-blockers, calcium-channel blockers, or renin-angiotensin system inhibitors), anti-platelet drugs and statins were also greater in patients with MASLD and significant fibrosis. Conversely, sex distribution and alcohol intake did not significantly differ among the three patient groups.

Table 1
Clinical and biochemical characteristics of adult outpatients with T1DM, stratified by presence of MASLD with or without coexisting significant fibrosis (non-invasively assessed by HSI and FIB-4 scores).

	Patients with HSI ≤ 36 (n = 738) (Group A)	Patients with HSI > 36 and FIB4 < 1.3 (n = 578) (Group B)	Patients with HSI > 36 and FIB4 ≥ 1.3 (n = 93) (Group C)	P-value for trends	*P-value for A vs. B	*P-value for A vs. C	*P-value for B vs. C
Age (years)	45 ± 16	44 ± 13	63 ± 12	< 0.001	n.s	< 0.001	< 0.001
Male sex (%)	54.7	55.4	47.2	0.245	n.s	< 0.05	< 0.05
BMI (kg/m^2)	22.6 ± 2.3	27.9 ± 4.0	29.3 ± 4.7	< 0.001	<0.001	< 0.001	< 0.001
Current smokers (%)	29.1	23.2	14.0	0.001	n.s	< 0.001	< 0.001
Regular physical activity (≥3.5 h/week) (%)	48.3	46.6	34.4	0.041	n.s	< 0.001	< 0.001
Moderate alcohol intake (%)[§]	17.4	14.0	11.8	0.230	n.s	n.s	n.s
Diabetes duration (years)	21 ± 12	21 ± 14	30 ± 14	< 0.001	n.s	< 0.001	< 0.001
Fasting glucose (mg/dL)	175 ± 73	182 ± 69	178 ± 68	0.462	n.s	n.s	n.s
HbA1c (mmol/mol)	60.7 ± 0.5	63.8 ± 0.5	65.4 ± 0.4	< 0.001	<0.001	n.s	n.s
Systolic blood pressure (mmHg)	125 ± 18	129 ± 16	139 ± 20	< 0.001	0.001	< 0.001	< 0.001
Diastolic blood pressure (mmHg)	75 ± 9	78 ± 9	77 ± 10	< 0.001	<0.001	n.s	n.s
Total cholesterol (mg/dL)	180 ± 33	184 ± 32	179 ± 43	0.083	n.s	n.s	n.s
HDL cholesterol (mg/dL)	61 ± 16	55 ± 15	61 ± 17	< 0.001	<0.001	n.s	n.s
LDL cholesterol (mg/dL)	103 ± 28	108 ± 28	99 ± 36	< 0.001	0.001	n.s	< 0.05
Triglycerides (mg/dL)	69 (56–94)	82 (62–115)	87 (64–128)	< 0.001	<0.001	0.001	n.s
AST (IU/L)	20 (16–25)	18 (15–23)	24 (19–32)	< 0.001	<0.001	< 0.001	< 0.001
ALT (IU/L)	17 (13–22)	21 (16–29)	23 (16–33)	< 0.001	<0.001	< 0.001	n.s
GGT (IU/L)	15 (11–21)	18 (13–28)	22 (14–40)	< 0.001	n.s	< 0.001	0.032
Platelet count (x 100,000/mm^3)	242 ± 71	258 ± 64	190 ± 56	< 0.001	<0.001	< 0.001	< 0.001
Creatinine (mg/dL)	0.85 ± 0.32	0.88 ± 0.49	1.07 ± 0.89	< 0.001	n.s	< 0.001	< 0.001
eGFR$_{CKD-EPI}$ (mL/min/1.73 m^2)	99 ± 20	98 ± 19	80 ± 25	< 0.001	n.s	< 0.001	< 0.001
Abnormal albuminuria (%)	12.1	13.8	30.4	< 0.001	n.s	< 0.001	< 0.001
Hypertension (%)	31.8	39.2	74.2	< 0.001	n.s	< 0.001	< 0.001
Total daily insulin dose (IU/day)	37 ± 15	45 ± 20	48 ± 17	< 0.001	<0.001	< 0.001	n.s.
Antiplatelet drug users (%)	10.9	9.9	38.7	< 0.001	n.s	< 0.001	< 0.001
Diuretic users (%)	5.6	8.8	36.6	< 0.001	n.s	< 0.001	< 0.001
Beta-blocker users (%)	5.4	5.7	26.9	< 0.001	n.s	< 0.001	< 0.001
Calcium-channel blocker users (%)	5.2	7.4	23.7	< 0.001	n.s	< 0.001	< 0.001
ACE-i/ARB users (%)	23.4	31.7	66.7	< 0.001	n.s	< 0.001	< 0.001
Statin users (%)	26.0	32.4	62.4	< 0.001	n.s	< 0.001	< 0.001

Cohort size: n = 1409. Data are expressed as mean ± SD, median and interquartile range (IQRs) or percentages. Differences among the three patient groups were tested by the chi-squared test for categorical variables, the one-way ANOVA for normally distributed continuous variables, and the Kruskal-Wallis test for non-normally distributed variables (i.e., serum liver enzymes and triglycerides). [§]Moderate alcohol intake was defined as 20 to 50 gs (140–350 g/week) and 30 to 60 gs (210–420 g/week) of alcohol per day for women and men, respectively. Abnormal albuminuria was defined as urine albumin-to-creatinine ratio ≥ 3.0 mg/mmol.
Abbreviations: ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; eGFR$_{CKD-EPI}$, estimated glomerular filtration rate calculated by the CKD-Epidemiology Collaboration study equation; GGT, gamma-glutamyl-transferase; FIB-4, fibrosis 4; HSI, hepatic steatosis index; n.s., not significant.
[*] Direct intergroup comparisons of all variables among patients with HSI ≤ 36 (group A), patients with HSI >36 and FIB-4 < 1.3 (group B), and those with HSI > 36 and FIB4 ≥ 1.3 (group C) were performed using the Bonferroni multiple-comparison test for continuous variables and the chi-squared test for categorical variables.

3.2. *MASLD with or without liver fibrosis and risk of diabetic retinopathy and CKD*

Fig. 1 shows the prevalence rates of diabetic retinopathy and CKD (defined as eGFR < 60 mL/min/1.73 m^2 or abnormal albuminuria) among participants stratified by the presence of MASLD with or without significant fibrosis. Notably, patients with MASLD and significant fibrosis had a remarkably greater prevalence of CKD (36.6 % vs. 14.0 % vs. 13.4 %, P < 0.001 by the chi-squared test), as well as a greater prevalence of diabetic retinopathy (51.1 % vs. 34.2 % vs. 26.3 %, P < 0.001) than patients with MASLD alone or those without steatosis. When patients with MASLD and FIB-4 ≥ 1.3 were subdivided into those with FIB-4 1.3–2.67 (i.e., subjects in the "gray zone") and those with FIB-4 >2.67 (**Fig. S3; see supplementary materials associated with this article on line**), we found a positive graded relationship between increasing FIB-4 scores and CKD prevalence (that was less evident for diabetic retinopathy), thus further reinforcing the possible link between microvascular diabetic complications and the severity of liver disease.

Fig. 2 shows the prevalence rates of diabetic retinopathy and CKD among the three patient subgroups after further stratification by sex. Both men and women with MASLD and significant fibrosis had higher prevalence rates of CKD and diabetic retinopathy than their counterparts with MASLD alone or without steatosis.

Figs. S4 and **S5 (see supplementary materials associated with this article on line)** show the prevalence rates of CKD and diabetic retinopathy among the three patient subgroups after further stratification either by median age (< 45 vs. ≥ 45 years) or by the presence of overweight/obesity (BMI < 25 vs. ≥ 25 kg/m^2), respectively. In most of the patient subgroups considered (except for the prevalence of CKD and retinopathy in younger participants where the number of cases was low), patients with MASLD and significant fibrosis had higher prevalence rates of CKD and diabetic retinopathy than their counterparts with MASLD alone or without steatosis, regardless of age and obesity status.

Table 2 shows the associations between MASLD, with or without coexisting significant fibrosis, and the risk of prevalent diabetic retinopathy or CKD in the whole cohort of participants. In unadjusted

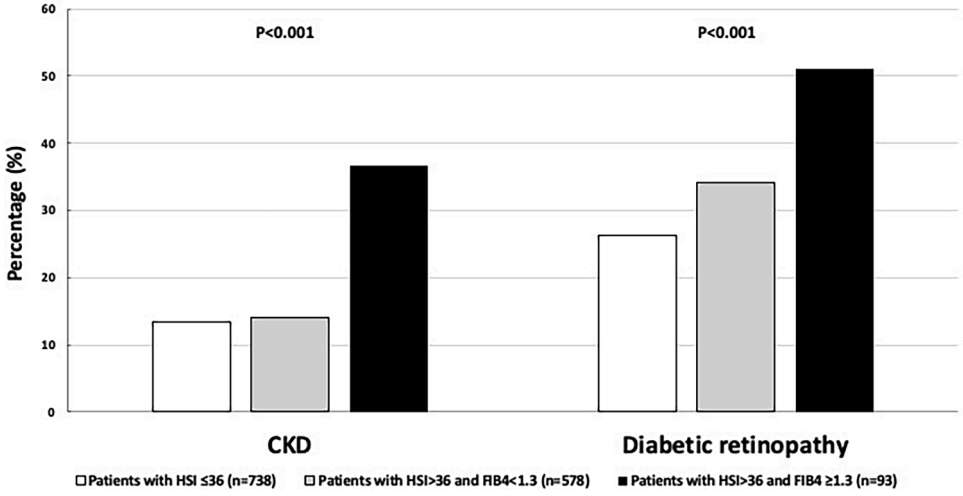

Fig. 1. Prevalence rates of CKD and diabetic retinopathy in adult outpatients with T1DM, stratified by presence of hepatic steatosis (MASLD) with or without coexisting significant fibrosis (non-invasively determined by HSI and FIB-4 scores). *P*-values are tested by the chi-squared test.

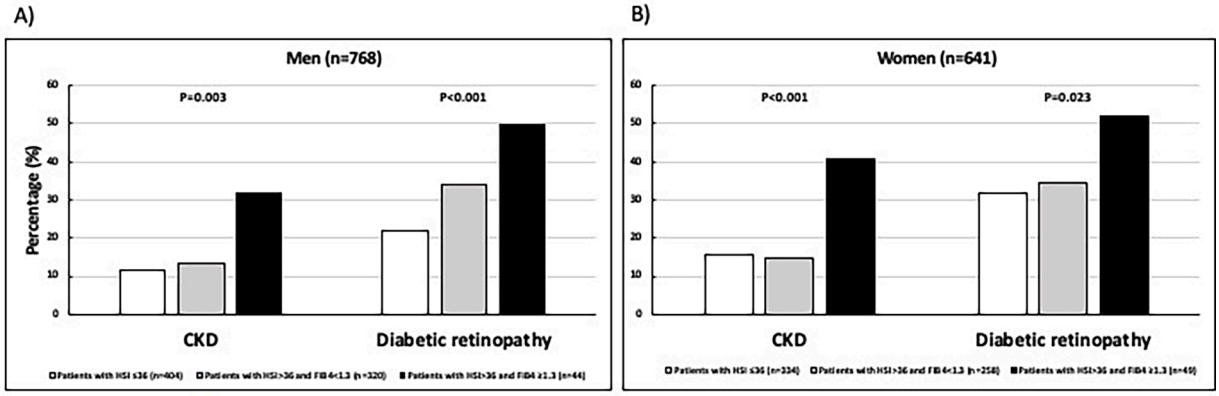

Fig. 2. Prevalence rates of CKD and diabetic retinopathy in adult outpatients with T1DM, stratified by sex and presence of hepatic steatosis (MASLD) with or without coexisting significant fibrosis (non-invasively determined by HSI and FIB-4 scores). Panel A reports data in men. Panel B reports data in women. *P*-values are tested by the chi-squared test.

regression models, patients with MASLD and significant fibrosis had about a three to four times greater risk of prevalent diabetic retinopathy (unadjusted OR 2.92, 95 % CI 1.87–4.54) and CKD (unadjusted OR 3.72, 95 % CI 2.32–5.96) compared to their counterparts without steatosis. After adjustment for sex, duration of diabetes, HbA1c, hypertension, daily alcohol intake and lipid-lowering medication use (model 2), patients with MASLD and significant fibrosis had a higher risk of CKD (adjusted OR 1.76, 95 % CI 1.05–2.96) but not retinopathy, compared to those without steatosis. In both unadjusted and adjusted regression models, patients with MASLD alone had a higher risk of prevalent diabetic retinopathy (model 2: adjusted OR 1.49, 95 % CI 1.13–1.46) but not CKD, compared to those without steatosis. Notably, excluding participants ($n = 220$) with MASLD who consumed moderate amounts of alcohol per day did not affect the results (model 3). In these logistic regression models, other variables that were independently associated with a higher risk of diabetic retinopathy or CKD were longer duration of diabetes, higher HbA1c and hypertension ($P < 0.001$ for all) (data not shown). As a sensitivity analysis, the results remained unchanged when we repeated the above-mentioned adjusted regression models after excluding participants with intermediate HSI values (HSI 30–36). In particular, patients with MASLD and significant liver fibrosis had about a three times greater risk of both diabetic retinopathy (OR 3.23, 95 % CI 1.82–5.75) and CKD (OR 3.11, 95 % CI 1.65–5.88) compared to their counterparts without steatosis.

Finally, we also performed logistic regression models to examine the separate associations of HSI $>$ 36 and FIB-4 index $\geq$ 1.3 with the risk of diabetic retinopathy or CKD (**Table S1; see supplementary materials associated with this article on line**). In line with the results reported above, in these multivariable logistic regression models the risk of CKD tended to be more strongly associated with FIB-4 index $\geq$ 1.3, rather than HSI $>$ 36. Conversely, the risk of diabetic retinopathy tended to be more strongly associated with HSI $>$ 36, rather than FIB-4 index $\geq$ 1.3.

4. Discussion

This is the most updated and largest multicenter cross-sectional study to explore the relationship between MASLD, with and without coexisting liver fibrosis, and the risk of prevalent CKD and diabetic retinopathy in adults with T1DM.

The main and novel findings of our cross-sectional study of nearly 1400 Italian adult outpatients with T1DM are as follows: (a) patients with HSI $>$ 36 and FIB-4 index $\geq$ 1.3 (suggestive of MASLD with significant fibrosis) had a greater risk of prevalent CKD and diabetic retinopathy than their counterparts with MASLD alone or without steatosis; (b) after adjustment for demographics, diabetes-related variables, hypertension, and current use of anti-hypertensive or lipid-lowering medications, patients with MASLD and significant fibrosis had a ~1.8-fold increased risk of prevalent CKD, but not retinopathy, compared to

Table 2
Associations between presence of MASLD with or without coexisting significant fibrosis (as non-invasively assessed by HSI and FIB-4 scores) and the risk of prevalent CKD or diabetic retinopathy in adult outpatients with T1DM.

Logistic regression models	Odds ratio (95 % CI)	*P*-value
CKD (yes vs. no)		
Unadjusted model		
HSI ≤ 36 ($n = 738$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 578$)	1.05 (0.77–1.44)	0.754
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	3.72 (2.32–5.96)	< 0.001
Adjusted model 1		
HSI ≤ 36 ($n = 738$)	*Ref.*	
HSI > 36 and FIB4 < 1.3 ($n = 578$)	1.01 (0–73–1.41)	0.939
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	2.87 (1.74–4.71)	< 0.001
Adjusted model 2		
HSI ≤ 36 ($n = 738$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 578$)	0.88 (0.62–1.26)	0.500
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	1.76 (1.05–2.96)	0.031
Adjusted model 3		
HSI ≤ 36 ($n = 613$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 495$)	0.89 (0.61–1.30)	0.551
HSI > 36 and FIB4 ≥ 1.3 ($n = 81$)	1.86 (1.07–3.23)	0.028
Diabetic retinopathy (yes vs. no)		
Unadjusted model		
HSI ≤ 36 ($n = 738$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 578$)	1.45 (1.14–1.84)	0.002
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	2.92 (1.87–4.54)	< 0.001
Adjusted model 1		
HSI ≤ 36 ($n = 738$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 578$)	1.55 (1.19–2.04)	0.001
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	1.56 (0.93–2.59)	0.091
Adjusted model 2		
HSI ≤ 36 ($n = 738$)	*Ref.*	–
HSI > 36 and FIB4 < 1.3 ($n = 578$)	1.49 (1.13–1.96)	0.005
HSI > 36 and FIB4 ≥ 1.3 ($n = 93$)	1.19 (0.71–2.01)	0.512
Adjusted model 3		
HSI ≤36 ($n = 613$)	*Ref.*	–
HSI >36 and FIB4 < 1.3 ($n = 495$)	1.62 (1.19–2.19)	0.002
HSI >36 and FIB4 ≥ 1.3 ($n = 81$)	1.28 (0.73–2.25)	0.382

Cohort size, $n = 1409$. Data are expressed as odds ratios (OR) and 95 % confidence intervals (CI), assessed by univariate and multivariate logistic regression analyses. Regression models were adjusted as follows: model 1: sex, diabetes duration and HbA1c; model 2: adjusted for the same variables included in model 1 *plus* hypertension (defined as blood pressure ≥140/90 mmHg and/or use of any antihypertensive agents), daily alcohol intake, and statin use; and model 3: adjusted for the same list of model 2's covariates after excluding participants with moderate alcohol intake ($n = 220$).
Abbreviations: HSI, hepatic steatosis index; FIB-4, fibrosis 4.

those without steatosis; (c) after adjustment for the same list of covariates, patients with MASLD alone had a higher risk (~1.5 fold) of diabetic retinopathy, but not CKD, compared to their counterparts without steatosis; and (d) the results remained unchanged even after excluding participants ($n = 220$) who consumed moderate amounts of alcohol per day.

Substantial evidence indicates that NAFLD is a growing public health problem in people with type 2 diabetes, causing important hepatic and extrahepatic complications [2,3,10–14]. NAFLD is currently not screened for in individuals with T1DM. The prevalence estimate of NAFLD in people with T1DM is highly variable. A recent meta-analysis of 20 observational studies reported a prevalence of imaging-defined NAFLD of 22 % (95 % CI 13.9–31.2 %) in adults with T1DM [31]. However, the prevalence rate of this liver disease was highly dependent on the diagnostic methodologies, being the highest in liver ultrasound-based studies where the pooled prevalence of NAFLD was around 30 % in adults with T1DM (ranging from 10 % to 64.8 %) and the lowest in magnetic resonance imaging-based studies where the pooled prevalence was around 10 % (ranging from 0 % to 30 %) [31]. In a cohort study of 530 Belgian adults with T1DM from a tertiary care hospital, Mertens et al. recently reported that the overall prevalence of NAFLD on ultrasonography was ~16 % [32].

To date, there are limited data (mainly derived from small single-center studies) regarding the possible adverse effects of NAFLD on the risk of diabetic retinopathy and CKD in adults with T1DM [16–18,33], which are two important chronic microvascular complications of diabetes. For instance, in 2010, in a cross-sectional study of 202 Italian adult outpatients with T1DM, Targher et al. [16] reported for the first time that ultrasound-detected NAFLD (present in ~55 % of these patients) was associated, independently of multiple confounding factors, with a higher prevalence of both CKD (defined as eGFR < 60 mL/min/1.73 m^2 or abnormal albuminuria) (adjusted OR 3.90, 95 % CI 1.5–10.1) and diabetic retinopathy of any degree (adjusted OR 3.31, 95 % CI 1.4–7.6). In 2012, in a study involving 343 adult outpatients with T1DM without chronic liver diseases (~50 % of whom had NAFLD on ultrasonography), Targher *et al.* reported that NAFLD was associated with a ~2-fold increased risk of prevalent CKD, independently of age, sex, BMI, smoking, diabetes-related factors and use of anti-hypertensive or lipid-lowering medications [18]. In this same group of patients, the authors also showed that NAFLD was associated with an increased prevalence of asymptomatic/symptomatic cardiovascular disease, independently of traditional cardiovascular risk factors, eGFR and albuminuria [34]. More recently, in a small cross-sectional study of 124 Italian adult patients (mean age 37 years) with T1DM, Tripolino *et al.* also reported that NAFLD (assessed by the HSI index) was independently associated with an increased prevalence of chronic vascular complications of diabetes, defined as a composite endpoint inclusive of carotid atherosclerosis, retinopathy, neuropathy, and nephropathy [33].

Collectively, the findings of our multicenter cross-sectional study corroborate and expand the results of the previous small single-center cross-sectional studies showing that T1DM patients with MASLD with and without coexisting significant fibrosis had a markedly higher risk of prevalent diabetic retinopathy and CKD than their counterparts without steatosis. Notably, the sample size of our study was at least ~5 times greater than that of previously published studies. Furthermore, this is the first large study to examine the associations between the FIB-4 index (i.e., a widely used non-invasive marker of liver fibrosis) and the presence of CKD and retinopathy in people with T1DM. In fact, in the previously published studies (as discussed above), there was no information about the severity of liver fibrosis, which is one of the strongest predictors of all-cause mortality and adverse (hepatic and extrahepatic) clinical outcomes in MASLD [7,9,10,35,36].

The potential implications of our findings for patient care are that the non-invasive detection of MASLD and significant fibrosis in adults with T1DM might identify a subset of subjects at higher risk of developing major chronic microvascular complications (especially CKD), thereby warranting evaluation and treatment of the main modifiable risk factors. An important aspect that further strengthens our observations is that an ever-increasing body of evidence supports a strong association between NAFLD/MASLD and increased prevalence and incidence of CKD and diabetic retinopathy also in patients with type 2 diabetes [8,37–41]. Moreover, and most interestingly, a small prospective study reported a positive association between ultrasound-detected NAFLD and the risk of developing new-onset CKD (defined as eGFR <60 mL/min/1.73 m^2 or abnormal albuminuria) in a cohort of 261 Italian patients with T1DM followed for a mean of ~5 years [17].

The putative underlying mechanisms responsible for the significant associations we observed between MASLD (with and without coexisting significant fibrosis) and the increased risk of CKD and diabetic retinopathy in adults with T1DM are not fully understood. Speculatively, the most obvious explanation for our findings is that the increased MASLD-related risk of diabetic retinopathy and CKD might be, at least in part, mediated by the shared cardiometabolic risk factors. However, it should be noted that after adjusting for sex, diabetes-related factors, hypertension, and use of anti-hypertensive and lipid-lowering medications, we found that patients with MASLD and significant fibrosis had a higher risk of CKD (but not retinopathy), while those with MASLD without significant fibrosis had a higher risk of retinopathy (but not

CKD). Notably, we did not adjust these results for age because this variable was already included in both the FIB-4 and eGFR formulas. We do not have sufficient data to provide any teleological reason for the observed differential associations of hepatic steatosis and fibrosis with the risk of diabetic retinopathy and CKD. Nonetheless, we think these findings provide further evidence supporting that MASLD with varying levels of liver fibrosis may contribute to the development and progression of CKD and diabetic retinopathy. Experimental evidence shows that NAFLD/MASLD promotes the systemic release of multiple proinflammatory, prooxidant, and profibrogenic mediators, playing a role in the pathophysiology of chronic vascular complications of diabetes [3, 42–44].

The current study has some important limitations. First, the design of our retrospective cross-sectional study does not allow us to establish causal or temporal relationships between MASLD, diabetic retinopathy and CKD. Second, we used an estimated GFR (i.e., the CKD-EPI equation [21]) instead of a direct measurement of GFR to define CKD. However, it should be noted that current GFR estimates can facilitate the detection, evaluation, and management of CKD in clinical practice. Furthermore, many scientific societies recommend using the CKD-EPI equation to estimate renal function in clinical practice and epidemiological studies. Third, the diagnosis of diabetic retinopathy was mainly based on fundoscopy, thus subtle diabetic retinopathy changes may have been missed. However, the possibility that subtle retinopathy changes might have gone partly unnoticed would have weakened rather than strengthened our findings. Finally, the diagnosis of hepatic steatosis was based on the HSI index (i.e., HSI >36 vs. HSI $\leq$ 36) and not liver ultrasonography. Similarly, we used the FIB-4 index for non-invasively diagnosing liver fibrosis (FIB-4 index $\geq$ 1.3) and not vibration-controlled transient elastography (FibroScan®). In clinical practice, ultrasonography and vibration-controlled transient elastography are the first-line imaging methods for non-invasively identifying hepatic steatosis and fibrosis [45]. However, these two imaging methodologies are expensive and not easily applied in large epidemiological studies like this. That said, HSI performed well in identifying hepatic steatosis compared with ultrasonography or magnetic resonance imaging in the general adult population [25], patients with type 2 diabetes [26], and those with T1DM [27]. Furthermore, we also showed a satisfactory diagnostic performance of HSI in identifying hepatic steatosis on ultrasonography in a subset of our participants (**Fig. S2; see supplementary materials associated with this article on line**). Although simple non-invasive blood-based biomarkers, such as HSI and FIB-4 scores, can be used as first-line tools [28,30], some evidence suggests that fatty liver index (FLI) could perform better than HSI for detecting hepatic steatosis in people with T1DM [32]. Moreover, the accuracy of non-invasive blood-based biomarkers for identifying liver fibrosis could be lower in subjects with diabetes than those without diabetes [46]. Further studies using imaging methodologies (such as magnetic resonance imaging-proton density fat fraction, magnetic resonance elastography, or vibration-controlled transient elastography) for detecting hepatic steatosis and fibrosis are necessary to further validate our findings in large cohorts of adult individuals with T1DM. Finally, we cannot *a priori* exclude that other unmeasured factors might at least partly explain the observed associations.

Notwithstanding these limitations, our study has important strengths, such as the multicenter study design, the large sample size, the completeness of the database, and the exclusion of patients with important comorbidities (such as, for example, active cancer, cirrhosis and prior history of ischemic heart disease or strokes), as we believe that the inclusion of patients with such comorbidities might have confounded the interpretation of data.

In conclusion, this multicenter cross-sectional study showed that MASLD with and without significant fibrosis (determined by validated non-invasive blood-based biomarkers) was associated with a greater risk of prevalent diabetic retinopathy and CKD in adult outpatients with T1DM, independently of multiple potential confounding factors. Further research is certainly required to corroborate these findings in other independent cohorts of individuals with T1DM from different countries and to understand whether MASLD with varying levels of liver fibrosis may increase the risk of developing CKD and other chronic microvascular complications in people with T1DM.

CRediT authorship contribution statement

Alessandro Mantovani: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Mario Luca Morieri:** Data curation, Validation, Writing – review & editing. **Raffaella Aldigeri:** Data curation, Writing – review & editing. **Luisa Palmisano:** Data curation, Writing – review & editing. **Maria Masulli:** Data curation, Writing – review & editing. **Katia Bonomo:** Data curation, Writing – review & editing. **Marco Giorgio Baroni:** Data curation, Writing – review & editing. **Efisio Cossu:** Data curation, Writing – review & editing. **Flavia Agata Cimini:** Data curation, Writing – review & editing. **Gisella Cavallo:** Data curation, Writing – review & editing. **Raffaella Buzzetti:** Data curation, Writing – review & editing. **Carmen Mignogna:** Data curation, Writing – review & editing. **Frida Leonetti:** Data curation, Writing – review & editing. **Simonetta Bacci:** Data curation, Writing – review & editing. **Roberto Trevisan:** Data curation, Writing – review & editing. **Riccardo Maria Pollis:** Data curation, Writing – review & editing. **Alessandra Dei Cas:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Saula Vigili de Kreutzenberg:** Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Giovanni Targher:** Conceptualization, Methodology, Investigation, Data curation, Supervision, Writing – original draft, Writing – review & editing, Formal 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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2023.101497.

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