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# Glycaemic control metrics and metabolic dysfunction–associated steatotic liver disease in children and adolescents with type 1 diabetes

Claudio Maffeis MD[1] | Claudia Piona MD[1] | Anita Morandi MD[1] | Marco Marigliano MD[1] | Elisa Morotti MD[1] | Valentina Mancioppi MD[1] | Erika Caiazza MD[1] | Chiara Zusi PhD[1] | Federica Emiliani BSc[1] | Alessandro Mantovani MD[2] | Antonio Colecchia MD[3] | Giovanni Targher MD[4,5]

[1]Section of Pediatric Diabetes and Metabolism, Department of Surgery, Dentistry, Pediatrics and Gynecology, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

[2]Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

[3]Gastroenterology Unit, Department of Specialistic Medicines, University Hospital of Modena and Reggio Emilia, Modena, Italy

[4]Department of Medicine, University of Verona, Verona, Italy

[5]Metabolic Diseases Research Unit, IRCCS Sacro Cuore—Don Calabria Hospital, Negrar di Valpolicella, Italy

**Correspondence**
Claudia Piona, MD, Section of Pediatric Diabetes and Metabolism, Department of Surgery, Dentistry, Pediatrics and Gynecology, University and Azienda Ospedaliera Universitaria Integrata of Verona, Piazzale Stefani, 1, 37126 Verona, Italy.
Email: claudia.piona@univr.it

## Abstract

**Aim:** The aim was to examine the prevalence of metabolic dysfunction–associated steatotic liver disease (MASLD), a risk factor for atherosclerotic cardiovascular disease, and its association with glycaemic control metrics in children and adolescents with type 1 diabetes (T1D).

**Materials and Methods:** We enrolled 244 children and adolescents with T1D (115 girls, mean age: 16.2 ± 3.2 years). The diagnosis of MASLD was defined by the presence of hepatic steatosis on ultrasonography in combination with at least one of five common cardiometabolic risk factors. Metrics of short-term and long-term glycaemic control, blood pressure, lipids, anthropometric characteristics and three genetic variants strongly related to MASLD susceptibility (rs738409 [patatin-like phospholipase domain-containing 3], rs58542926 [transmembrane 6 superfamily member 2] and rs1260326 [glucokinase regulator]) were assessed. Characteristics of these subjects with and without MASLD were compared using the unpaired Student *t* test, Mann–Whitney test or $\chi^2$ test as appropriate. Logistic regression analyses were performed to determine the main independent predictors of MASLD.

**Results:** The prevalence of MASLD was 27.5% in children and adolescents with T1D. Blood pressure, total cholesterol, low-density lipoprotein (LDL) cholesterol, non-high-density lipoprotein cholesterol, HbA1c and time above range (TAR) were significantly higher in subjects with MASLD than in those without MASLD. Mean HbA1c values from diabetes onset (adjusted odds ratio [OR]: 1.703, 95% confidence interval [CI]: 1.040–2.787, $p = 0.034$), TAR (adjusted OR: 1.028, 95% CI: 1.009–1.047, $p = 0.006$) and plasma LDL cholesterol (adjusted OR: 1.045, 95% CI: 1.013–1.078, $p = 0.004$) were independently associated with the presence of MASLD.

**Conclusions:** MASLD is a common condition in children and adolescents with T1D. The mean HbA1c values from diabetes onset, TAR and LDL cholesterol levels were the independent predictors of MASLD.

**KEYWORDS**
children, continuous glucose monitoring, glycaemic control, metabolic dysfunction–associated steatotic liver disease, prevalence, type 1 diabetes

## 1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide in both adults and adolescents. NAFLD is closely associated with insulin resistance, overweight/obesity, type 2 diabetes, atherogenic dyslipidaemia and, consequently, increased cardiovascular morbidity and mortality.[1–3] A consensus of international experts belonging to the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver has recently proposed to rename NAFLD as metabolic dysfunction–associated steatotic liver disease (MASLD), thus better emphasizing the pathogenic role of metabolic dysfunction in the development of this common and burdensome liver disease.[4,5] The diagnosis of MASLD in the paediatric population is based on the identification of hepatic steatosis (as assessed using blood-based biomarkers, imaging methods or liver biopsy) in combination with at least one common cardiometabolic risk factor, including excess adiposity, the presence of prediabetes or diabetes, increased blood pressure or atherogenic dyslipidaemia (high triglycerides [TG] or low high-density lipoprotein [HDL] cholesterol).[5]

Specific genetic polymorphisms may affect the development and progression of MASLD, as reported in previous studies conducted in children and adolescents.[6] Recently, we also reported that MASLD was strongly associated with three genetic variants, that is, transmembrane 6 superfamily member 2 (*TM6SF2*) rs58542926, patatin-like phospholipase domain-containing 3 (*PNPLA3*) rs738409 and glucokinase regulator (*GCKR*) rs1260326, and more slightly with *ELOVL2* rs2236212, in children and adolescents with obesity.[7] However, no data on this issue are currently available in children and adolescents with type 1 diabetes (T1D).

Current recommendations of the International Scientific Societies for Diabetes, Endocrinology and Hepatology do not suggest regular screening for MASLD in individuals with T1D.[8] However, recent data have reported that MASLD is a common condition in adults with T1D, and MASLD is independently associated with an increased risk of developing macro- and micro-vascular diabetic complications in this patient population, leading to an increased long-term risk of morbidity and mortality.[9,10] To date, observational studies assessing the prevalence of MASLD and associated comorbidities in children and adolescents with T1D are scarce, showing heterogeneous prevalence data of MASLD ranging from 12.3% to 27.5%.[11] Moreover, to the best of our knowledge, the association between MASLD and short-term and long-term glycaemic control (as assessed using continuous glucose monitoring [CGM] metrics and HbA1c) has not been widely explored in children and adolescents with T1D.[12]

Therefore, the main aims of this exploratory cross-sectional study were to assess (a) the prevalence of imaging-defined MASLD and (b) the association between MASLD and short-term and long-term glycaemic control metrics in an Italian cohort of children and adolescents with established T1D.

## 2 | MATERIALS AND METHODS

### 2.1 | Study protocol and participants

This study was conducted at the Regional Center for Pediatric Diabetes, the Section of Endocrinology, Diabetes and Metabolism, and the Gastroenterology Unit of the University Hospital of Verona. The local Institutional Ethics Committee approved the study protocol, and written informed consent was obtained from the study participants and their parents. A total of 244 children and adolescents with established T1D were consecutively enrolled. Inclusion criteria of the study were as follows: age >10 years and a diagnosis of T1D that was confirmed by the presence of one or more diabetes-associated autoantibodies (GADA, ZnT8A, IAA or IA–2A) at least 2 years before study enrolment. Exclusion criteria of the study were age <10 years; monogenic diabetes; cystic fibrosis–related diabetes, type 2 diabetes, Hashimoto thyroiditis, celiac disease or other autoimmune diseases. None of the participants had known chronic liver disease, cardiovascular disease or other metabolic diseases, as determined from medical history, physical examination and blood tests. All participants did not take any other medications other than insulin.

### 2.2 | Demographic, clinical, blood pressure and glycaemic parameters

At the time of study enrolment, all participants underwent a physical examination where anthropometrics (height and body weight) and blood pressure were measured. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in metres squared. In subjects aged <18 years, BMI values were standardized by calculating age and sex-specific BMI percentiles according to the World Health Organization child growth standards.[13] Blood pressure (BP) was measured on the left arm using a digital sphygmomanometer and

appropriate cuffs for the child's age and arm circumference. The average of three BP measurements was recorded. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentiles were calculated based on normative values for sex, age and height.[14] At the time of study enrolment, the study participants were asked to provide retrospective estimates of their daily alcohol consumption over the 4 weeks preceding the interview, and the reported alcohol consumption was converted into grams of alcohol (e.g. a 33-cl bottle of beer corresponded to ~12 g of absolute alcohol). Age at onset, duration of T1D, pubertal status (Tanner stages I–V),[15] modalities of insulin administration (i.e. multiple daily injections or continuous subcutaneous insulin infusion), daily insulin dosages and information on the type of glucose monitoring devices used (i.e. self-monitoring of capillary blood glucose or CGM) were recorded for all participants. In patients using CGM, either the intermittently scanned CGM device (first-generation Abbott FreeStyle Libre 1 Glucose Monitoring System) or the real-time CGM device (i.e. Dexcom G5 CGM System or Dexcom G6 CGM System or Guardian 4), the CGM data available in the 4 weeks preceding the enrolment visit were also collected. This sampling period of CGM data provides a good estimation of the long-term glycaemic control and glucose variability in children with T1D.[16] According to international recommendations, the following short-term glycaemic control metrics were calculated from CGM data[17]: time in range 70–180 mg/dL (3.9–10.0 mmol/L, TIR); time below range <70 mg/dL (<3.9 mmol/L, TBR); time below range 54–69 mg/dL (3.0–3.9 mmol/L) (low glucose or level 1 hypoglycaemia, TBR1); time below range <54 mg/dL (<3.0 mmol/L) (very low glucose or level 2 hypoglycaemia, TBR2); time above range >180 mg/dL (>10.1 mmol/L, TAR); time above range 181–250 mg/dL (10.1–13.9 mmol/L) (high glucose or level 1 hyperglycaemia, TAR1); time above range >250 mg/dL (>13.9 mmol/L) (very high glucose or level 2 hyperglycaemia, TAR2); mean sensor glucose; coefficient of variation; and standard deviation (SD) of mean glucose. Moreover, the time in tight range 70–140 mg/dL (3.9–7.8 mmol/L) (TITR) and the glycaemia risk index (GRI) and its hypoglycaemic and hyperglycaemic components were calculated as novel CGM metrics.[18–20] To ensure adequate CGM data, participants were included in the analysis if at least 70% of expected CGM readings were available.

## 2.3 | Biochemical parameters

Venous blood and urine samples were collected from all participants during the enrolment visit. HbA1c was measured using an automated cation-exchange high-performance liquid chromatography system (Bio-Rad); the instrument was calibrated against Diabetes Control and Complication Trial–approved standards. All other biochemical parameters (i.e. aspartate aminotransferase, alanine aminotransferase [ALT], glutamyl-transpeptidase, platelet count, TGs, total cholesterol and HDL cholesterol) were analysed in a single reference centralized laboratory according to international standards. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation. Non-HDL cholesterol was calculated as total cholesterol *minus* HDL cholesterol. In addition, HbA1c values were measured quarterly starting from T1D onset and extracted by clinical chart reviews. In addition, visit-to-visit HbA1c variability (HbA1c SD) was calculated as an index of long-term glycaemic variability, and the percentage of time of the disease spent with HbA1c greater than 7.0% (53 mmol/molHb) and 7.5% (58 mmol/molHb) was calculated considering that each HbA1c value was measured in nearly 3-month intervals. These additional long-term glycaemic indices may reflect chronic hyperglycaemic exposure, integrating the degree of glycaemic control and the time spent with suboptimal glycaemic control. Finally, the insulin sensitivity (IS) index was calculated using the SEARCH ISS model: ln IS = 4.64725–0.02032 (waist circumference [cm]) – 0.09779 (HbA1c [%]) – 0.00235 (TGs [mg/dL]).[21] IS was developed using a hyperinsulinaemic-euglycaemic clamp technique, and it has been broadly validated in adolescents with T1D.

## 2.4 | Genetic analysis

Genomic DNA was extracted from peripheral blood leucocytes using salting-out procedures. Genotyping was carried out using predesigned TaqMan probes (Applied Biosystem, USA) according to the manufacturer's protocol. Polymorphism genotyping was performed using a 7900 HT Real-Time PCR system (Applied Biosystem). Three genetic variants robustly associated with MASLD development and progression, namely rs738409 (*PNPLA3*), rs58542926 (*TM6SF2*) and rs1260326 (GCKR), were selected. Only the samples and marker call rates greater than 90% were used for quality control. The allele distribution of these three genotyped polymorphisms was compatible with the Hardy–Weinberg equilibrium.

## 2.5 | Liver ultrasonography and vibration-controlled transient elastography

The diagnosis of MASLD was defined by the presence of hepatic steatosis in combination with at least one of five common cardiometabolic risk factors typically featuring the metabolic syndrome, in the absence of other competing causes of hepatic steatosis.[5] Specifically, the presence of hepatic steatosis was evaluated by a single expert physician using ultrasonography with a convex 3.5-MHz probe. The severity of hepatic steatosis (mild, moderate or severe) was defined based on characteristic imaging features: bright liver pattern, liver–kidney contrast, vascular blurring and deep hepatic attenuation.[22] Vibration-controlled transient elastography (FibroScan) was performed by a single expert physician using the M probe, or XL probe in the case of obesity,[23] and the final value of liver stiffness measurement (LSM) (expressed in kPa) was obtained using standardized procedures.[24]

## 2.6 | Statistical analysis

Data were analysed using the SPSS, version 22.0, software package (SPSS Inc., Chicago, USA). All continuous variables were normally distributed and reported as mean and SD unless otherwise specified.

Categorical variables were expressed as absolute values and relative frequencies. Unpaired Student *t* test or Mann–Whitney test for continuous variables and $\chi^2$ test for categorical variables were used to compare data between subjects with and without MASLD. Logistic regression analysis was used to assess the main independent predictors of MASLD. In particular, we developed three adjusted logistic regression models, where MASLD was the dependent variable. The first regression model was adjusted for age, sex, diabetes duration, BMI, HbA1c and LDL cholesterol. The second regression model was adjusted for age, sex, diabetes duration, BMI, mean HbA1c and LDL cholesterol. The third regression model was adjusted for age, sex, diabetes duration, BMI, TAR2 and LDL cholesterol. Covariates included in these logistic regression models were chosen as potential confounding variables based on their biological plausibility or statistical associations with MASLD in univariable regression analyses. The statistical power analysis of the study showed that our convenience sample of 244 children/adolescents was associated with a 2.8% standard error of the observed prevalence of MASLD (i.e. the primary study outcome) and with an 85% power to detect, with a 5% α-error, an association between MASLD and any variable producing an odds ratio (OR) of 1.6 for each SD variable increase, within any logistic regression model with variable covariates explaining 10% of the risk variance. The significance level for all tests was set at $p < 0.05$. All statistical tests were two tailed.

## 3 | RESULTS

Overall, 244 children and adolescents with established T1D were recruited. MASLD was diagnosed in 67 subjects (27.5% of the total), most of whom ($n = 56$) had mild hepatic steatosis on ultrasonography.

Table 1 presents the main clinical, demographic and biochemical characteristics of the study participants, stratified by MASLD status. All participants were White and of European ancestry. Patients with MASLD had higher values of BP (SBP *z*-score: $p = 0.034$, DBP *z*-score: $p = 0.032$), FibroScan-assessed LSM ($p = 0.029$), total cholesterol ($p = 0.043$), LDL cholesterol ($p = 0.019$) and non-HDL cholesterol ($p = 0.008$) than their counterparts without MASLD. Conversely, no significant differences in age, sex, pubertal status, adiposity measures, TGs, IS, serum liver enzymes and alcohol consumption were observed between patients with and those without MASLD (all $p > 0.05$). Additionally, the distribution of rs738409 (*PNPLA3*), rs58542926 (*TM6SF2*) and rs1260326 (*GCKR*) genetic variants did not significantly differ between the two patient groups.

Table 2 presents the insulin administration modalities, insulin requirements, HbA1c measured during the enrolment visit, long-term glycaemic control metrics and CGM-derived data of short-term glycaemic control in the study participants, stratified by MASLD status. Patients with MASLD had worse glycaemic control indices, as documented by higher levels of HbA1c ($p < 0.001$), mean glucose ($p = 0.003$), TAR (TAR1: $p = 0.042$, TAR2: $p = 0.014$) and GRI ($p = 0.020$). Moreover, patients with MASLD spent less time in TIR ($p = 0.012$) and TITR ($p = 0.011$) compared to their counterparts without MASLD. Insulin administration modalities, type of glucose monitoring system used and daily insulin doses did not significantly differ between the two patient groups.

Table 3 presents the main independent predictors of MASLD assessed using logistic regression analyses. In adjusted model 1, HbA1c level was the only independent predictor of MASLD. In adjusted model 2, mean HbA1c and plasma LDL cholesterol levels were the independent predictors of MASLD. Finally, in adjusted model 3, TAR and plasma LDL cholesterol were the independent predictors of MASLD. The small ORs associated with TAR and plasma LDL cholesterol (OR: 1.028 and 1.045, respectively) are likely due to the fact that these ORs correspond to a unitary increase in each variable, and for both TAR and LDL cholesterol, a unitary increase is a small change. Considering the 5th–95th percentile intervals, TAR ranges from 10% to 55%, and plasma LDL cholesterol level ranges from 47 to 122 mg/dL. Indeed, for both variables, the 75th percentile is associated with a double risk of MASLD compared to the 25th percentile, thus suggesting a possible meaningful effect. Table 4 presents the risk changes across the percentile categories of the variables associated with MASLD.

Table S1 indicates that the significant associations between MASLD and short- and long-term glycaemic control metrics were not affected by adjustment for age, sex, diabetes duration, BMI, plasma LDL cholesterol or non-HDL cholesterol levels.

## 4 | DISCUSSION

The main results of our exploratory cross-sectional study, involving 244 Italian children and adolescents with established T1D, are as follows: (a) the prevalence of MASLD on ultrasonography was 27.5%, and (b) HbA1c, TAR and plasma LDL cholesterol levels were independently associated with MASLD.

Literature data on the prevalence of MASLD in children and adolescents with T1D are highly variable.[10] Although it is difficult to determine the exact causes of this high variability in MASLD prevalence in people with T1D, it is likely that age, ethnicity, diabetes duration, BMI standard deviation score (SDS), glycaemic control and methods used for diagnosing MASLD may contribute to explaining these inter-study differences in MASLD prevalence. For instance, an observational study of 74 Egyptian children and adolescents with T1D reported a prevalence of hepatic steatosis on ultrasonography of 62.2%.[25] In that study, children and adolescents with hepatic steatosis had a non-optimal glycaemic control (mean HbA1c of 11.7%) and a relatively high BMI SDS. Another observational study involving 110 Turkish children with T1D reported a prevalence of MASLD of 15.5% on ultrasonography.[26] In this study, the mean age and diabetes duration were 9.2 years and 3 years, respectively. Again, a study of 50 children and young adults with T1D living in Thailand reported a prevalence of MASLD of 10%.[27] This study diagnosed hepatic steatosis using magnetic resonance imaging (MRI)-proton density fat fraction. A similar prevalence of MRI-diagnosed MASLD of 8.8% was reported by Cusi et al.[28] A small cross-sectional study of 93 German

**TABLE 1** Clinical, demographic and biochemical characteristics in T1D children and adolescents stratified by MASLD status.

| | Subjects without MASLD ($n = 177$) | Subjects with MASLD ($n = 67$) | *p*-Value |
|---|---|---|---|
| Age (years) | 16.2 (3.2) | 16.2 (3.1) | 0.853 |
| Age at onset (years) | 7.6 (3.7) | 6.8 (4.1) | 0.150 |
| Diabetes duration (years) | 8.6 (4.0) | 9.4 (4.0) | 0.122 |
| Sex | | | |
| Male *n* (%) | 97 (54.8) | 32 (47.8) | 0.325 |
| Female *n* (%) | 80 (45.2) | 35 (52.2) | |
| Puberty | | | |
| Prepubertal *n* (%) | 16 (9.1) | 6 (8.9) | 0.903 |
| Pubertal *n* (%) | 25 (14.1) | 8 (11.9) | |
| Post-pubertal *n* (%) | 136 (76.8) | 53 (79.2) | |
| BMI (kg $m^{-2}$) | 21.9 (3.3) | 22.3 (3.9) | 0.499 |
| BMI (kg $m^{-2}$) *z*-score | 0.39 (0.80) | 0.35 (0.88) | 0.777 |
| BMI *z*-score >1 *n* (%) | 39 (22.0) | 14 (20.9) | 0.764 |
| BMI *z*-score >2 *n* (%) | 1 (0.56) | 1 (1.49) | |
| WC (cm) | 74.4 (8.9) | 74.5 (10.8) | 0.959 |
| SBP (mm Hg) | 108.4 (9.9) | 109.5 (8.9) | 0.425 |
| SBP (*z*-score) | **−0.42 (0.84)** | **−0.17 (0.71)** | **0.034** |
| DBP (mm Hg) | 68.6 (7.2) | 70.0 (6.5) | 0.173 |
| DBP (*z*-score) | **0.14 (0.67)** | **0.33 (0.54)** | **0.032** |
| Total cholesterol (mmol $L^{-1}$, mg $dL^{-1}$) | **3.94 (0.76), 152.6 (29.4)** | **4.16 (0.80), 160.9 (31.1)** | **0.043** |
| HDL cholesterol (mmol $L^{-1}$, mg $dL^{-1}$) | 1.54 (0.38), 59.8 (14.9) | 1.50 (0.34), 58.3 (13.3) | 0.444 |
| LDL cholesterol (mmol $L^{-1}$, mg $dL^{-1}$) | **2.06 (0.62), 79.3 (24.1)** | **2.31 (0.62), 89.1 (24.0)** | **0.019**[a] |
| Non-HDL cholesterol (mmol $L^{-1}$, mg $dL^{-1}$) | **2.39 (0.66), 92.7 (25.6)** | **2.65 (0.70), 102.7 (26.7)** | **0.008**[a] |
| TG (mmol $L^{-1}$, mg $dL^{-1}$) | 0.68 (0.53–0.81), 61.0 (47.0–72.0) | 0.70 (0.51–0.86), 62.5 (46.0–76.2) | 0.878 |
| IS | 9.29 (1.90) | 9.03 (2.30) | 0.380 |
| ALT (Units/L)[b] | 19.0 (16.0–22.0) | 19.0 (16.0–23.5) | 0.824 |
| AST (Units/L)[b] | 19.0 (16.0–24.0) | 19.0 (15.0–22.7) | 0.543 |
| GGT (Units/L)[b] | 12.0 (10.0–15.0) | 13.0 (10.0–15.0) | 0.688 |
| FibroScan-assessed LSM (kPa) | 4.4 (1.0) | 4.9 (2.5) | **0.029** |
| FibroScan-assessed LSM (kPa) >7%, *n* (%) | 9 (5.0%) | 2 (3.0%) | 0.49 |
| Alcohol consumption (grams over the 4 weeks preceding the study visit) | 12.0 (0.0–100) | 24.0 (0.0–64.0) | 0.866 |
| *TM6SF2*, rs58542926, $n = 218$ (genotypes:CT/CC) | 20/137 | 7/54 | 0.799 |
| *PNPLA3*, rs738409, $n = 222$ (genotypes:GG/GC/CC) | 10/76/76 | 4/28/28 | 0.763 |
| *GCKR*, rs1260326, $n = 222$ (genotypes:TT/CT/CC) | 38/77/45 | 10/37/15 | 0.270 |

*Notes*: Sample size $n = 244$, except where indicated. Data are presented as mean (SD) or median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AST aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; GCKR, glucokinase regulator; GGT, glutamyl-transpeptidase; HDL, high-density lipoprotein; IS insulin sensitivity; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; PNPLA3, patatin-like phospholipase domain-containing 3; SBP, systolic blood pressure; SD, standard deviation; TG, triglycerides; TM6SF2, transmembrane 6 superfamily member 2; T1D, type 1 diabetes; WC, waist circumference.

[a]Significant after adjustment for age, sex and diabetes duration.

[b]None of the participants had elevated serum liver enzymes.

Significant differences ($p < 0.05$) in bold.

children with T1D reported that 10.8% of these subjects had MASLD.[29] Finally, previous studies on the prevalence of MASLD in adults with T1D similarly reported heterogeneous results. A systematic review, including 20 studies from 2009 to 2019, showed that the pooled prevalence in adults was 22% (95% CI: 13.9%–31.2%).[11] A more recent study involving 530 adults with T1D

**TABLE 2** Insulin treatment and metrics measuring short- and long-term glycaemic control in T1D children and adolescents stratified by MASLD status.

| | Subjects without MASLD ($n = 177$) | Subjects with MASLD ($n = 67$) | *p*-Value |
|---|---|---|---|
| MDI *n* (%)/CSII *n* (%) | 121 (68.4)/56 (31.6) | 46 (68.6)/21 (31.4) | 0.965 |
| SMBG *n* (%)/CGM *n* (%) | 13 (7.4)/164 (92.6) | 7 (10.4)/60 (89.5) | 0.430 |
| Total insulin (kg Body Weight$^{-1}$ day$^{-1}$) | 0.83 (0.24) | 0.87 (0.25) | 0.274 |
| Regular or short-acting insulin (kg Body Weight$^{-1}$ day$^{-1}$) | 0.42 (0.17) | 0.47 (0.17) | 0.147 |
| Long-acting insulin (kg Body Weight$^{-1}$ day$^{-1}$) | 0.41 (0.11) | 0.42 (0.12) | 0.794 |
| HbA1c (%, mmol mol$^{-1}$) | **7.93 (0.81), 63.3 (9.0)** | **8.42 (0.89), 68.0 (10.1)** | **<0.001**[a] |
| Mean HbA1c (%) | **7.94 (0.73)** | **8.17 (0.53)** | **0.007**[a] |
| Visit-to-visit HbA1c variability (%) | 0.63 (0.23) | 0.67 (0.35) | 0.304 |
| TIR 70–180 mg/dL | **49.0 (13.6)** | **42.8 (13.2)** | **0.012**[a] |
| TITR | **30.1 (10.2)** | **25.3 (9.2)** | **0.011**[a] |
| TBR | 5.0 (3.8) | 4.6 (3.7) | 0.501 |
| TBR1 | 3.3 (2.1) | 3.1 (2.3) | 0.538 |
| TBR2 | 1.8 (1.5) | 1.5 (1.3) | 0.500 |
| TAR | **44.9 (14.6)** | **52.4 (15.4)** | **0.005**[a] |
| TAR1 | **24.5 (8.7)** | **27.3 (7.6)** | **0.042**[a] |
| TAR2 | **19.4 (12.7)** | **25.3 (14.3)** | **0.014**[a] |
| Mean glucose (mg/dL, mmol/L) | **180.5 (30.6), 10.0 (1.7)** | **195.5 (33.7), 10.9 (1.9)** | **0.003**[a] |
| GRI | **64.0 (19.6)** | **71.9 (17.8)** | **0.020**[a] |
| GRI hypoglycaemia component | 4.4 (3.4) | 3.9 (3.3) | 0.499 |
| GRI hyperglycaemia component | **31.5 (13.5)** | **37.8 (14.5)** | **0.013** |
| %CV | 41.9 (8.2) | 40.5 (5.5) | 0.310 |
| SD of mean glucose (mg/dL, mmol/L) | 75.2 (16.5), 4.2 (0.9) | 78.9 (15.2), 4.4 (0.8) | 0.196 |

*Notes*: Sample size, $n = 244$. Data are presented as mean (SD) or median (interquartile range).

Abbreviations: CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; CV, coefficient of variation; GRI, glycaemia risk index; MASLD, metabolic dysfunction–associated steatotic liver disease; MDI, multiple daily injection; SD, standard deviation; SMBG, self-monitoring of capillary blood glucose; TAR, time above range >180 mg/dL (>10.1 mmol/L); TAR1, time above range 181–250 mg/dL (10.1–13.9 mmol/L) (high glucose or level 1 hyperglycaemia); TAR2, time above range >250 mg/dL (>13.9 mmol/L) (very high glucose or level 2 hyperglycaemia); TBR, time below range <70 mg/dL (<3.9 mmol/L); TBR1, time below range 54–69 mg/dL (3.0–3.9 mmol/L) (low glucose or level 1 hypoglycaemia); TBR2, time below range <54 mg/dL (<3.0 mmol/L) (very low glucose or level 2 hypoglycaemia); TIR, time in range 70–180 mg/dL (3.9–10.0 mmol/L); TITR, time in tight range 70–140 mg/dL (3.9–7.8 mmol/L); T1D, type 1 diabetes.

[a]Significant after adjustment for age, sex and diabetes duration.

Significant differences ($p < 0.05$) in bold.

reported a prevalence of hepatic steatosis of 16.2% on ultrasonography.[30]

Previous studies conducted in children and adolescents reported that obesity was a strong clinical risk factor for MASLD.[1,31] In our study, the prevalence of obesity was lower than that reported in the SWEET registry[32] and other studies conducted in the Italian population.[33] This might partly explain the non-significant association between BMI SDS and MASLD we observed in the study. It is known that MASLD has a genetic predisposition, and obesity appears to be necessary to trigger the expression of MASLD in the phenotype.[7] Therefore, it is not surprising that the distribution of the most studied genetic variants for MASLD is similar in subjects with and without MASLD. Although the strongest genetic risk alleles for MASLD, such as the I148M allele in *PNPLA3*, the E167K allele in *TM6SF2* and the P446L allele in the *GCKR* gene, have been associated with an increased liver fat content and progression to liver fibrosis, the absence of obesity might partly reduce the overall effect of these three genetic variants by altering their expression. Indeed, the *PNPLA3* and *GCKR* variants are modulated by food intake through glucose and insulin fluctuations, whereas the *TM6SF2* variant induces TG secretion by affecting hepatic fat accumulation. Several studies assessing the effects of gene–environment interactions on the development and progression of MASLD have highlighted that the absence of obesity and a healthy diet can attenuate the individual's genetic predisposition to MASLD.[34,35] Thus, the findings reported here raise the possibility that these risk alleles may have a moderate effect in lean individuals with good glycaemic control. Only a previous study has investigated the genetic associations between MASLD-related risk genes and T1D.[36] Consistent with our results, in a Finnish study of 121 adults with T1D, Parente et al. did not find any significant association between the *PNPLA3* and *TM6SF2* genetic variants and MASLD.[36]

**TABLE 3** Independent predictors of MASLD in T1D children and adolescents.

| Dependent variable | Covariates in logistic regression models | OR (95% CI) | *p*-Value |
|---|---|---|---|
| MASLD<br>Model 1<br>$p = 0.010$<br>$R^2$ Negerkerke = 13.3 | Age (years) | 0.953 (0.817–1.112) | 0.545 |
| | Diabetes duration (years) | 1.085 (0.980–1.200) | 0.116 |
| | Sex (male vs. female) | 0.971 (0.474–1.992) | 0.937 |
| | BMI (kg/m$^2$) | 1.003 (0.895–1.125) | 0.954 |
| | HbA1c (%) | 1.869 (1.222–2.859) | **0.004** |
| | LDL cholesterol (mg/dL)[a] | 1.012 (0.997–1.028) | 0.120 |
| MASLD<br>Model 2<br>$p < 0.001$<br>$R^2$ Negerkerke = 10.1 | Age (years) | 0.995 (0.852–1.160) | 0.944 |
| | Diabetes duration (years) | 1.066 (0.964–1.179) | 0.214 |
| | Sex (male vs. female) | 0.910 (0.540–2.236) | 0.795 |
| | BMI (kg/m$^2$) | 0.986 (0.880–1.104) | 0.804 |
| | Mean HbA1c (%) | 1.703 (1.040–2.787) | **0.034** |
| | LDL cholesterol (mg/dL)[a] | 1.016 (1.001–1.032) | **0.044** |
| MASLD<br>Model 3<br>$p < 0.001$<br>$R^2$ Negerkerke = 18.6 | Age (years) | 1.035 (0.849–1.262) | 0.734 |
| | Diabetes duration (years) | 0.960 (0.835–1.104) | 0.567 |
| | Sex (male vs. female) | 0.930 (0.376–2.298) | 0.875 |
| | BMI (kg/m$^2$) | 0.910 (0.782–1.058) | 0.220 |
| | TAR | 1.028 (1.009–1.047) | **0.006** |
| | LDL cholesterol (mg/dL)[a] | 1.045 (1.013–1.078) | **0.004** |

*Notes*: Sample size, $n = 244$. Data are expressed as OR and 95% CI.
Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASLD, metabolic dysfunction–associated steatotic liver disease; OR, odds ratio; TAR, time above range; T1D, type 1 diabetes.
[a]When we replaced LDL cholesterol with non-HDL cholesterol in the regression model, the association between MASLD and non-HDL cholesterol was not significant, and the overall results of the logistic regression model did not change.
Significant differences ($p < 0.05$) in bold.

**TABLE 4** Risk of MASLD based on percentile categories of HbA1c (model 2), TAR and LDL cholesterol (model 3), with all other predictors included in the regression models kept at their average value.

| Percentile | HbA1c (%) | Risk of MASLD (%) | TAR (%) | Risk of MASLD (%) | LDL cholesterol (mg/dL) | Risk of MASLD (%) |
|---|---|---|---|---|---|---|
| 5th | 6.70 | 15.4 | 19.37 | 10.0 | 47.2 | 12.2 |
| 25th | 7.50 | 21.9 | 30.9 | 15.7 | 64.4 | 18.1 |
| 50th | 8.00 | 27.5 | 45.46 | 27.5 | 81.2 | 27.5 |
| 75th | 8.60 | 33.5 | 57.48 | 37.5 | 94.6 | 33.3 |
| 95th | 9.40 | 43.5 | 72.92 | 54.3 | 122.5 | 51.4 |

Abbreviations: LDL, low-density lipoprotein; MASLD, metabolic dysfunction–associated steatotic liver disease; TAR, time above range; T1D, type 1 diabetes.

When we assessed the main predictors of MASLD, we found that TAR and mean HbA1c were independently associated with the presence of MASLD. This suggests that the exposition to poor glycaemic control, both in the short- and long term, plays a crucial role in MASLD development among children and adolescents with T1D, further supporting previous studies assessing HbA1c as a metric of long-term glycaemic control. Indeed, Della Pepa et al. showed that adults with T1D with HbA1c greater than 7.6% had a higher proportion of MASLD, as identified by the fatty liver index or the hepatic steatosis index, than those with HbA1c less than 7.6%.[37] Therefore, a recent study conducted on a large sample of children and adolescents with T1D, in whom abnormal serum liver enzyme levels diagnosed hepatic steatosis, reported a higher prevalence of MASLD in those with poorly controlled T1D (i.e. HbA1c >11%).[38]

Although the design of our study does not allow us to explore the precise mechanisms underlying the association between unfavourable glycaemic control and the risk of MASLD, it is reasonable to assume that chronic hyperglycaemia may promote an increased influx of glucose into hepatocytes, which is a substrate for increased hepatic TG synthesis. Moreover, insulin administration by subcutaneous insulin injections or infusion for treating T1D does not respect the physiologic method of insulin secretion from pancreatic β cells reaching the liver via the portal vein. Hepatic insulin clearance activity may reduce the amount of insulin available for systemic circulation and

extrahepatic tissues. In people with T1D, lower insulin concentrations reach the liver from the subcutaneous injection site, reducing hepatic gluconeogenesis and hepatic glucose output less efficiently, thus further contributing to increased hepatic free fatty acid (FFA) synthesis.[39,40] That said, it is also possible to hypothesize that peripheral hyperinsulinaemia described in subjects with T1D may impact the dynamic interplay between adipose tissue and liver, thus promoting hepatic de novo lipogenesis (DNL). Hepatic DNL is increased in people with MASLD[41] and those with peripheral insulin resistance.[42] Hepatic DNL has also been demonstrated to be directly related to 24-h plasma glucose and insulin concentrations, suggesting that, in the context of insulin resistance, increased glucose and/or insulin concentrations may stimulate hepatic DNL in people with MAFLD.[43] Using a hyperinsulinaemic-euglycaemic clamp with insulin dosages specifically targeting adipose, liver and peripheral/muscle tissues, in combination with glucose and glycerol isotope tracers, Cree-Green et al. showed that adolescents with T1D had lower peripheral, hepatic and adipose IS than their counterparts without diabetes, despite a lack of traditional markers of metabolic syndrome and insulin resistance, such as low HDL cholesterol, low adiponectin, high TGs, high ALT or increased hepatic or visceral fat accumulation.[44] Therefore, it is likely that in children and adolescents with T1D, insulin resistance may lead to decreased glucose disposal into muscle and adipose tissues, promoting a diversion of circulating glucose to and cleared by the liver, as well as increased non esterified fatty acid flux from adipose tissue lipolysis. Consequently, increased lipogenic substrate availability may promote lipogenesis in children and adolescents with T1D and MASLD, as demonstrated in insulin-resistant obese adults.[45]

In our study, higher plasma LDL cholesterol levels were found to be independently associated with MASLD. Increased fatty acid accumulation in the liver per se is associated with a higher plasma atherogenic risk profile. This is relevant to the long-term health of children and adolescents with T1D. Notably, the SWEET registry recently reported that one out of three children and adolescents had a higher plasma LDL cholesterol concentration than desirable, as suggested by the International Society for Pediatric and Adolescent Diabetes guidelines (LDL cholesterol >100 mg/dL).[46]

The association between MASLD, poor glycaemic control and LDL cholesterol, two major risk factors of morbidity, found in this study, and the association between MASLD and the long-term diabetes complications already demonstrated in adults suggest that early diagnosis of MASLD could be useful for children and adolescents with T1D. Although longitudinal studies are necessary to confirm the role of MASLD in accelerating the development of diabetes comorbidities in children and adolescents with T1D, the introduction of a screening test for MASLD could be considered in people with T1D.

Our study has important limitations that should be mentioned. First, the exploratory cross-sectional design of our study does not allow us to establish any causal and temporal relationship for the observed associations. Second, hepatic steatosis was evaluated using ultrasonography, which is the first-line imaging technique for non-invasively identifying hepatic steatosis and has a good sensitivity and specificity for detecting moderate and severe hepatic steatosis. However, it is important to underline that the sensitivity of ultrasonography is reduced when hepatic fat infiltration is below 25%–30%.[47] Moreover, ultrasonography cannot precisely measure the hepatic fat content or specifically distinguish between isolated steatosis and metabolic dysfunction-associated steatohepatitis with varying levels of liver fibrosis. That said, although liver biopsy remains the 'gold standard' method for diagnosing and staging MASLD, none of our paediatric patients were candidates for liver biopsy as they had normal serum liver enzyme levels and did not satisfy the criteria established by current guidelines.[48] Third, although we used vibration-controlled transient elastography (FibroScan) for the non-invasive assessment of liver fibrosis, our FibroScan machine was not equipped with a controlled attenuation parameter for non-invasively quantifying liver fat content.[48] Fourth, the study was conducted on children with T1D of European ancestry, so our results cannot be extended to youths of other ethnic backgrounds. Finally, we cannot exclude that other unmeasured factors might partly explain the observed associations.

The main strength of our study is the simultaneous measurement of both hepatic steatosis and fibrosis combined with a complete data set of clinical and biochemical parameters, as well as metrics of short-term and long-term glycaemic control and variability.

In conclusion, the results of this cross-sectional study showed that ultrasound-detected MASLD is a common condition in children and adolescents with T1D, and short- and long-term glycaemic control metrics (i.e. mean HbA1c and TAR) were independently associated with MASLD. These findings further underline the clinical importance of achieving and maintaining good long-term glycaemic control since childhood, as well as the need to prevent MASLD development from childhood. Future prospective and mechanistic studies are required to corroborate these findings and better decipher the pathological mechanisms underlying our observed associations.

## AUTHOR CONTRIBUTIONS

Claudia Piona, Chiara Zusi and Antonio Colecchia researched and collected the data. Claudia Piona, Chiara Zusi and Claudio Maffeis analysed the data. Anita Morandi, Marco Marigliano, Elisa Morotti, Valentina Mancioppi, Erika Caizza, Chiara Zusi and Federica Emiliani researched the data. Claudio Maffeis, Giovanni Targher, A.M. and Antonio Colecchia designed the study. Claudio Maffeis, Claudia Piona and Chiara Zusi co-wrote and edited the manuscript. All the authors discussed and edited the manuscript. Claudio Maffeis is the guarantor of this work and therefore has full access to the data in the study and takes responsibility for the integrity and accuracy of the data analysis.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

*Claudia Piona* https://orcid.org/0000-0001-5168-8317
*Anita Morandi* https://orcid.org/0000-0002-2631-9330
*Marco Marigliano* https://orcid.org/0000-0002-3232-8807
*Giovanni Targher* https://orcid.org/0000-0002-4325-3900

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## SUPPORTING INFORMATION

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