RESEARCH LETTER

Impact of metabolic dysfunction–associated steatotic liver disease on markers of left ventricular function and mitral annular velocities in patients with type 1 diabetes: an exploratory study

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Introduction Patients with type 1 diabetes (T1D) develop hyperglycemia due to insulin deficiency resulting from immune-mediated pancreatic β-cell destruction.[1] Similarly to the general population, cardiovascular diseases are the leading cause of mortality and morbidity in this group of patients.[2] Thought-provokingly, major adverse cardiovascular events (MACEs) are reported to occur in patients with T1D roughly 10 to 15 years earlier than in the general population.[3]

Insulin deficiency and hyperglycemia facilitate disruption in autonomic signaling due to neuropathy, impairment of energy metabolism in myocardial cells, increase in oxidative stress and low-grade inflammation, and acceleration of atherosclerosis, which results in coronary microvascular dysfunction and occurrence of ischemic events, regardless of the presence of traditionally recognized risk factors, such as hyperlipidemia or hypertension.[2,4] Patients with T1D tend to exhibit altered heart function parameters, such as early and late diastolic mitral inflow velocities (mitral E and mitral A, respectively) as well as early diastolic mitral annular velocity (e'), many years before they experience heart failure (HF) symptoms.[4]

Metabolic dysfunction–associated steatotic liver disease (MASLD), a condition immanently linked with insulin resistance and accelerated atherosclerosis, has been widely demonstrated to correlate with cardiovascular risk in multiple populations.[5]

Given that MASLD is reportedly associated with insulin resistance and atherosclerosis and may interact with complex effects of insulin deficiency and subsequent hyperglycemia, in this study, we aimed to explore and evaluate the impact of MASLD on the heart function in T1D patients without symptoms of HF.[2]

Patients and methods The participants were consecutively recruited at the Diabetology Clinic of the Central Teaching Hospital in Lodz, Poland, from October 1, 2021 through September 1, 2022. The only inclusion criterion was a diagnosis of T1D. Individuals diagnosed with other types of diabetes, those treated with metformin, pregnant, presenting symptoms of or treated for HF, as well as patients with active hepatitis, alcohol addiction, and either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding the upper reference limit more than 2 times were excluded from the study.

We reviewed each patient's medical history and performed a medical interview along with a physical examination and anthropometric measurements, including body weight, height, and waist circumference. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared.

The study was approved by the Bioethics Committee of the Medical University of Lodz (RNN/205/21/KE). All study participants received an information brochure and signed a written informed consent on enrolment.

Biochemistry Each patient underwent a set of laboratory tests. All blood and urine samples

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Received: December 15, 2023.
Revision accepted: March 18, 2024.
Published online: March 20, 2024.
Pol Arch Intern Med. 2024; 134 (3): 16709
doi:10.20452/pamw.16709

were collected in the morning after a minimum 8-hour fast. Glycated hemoglobin (HbA_{1c}) and C-reactive protein (CRP) concentrations were measured using the immunoturbidimetric assay (DxC, Beckman Coulter, Brea, California, United States). The spectrophotometric method was used to determine AST, ALT, γ-glutamyl transferase (GGT), creatinine, uric acid, and lipid levels (DxC AU, Beckman Coulter). Thyroid-stimulating hormone level was quantified using the chemiluminescent immunoassay (Alinity, Abbott, Green Oaks, Illinois, United States). The same method was used to determine the N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations (Cobas, Roche, Basel, Switzerland). The albumin-to-creatinine ratio (ACR) was calculated based on immunoturbidimetric and isotope dilution mass spectrometry (AU, Beckman Coulter). Additionally, we used the Human Apolipoprotein C3 (APOC3) enzyme-linked immunosorbent assay (ELISA) kit and the Human Adiponectin ELISA kit (Biorbyt Ltd., Cambridge, United Kingdom) to measure the APOC3 and adiponectin concentrations, respectively.

Echocardiography The same experienced physician (ZS) performed all echocardiographic examinations using a commercially available ultrasound device (GE Vivid Q, General Electric, Boston, Massachusetts, United States). All measurements were carried out according to the recommendations of the European Association of Cardiovascular Imaging,[6] and all recorded images were digitally stored afterward.

Heart chambers were measured linearly in the long-axis view using M-mode tracing. Chamber diameters and volumes were calculated using a 2-dimensional imaging technique in a 4-chamber view. The ejection fraction was determined using the biplane method of disk summation. Left ventricular (LV) mass was approximated from M-mode linear measurements using the cube formula. Mitral E and A were measured using pulsed-wave Doppler in an apical 4-chamber view. Tissue Doppler imaging (TDI) velocities, including lateral (lat) and septal (sept) e', peak systolic velocity (s'), and peak late diastolic velocity (a'), were obtained in an apical 4-chamber view. Based on this, mitral E/A and mitral E/e' ratios were calculated. The tricuspid annular plane systolic excursion was determined in an apical view using M-mode tracing. Isovolumic relaxation time and deceleration time of mitral E velocity were recorded in an apical 4-chamber view with pulsed-wave Doppler.

Risk of metabolic dysfunction–associated steatotic liver disease Liver biopsy remains a gold standard of MASLD diagnosis. Nevertheless, the fatty liver index (FLI) is a recognized surrogate marker of hepatic steatosis correlating with intrahepatic fat content.[7] The formula for FLI calculation is as follows:

$$FLI = (e^{0.953 \times \ln(\text{TG concentration in mmol/l}) + 0.139 \times \text{BMI} + 0.718 + \ln(\text{GGT concentration in U/l}) + 0.053 \times \text{waist circumference in cm} - 15.745}) / (1 + e^{0.953 \times \ln(\text{TG concentration in mmol/l}) + 0.139 \times \text{BMI} + 0.718 + \ln(\text{GGT concentration in U/l}) + 0.053 \times \text{waist circumference in cm} - 15.745}) \times 100,$$ [8]

where TG stands for triglycerides. Using the FLI score, we stratified the study participants into groups with a high (FLI ≥60) and low or intermediate MASLD risk (FLI <60).[9]

Statistical analysis To perform statistical analyses, we used Statistica 13.1 software (StatSoft Inc., Tulsa, Oklahoma, United States). Normality of the data distribution was determined using the Shapiro–Wilk test. Continuous variables were presented as mean and SD or median and interquartile range (IQR), according to their distribution. To compare the normally and non-normally distributed variables between the groups, the *t* test and Mann–Whitney test were used, respectively. Statistical significance was set at the level of *P* below 0.05. Spearman correlation was used to select potential continuous predictors of the E/e' ratio. All predictors correlated with the E/e' ratio with a *P* value lower than 0.05, together with FLI, were then analyzed using univariable and multivariable regression models. The first model comprised all predictors, and the second model was built using the parameters selected by applying a backward stepwise approach, with a *P* value below 0.05 to enter and remove.

Results A total of 65 patients participated in the study. Of them, 10 were excluded from further analysis due to missing data. Clinical characteristics of the study participants are summarized in Supplementary material, *Table S1*. The mean (SD) age of the patients was 38 (9.6) years, and the mean (SD) diabetes duration was 21.8 (11.3) years. The median BMI in the study population was 23.39 kg/m^2 (IQR, 21.61–27.25), and the median HbA_{1c} level was 8.05% (IQR, 7.15%–9.9%).

Metabolic dysfunction–associated steatotic liver disease The patients with a high risk of MASLD (FLI ≥60) accounted for 20% of the study group, and did not differ from the individuals with a low or intermediate MASLD risk (FLI <60) in terms of age, diabetes duration, HbA_{1c} and NT-proBNP levels, or hepatic or renal performance (**TABLE 1**). The patients with a high risk of MASLD had higher body weight (94 vs 65 kg; P <0.001), waist circumference (110 vs 78.5 cm; P <0.001), and BMI (30.5 vs 22.8 kg/m^2; P <0.001), as compared with the group with a low or intermediate MASLD risk. Notably, the participants with a high risk of MASLD presented with worse lipid profiles, as they had higher concentrations of low-density lipoprotein cholesterol (LDL-C; 3.31 vs 2.8 mmol/l, P = 0.04), non–high-density lipoprotein cholesterol (non–HDL-C; 3.87 vs 3.21 mmol/l; P = 0.03), and TGs (148.8 vs 80.6 mg/dl; P <0.001). The patients with a low or intermediate MASLD risk had significantly lower CRP levels than the high-risk group (1.4 vs 4.3; P = 0.03).

Echocardiography The patients with a high risk of MASLD presented with larger LV diameters and greater LV mass (165.7 vs 121.5 g; P <0.001) but not an increased LV mass index (74.8 vs 69.7 g/m^2; P = 0.31), as compared with the low- or intermediate-risk individuals. Similarly, their left atrial diameters and volumes were significantly greater than those observed in the low- or intermediate-risk group, whereas the left atrial volume index did not differ between the groups. The study participants did not vary in EF, mitral A, TDI-based sept s' and a', or TDI-based lat e' and a'. However, the patients with a high risk of MASLD presented with a lower mitral E/A ratio (1.03 vs 1.43; P = 0.01), which may indicate worse diastolic heart function in this group. The participants with a low or intermediate MASLD risk exhibited a lower TDI-based lat s' (10 vs 11.3; P = 0.02) and lower TDI-based sept e' (9 vs 12; P = 0.03), as compared with the high-risk group. They also had a greater mean e' on echocardiography (10.6 vs 12.9 cm/s; P = 0.047).

Impact of anthropometric and laboratory parameters on increased left ventricular filling pressure All parameters significantly correlated with the E/e' ratio (Supplementary material, *Table S2)* were subsequently analyzed using univariable and multivariable regression models. In univariable models, age, along with APOC3 and NT-proBNP levels independently correlated with the E/e' ratio increase. The model utilizing these 3 parameters together with the FLI had a coefficient of determination (R^2) of 0.4614, with age and NT-proBNP identified as the only significant predictors. The second model, with an R^2 of 0.4649 and P <0.001, was constructed using stepwise backward elimination, and comprised age, APOC3 and NT-proBNP levels, and BMI, of which all were identified as significant. Univariable and multivariable regression models for the mitral E/e' ratio are presented in Supplementary material, *Table S3*.

Discussion Our study provides data on a correlation between the risk of MASLD and an increased body weight, waist circumference, BMI, and worse lipid profile in patients with T1D. Moreover, our results support hypotheses on the links between MASLD, T1D, accelerated worsening of the mitral E/A ratio, and indicators of myocardial stiffening, namely, decreased e' and s'.

MASLD has recently replaced the diagnosis of nonalcoholic fatty liver disease (NAFLD), and describes a continuum of hepatic pathologies and complications in patients with signs of steatotic liver disease on imaging studies or biopsy, who meet at least 1 cardiometabolic criterion (the cardiometabolic criteria are listed in Supplementary material, *Table S4*).[10,11]

Approximately 99% of patients with NAFLD fulfill the MASLD criteria.[12] MASLD, similarly to NAFLD, may be considered the hepatic expression of complex systemic disturbances and disorders, such as decreased insulin sensitivity and altered lipid metabolism, that build up and subsequently affect multiple organs.[9,13]

T1D seems to facilitate the process of intrahepatic fat deposition, as the approximated NAFLD prevalence among patients with T1D is up to 40%.[14] Furthermore, an increase in NAFLD prevalence was observed even in the pediatric population. In children with T1D, NAFLD prevalence was reported to exceed 11%, whereas this rate in nondiabetic children is below 2.6%.[156] In our study group, 20% of patients with T1D presented with a high risk of MASLD.

The high risk of MASLD in our study cohort corresponded with significantly increased body weight, BMI, and waist circumference, along with significantly higher LDL-C, non–HDL-C, and TG concentrations, as compared with the low or intermediate MASLD risk group.

Dyslipidemia is a confirmed risk factor for MACEs. Nevertheless, concomitant hyperglycemia and pathologic consequences of insulin deficiency seem to accelerate processes that may result in these events.[2] This finding further strengthens the universal recommendations to actively screen patients for lipid metabolism disorders, implement counteractive measures as soon as possible, and consistently monitor patient BMI and intervene if it reaches the overweight or obese category.

As previously demonstrated, NAFLD may affect the cardiac structure and promote diastolic heart dysfunction development.[16] In our study cohort, the patients with a high risk of MASLD presented with a lower mitral E/A ratio, and slower e' and s', which suggests myocardial stiffening. Our findings comply with those from a recent Chinese study,[16] in which nonobese patients with MASLD had a significantly decreased mitral E/A ratio. In another large, multicenter study involving a cohort of 1800 patients at a median age of 50 years, representing the general population, patients with NAFLD presented with markers of subclinical diastolic heart dysfunction, such as reduced E/A ratio, increased E/e' ratio, and slower e'.[17]

Multivariable regression models in our study revealed a significant correlation between age, BMI, and NT-proBNP and APOC3 levels with an increased E/e' ratio. APOC3 is a protein synthesized predominantly in the liver and intestines. It inhibits the liver uptake of TG-rich lipoproteins and slows their catabolism and clearance.[18] It may suppress lipoprotein lipase activity, interfere with lipolysis, and positively correlate with plasma TG levels.[18] Decreased levels of APOC3 may have a cardioprotective effect.[19] Patients with T1D exhibit an elevated APOC3 level, independently of diabetes metabolic control, possibly due to the gene suppression loss resulting from hypoinsulinemia.[20] Recently published data suggest that concentrations of circulating APOC3 predict the occurrence of cardiovascular events in patients with T1D, regardless of their lipid profile, diabetes duration, and HbA_{1c} levels.[20] In our study cohort, circulating levels of APOC3

TABLE 1 Comparison of groups with a high and low/intermediate risk of metabolic dysfunction–associated steatotic liver disease (continued on the next page)

Parameter	High risk: FLI ≥60 (n = 11)	Low/intermediate risk: FLI <60 (n = 44)	*P* value
General characteristics			
Age, y	41.7 (9.4)	37.0 (9.5)	0.16
BMI, kg/m^2	30.5 (28.5–34.7)	22.8 (21.3–24.7)	<0.001
Body weight, kg	94 (82.5–105)	64.5 (58–70.5)	<0.001
DDI per body weight kg, U/kg	0.62 (0.48–0.67)	0.59 (0.46–0.79)	0.84
DDI, U	50 (48–60)	36 (31–49)	0.01
Diabetes duration, y	23 (8)	21.5 (12.1)	0.69
Height, cm	173.4 (14)	167.8 (8.4)	0.1
Waist circumference, cm	110 (98–118)	78.5 (73.5–85)	<0.001
Biochemistry			
ACR, mg/g	4.6 (2.6–34.7)	4.6 (2.6–11.8)	0.67
ALT, U/l	25.4 (18–35)	16.75 (12.75–25.1)	0.07
AST, U/l	21.8 (17.1–39.1)	19.75 (16.45–25.7)	0.21
CRP, mg/l	4.3 (1.5–7.9)	1.4 (0.75–3.45)	0.03
eGFR, ml/min/1.73 m^2	105.2 (17.2)	104.8 (20.8)	0.96
GGT, U/l	39.7 (14.5–46.6)	18.75 (11.4–30.45)	0.06
HbA_{1c}, %	7.6 (6.4–8.8)	8.15 (7.2–10.15)	0.33
HDL-C, mmol/l	1.46 (0.25)	1.55 (0.36)	0.44
LDL-C, mmol/l	3.31 (0.9)	2.8 (0.66)	0.04
Non–HDL-C, mmol/l	3.87 (1.08)	3.21 (0.85)	0.03
NT-proBNP, pg/ml	46.7 (28.5–55.8)	44.9 (23.2–105.3)	0.94
TG, mg/dl	148.8 (89.5–158.5)	80.6 (59.3–113.4)	<0.001
Total cholesterol, mmol/l	5.32 (1.1)	4.76 (0.93)	0.09
TSH, µIU/ml	1.58 (0.78–2.92)	1.59 (0.88–2.31)	0.99
Uric acid, µmol/l	304.4 (246.3–333.9)	244.95 (200–311.9)	0.23
Experimental biomarkers			
APOC3, ng/ml	25.47 (15.39–32.8)	22.19 (15.18–33.43)	0.7
LN APOC3	3.19 (0.52)	3.09 (0.66)	0.63
Echocardiography			
E/e'	7 (6.2–8)	6.8 (5–8)	0.25
EF, %	64 (4)	65 (4)	0.59
IVSD, mm	15 (1)	13 (2)	0.01
LA volume index, ml/m^2	24 (5)	24 (4)	0.75
LA volume, ml	54 (11)	42 (10)	0.01
LV EDV, ml	85.2 (12.3)	76.1 (15.6)	0.12
LV ESV, ml	31.0 (6.6)	27.0 (6.2)	0.1
LV mass index, g/m^2	74.8 (12.)	69.7 (13.3)	0.31
LV mass, g	165.7 (35.)	121.5 (29.8)	<0.001
LVDD, mm	50 (5)	45 (4)	<0.001
LVSD, mm	32 (4)	29 (3)	0.02
Mean e', cm/s	10.6 (3)	12.9 (2.9)	0.047
Mitral A, cm/s	75 (18)	61 (115)	0.03
Mitral DT, ms	237 (52)	233 (42)	0.96
Mitral E, cm/s	76 (21)	83 (20)	0.38
Mitral E/A	1.03 (0.28)	1.43 (0.43)	0.01
RV TAM, mm	27 (3)	26 (3)	0.63
RVDD, mm	27 (2)	25 (3)	0.12
TDI-based lat a', cm/s	10 (3)	8 (2)	0.11
TDI-based lat e', cm/s	11.7 (3.8)	8 (3.4)	0.08

TABLE 1 Comparison of groups with a high and low/intermediate risk of metabolic dysfunction–associated steatotic liver disease (continued from the previous page)

Parameter	High risk: FLI ≥60 (n = 11)	Low/intermediate risk: FLI <60 (n = 44)	*P* value
TDI-based lat s', cm/s	10 (9–13)	8 (7–12)	0.02
TDI-based sept a', cm/s	9 (2.5)	8.1 (1.7)	0.22
TDI-based sept e', cm/s	9 (3)	12 (2)	0.03
TDI-based sept s', cm/s	8 (1.2)	8.7 (1.6)	0.85
Vp, cm/s	13 (13–15)	13 (13–14)	0.78

Data are shown as mean (SD) or median and interquartile range, depending on the distribution. *P* values <0.05 were considered significant.

SI conversion factors: to convert ALT, AST, and GGT to µkat/l, multiply by 0.0167; CRP to nmol/l, by 9.524; NT-proBNP to ng/l, by 1; TG to mmol/l, by 0.0113.

Abbreviations: ACR, albumin/creatinine ratio; ALT, alanine aminotransferase; APOC3, apolipoprotein C3; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DDI, daily dose of insulin; EF, ejection fraction; eGFR, estimated glomerular filtration rate; FLI, fatty liver index; GGT, γ-glutamyl transferase; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IVSD, intraventricular septum thickness at end--diastole; LA, left atrial; LDL-C, low-density lipoprotein cholesterol; LN APOC3, natural logarithm of apolipoprotein C3 level; LV, left ventricular; LV EDV, left ventricular end-diastolic volume; LV ESV left ventricular end-systolic volume; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; mitral A, late diastolic mitral inflow velocity; mitral DT, deceleration time of mitral E velocity; mitral E, early diastolic mitral inflow velocity, non–HDL-C, non–high-density lipoprotein cholesterol, NT-proBNP, N-terminal pro–B-type natriuretic peptide; RV TAM, tricuspid annular motion; RVDD, right ventricular diastolic diameter; TDI, tissue Doppler imaging; TDI-based lat a', lateral mitral annular peak late diastolic velocity; TDI-based lat e', lateral mitral annular early diastolic velocity; TDI-based sept a', septal mitral annular peak late diastolic velocity; TDI-based sept e', septal mitral annular early diastolic velocity; TDI-based sept s', septal mitral annular peak systolic velocity; TDI-based lat sept s', lateral mitral annular peak systolic velocity; TG, triglycerides; TSH, thyroid-stimulating hormone; Vp, flow velocity propagation at the mitral annulus

were positively associated with the E/e' ratio and globally declined diastolic heart function. These findings offer an intriguing aspect of APOC3 worthy of further exploration.

Certain limitations to this study need to be acknowledged. First, it was a relatively small, single--center study, and further research in larger cohorts is needed to gather more comprehensive data. Moreover, patients using any medication apart from insulin constituted less than 25% of our study group. Therefore, we could not sufficiently incorporate these data in statistical analyses and decided not to include them. Additionally, due to organizational challenges, we decided to use FLI, a surrogate index of MASLD, instead of a gold-standard liver biopsy. FLI has been previously validated against the mentioned gold standard and offers satisfactory sensitivity and specificity. Nevertheless, further observational and longitudinal research is warranted to explore the mentioned predictors, depict the magnitude of their impact, and confirm their significance in real-life practice.

Conclusions MASLD may be associated with an impaired diastolic heart function in patients with T1D. In comparison with the individuals with low or intermediate risk of MASLD, the patients with a high risk of MASLD presented with significantly greater BMI, body weight, and waist circumference, worsened mitral E/A ratio, and markedly altered mitral annular velocities. However, further longitudinal studies are needed to comprehensively depict the extent of MASLD's effect on the rate of diabetic cardiomyopathy progression. Nonetheless, we hypothesize that it would be appropriate to incorporate screening for MASLD into routine care for patients with T1D to identify individuals at a risk of cardiovascular complications. Additionally, our data seem to support a universal recommendation; namely, to mitigate cardiovascular risk, patients with T1D, similarly to the general population, should aim to maintain a normal BMI.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING The study was supported by funds from the Medical University of Lodz.

CONFLICT OF INTEREST None declared.

HOW TO CITE Czarnik K, Sablik Z, Borkowska A, et al. Impact of metabolic dysfunction–associated steatotic liver disease on markers of left ventricular function and mitral annular velocities in patients with type 1 diabetes: an exploratory study. Pol Arch Intern Med. 2024; 134: 16709. doi:10.20452/pamw.16709

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