Predictors of early cardiac changes in patients with type 1 diabetes mellitus: An echocardiography-based study

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ABSTRACT

In patients with type 1 diabetes mellitus (T1DM) imaging studies have demonstrated an increased prevalence of left ventricular diastolic dysfunction and increased left ventricular mass (LVM) unrelated to arterial hypertension and ischemic heart disease. The aim of our study was to identify potential predictors of early subclinical changes in cardiac chamber size and function in such patients. Sixty-one middle-aged asymptomatic normotensive patients with T1DM were included in the study. Conventional and tissue Doppler echocardiography was performed and fasting serum levels of glucose, glycated hemoglobin (HbA1c), lipids, and creatinine were measured. We found moderate bivariate correlations of body mass index (BMI) with left atrial volume ($r = 0.47$, $p < 0.01$), LVM ($r = 0.42$, $p < 0.01$), left ventricular relative wall thickness ($r = 0.32$, $p = 0.01$), and all observed parameters of diastolic function of both ventricles. The five-year average value of HbA1c weakly correlated with the Doppler index of left ventricular filling pressure E/e´sept ($r = 0.27$, $p = 0.04$). We found no significant association of diabetes duration, five-year trend of HbA1c, serum lipids, and glomerular filtration rate with cardiac structure and function. After adjusting for other parameters, BMI remained significantly associated with left atrial volume, LVM as well as with the transmitral Doppler ratio E/A. In our study, BMI was the only observed parameter significantly associated with subclinical structural and functional cardiac changes in the asymptomatic middle-aged patients with T1DM.

KEYWORDS: Type 1 diabetes mellitus; T1DM; body mass index; BMI; left ventricular mass; left atrial volume; diastolic dysfunction; tissue Doppler imaging

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INTRODUCTION

Diabetes mellitus has been increasingly recognized as an important risk factor for heart failure unrelated to arterial hypertension, ischemic, and valvular heart disease [1,2]. The entity was first described in 1972 as diabetic cardiomyopathy [3]. Many different mechanisms have been proposed and the etiology appears to be multifactorial [4,5]. Most studies have included patients with type 2 diabetes mellitus (T2DM), but the link between type 1 diabetes mellitus (T1DM) and heart failure has also been documented [6-9]. In our previous work, we showed that even asymptomatic middle-aged adults with T1DM have some structural and functional changes in both ventricles compared to the age- and gender-matched healthy controls [10]. However, only limited data exist on the contribution of diabetes duration, long-term glycemic control, body mass index (BMI) as well as the frequently coexisting dyslipidemia and renal dysfunction to early adverse changes in the heart of patients with T1DM [11,12]. The aim of our study was to find potential predictors of early structural and functional changes in asymptomatic middle-aged T1DM patients without ischemic, hypertensive, and valvular heart disease.

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MATERIALS AND METHODS

Study design and participants

The study was conducted at the Department of Cardiology and Angiology, University Medical Centre Maribor, Slovenia. It was approved by the National Medical Ethics Committee of the Republic of Slovenia (Medical Ethics Committee approval number 130/10/13). All participants signed informed consent to participate in the study.

We prospectively enrolled 61 asymptomatic patients with T1DM who attended diabetic outpatient clinic of the

University Medical Centre Maribor, Slovenia for more than 5 years and met the inclusion/exclusion criteria. The inclusion criteria were age between 30 and 55 years and the duration of T1DM of more than 5 years. The exclusion criteria were: arterial hypertension; ischemic heart disease; clinical signs of heart failure at enrolment and in the past; bundle branch block or non-sinus rhythm in the electrocardiogram (ECG) and advanced nephropathy (glomerular filtration rate [GFR] below 60 mL/min). Based on the echocardiographic results, we further excluded patients with left ventricular ejection fraction below 50%, left ventricular wall motion abnormalities, valvular stenoses of any degree, more than mild valvular regurgitations, and low-quality echocardiographic image.

Before enrolment, all medical records of the included patients were verified and medical history obtained. Anthropometric measurements (weight and height) were taken during the physical examination in the morning after overnight fasting. Rigid stadiometer and digital scales were used to measure height and weight, respectively. BMI was calculated as weight in kilograms divided by the square of height in meters. Patients with BMI ≥ 25 were classified as overweight and BMI ≥ 30 was defined as obesity. Patients were asked to bring home blood pressure measurements to the enrolment visit. Home blood pressure measurements were obtained by patients using an automated blood pressure monitor twice daily 7 consecutive days prior to the enrolment. Ambulatory blood pressure was obtained in the presence of the investigator at enrolment using an automated blood pressure monitor. The average value of the two consecutive ambulatory measurements was saved for statistical analysis. All blood pressure measurements were obtained after 5 minutes of rest in the seated position. The presence of arterial hypertension was defined as the average home blood pressure ≥135/85 mmHg and the office blood pressure ≥140/90 mmHg. All patients with arterial hypertension including those receiving antihypertensive medications were excluded from the study.

The standard 12-lead ECG was recorded in the supine position under resting conditions. Patients with ischemic heart disease were excluded based on medical history, resting ECG changes, and the presence of left ventricular regional wall motion abnormalities.

Echocardiography

Two-dimensional echocardiography was performed in all patients by a single experienced echocardiographer on the same ultrasound machine (iE33, Philips Medical Systems, WA, USA) and included detailed two-dimensional, pulsed wave Doppler and tissue Doppler imaging (TDI) evaluation. All measurements were based on the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [13-15].

Biplane area-length formula was used to calculate the maximal end-systolic volume of the left atrium. Linear method (Cube formula) based on left ventricular measurements in the parasternal long axis view was used to calculate left ventricular mass (LVM). Relative wall thickness was calculated as 2 times the posterior wall thickness divided by the left ventricular end-diastolic diameter. Left ventricular ejection fraction was calculated by the biplane modified Simpson's method [13,14]. Two-dimensional measurements were indexed to the body surface area (BSA).

Peak mitral and tricuspid inflow velocities were measured by pulsed wave Doppler [15]. All Doppler measurements of the right ventricle were added the suffix - t.

Peak myocardial systolic and diastolic velocities were measured by TDI at the septal part of the mitral annulus (s´sept, e´sept, a´sept) and at the lateral part of the tricuspid annulus (s´t, e´t, a´t). Myocardial acceleration during isovolumetric contraction (IVA) was calculated for both ventricles using TDI as the ratio between the peak isovolumetric velocity and the acceleration time. Acceleration time was defined as the time interval from baseline to the peak isovolumetric velocity [15]. Three consecutive Doppler measurements were averaged for statistical analysis. All Doppler measurements were performed at the frame rate ≥150 Hz.

Laboratory measurements

Blood samples were obtained in the fasting state from all patients. Serum levels of glycated hemoglobin (HbA1c), glucose, creatinine, triglycerides, and total cholesterol were measured. The results of HbA1c obtained at 6-month follow-up visits in the preceding 5 years were averaged to assess the long-term glycemic control.

HbA1c was measured by the ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, PA, USA) [16]. The isotope dilution mass spectrometry traceable enzymatic assay (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA) was performed to measure serum creatinine. GFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation and indexed to the normalized BSA of 1.73 m^2 [16]. Triglycerides were measured by the enzymatic method (Siemens HealthCare Diagnostics Inc., Newark, NJ, USA) and total serum cholesterol by the cholesterol esterase enzymatic assay (Siemens HealthCare Diagnostics Inc., Newark, NJ, USA) [16].

Statistical analysis

IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, New York, USA) was used for

statistical analysis. Continuous variables were shown as means ± standard deviations. Shapiro–Wilk test confirmed the normal distribution of continuous variables. Categorical variables were presented as percentages. The degree of association between clinical/laboratory data and echocardiography measurements was demonstrated using the Pearson's correlation coefficient (r). Kendall's tau was used to evaluate the trend of HbA1c during the 5-year period. Multiple linear regression analysis was performed to assess whether statistically significant bivariate correlations of BMI with cardiac chamber size and function continues after adjustment for other observed confounders. The value of $p < 0.05$ was considered statistically significant for all calculations.

RESULTS

Sixty-one patients with a mean age of 44.1 ± 5.3 years were enrolled in the study. The study group consisted of 34 men (55.7%) and 27 women (44.3%). Thirty patients (49.2%) were treated with continuous subcutaneous insulin infusion and 31 patients (50.8%) with multiple daily injections of insulin. Mean diabetes duration was 17.9 ± 7.8 years. Thirty patients (49.1%) were overweight and 13 patients (21.3%) were obese with a mean BMI of 26.9 ± 3.9. Mean systolic and diastolic blood pressure values were 125.2 ± 9.6 mmHg and 78.7 ± 6.4 mmHg, respectively. Mean fasting glucose level was 6.7 ± 2.7 mmol/L. Mean HbA1c at enrolment and the mean 5-year average were 7.4 ± 1.1% and 7.2 ± 0.7%, respectively. The mean trend of HbA1c expressed by Kendall's tau was 0.0 ± 0.4. Mean GFR was 105.0 ± 23.3 mL/min/1.73 m², mean serum levels of triglycerides and total cholesterol were 1.0 ± 0.6 mmol/L and 4.8 ± 0.8 mmol/L, respectively. Demographic and clinical data are presented in Table 1.

Echocardiographic measurements are presented in Table 2. The mean LVM indexed to BSA was 74.2 ± 13.2 g/m², and the mean left atrial volume indexed to BSA was 29.6 ± 3.7 ml/m². Mean left ventricular relative wall thickness was 0.41 ± 0.05. The mean values of IVA for the left and the right ventricle were 235.2 ± 71.7 cm/s² and 283.4 ± 79.4 cm/s², respectively. Mean e´sept and E/e´sept were 8.9 ± 1.9 cm/s and 9.2 ± 1.9, respectively and mean e´t and E/e´t were 13.4 ± 2.9 cm/s and 4.0 ± 1.1 cm/s, respectively.

TABLE 1. Demographic, clinical, and laboratory data of patients (N=61)

Parameter	Mean±SD
Age (years)	44.1±5.3
Diabetes duration (years)	17.9±7.8
Body mass index (kg/m²)	26.9±3.9
Systolic blood pressure (mmHg)	125.2±9.6
Diastolic blood pressure (mmHg)	78.7±6.4
Glycated hemoglobin at enrolment (%)	7.4±1.1
5-year average value of glycated hemoglobin (%)	7.2±0.7
Fasting serum glucose (mmol/L)	6.6±2.7
Glomerular filtration rate (mL/min/1.73 m²)	105.0±23.3
Total cholesterol (mmol/L)	4.8±0.8
Triglycerides (mmol/L)	1.0±0.6

SD: Standard deviation

Bivariate correlations of clinical and laboratory variables with cardiac chamber size are presented in Table 3. For all observed parameters, except BMI, indexed values of chamber size were used for correlation analysis. The correlations with Doppler parameters are presented in Table 4. Only BMI showed moderate correlations with all echocardiographic variables of the left atrial and the left ventricular size: left atrial volume (r = 0.47, $p < 0.01$), left ventricular end-diastolic diameter (r = 0.27, $p = 0.04$), left ventricular relative wall thickness (r = 0.32, $p = 0.01$), and LVM (r = 0.42, $p < 0.01$). BMI also moderately correlated with all observed Doppler parameters of left ventricular diastolic function (E/A, r = −0.39, $p < 0.01$; e´sept, r = −0.31, $p = 0.02$; E/e´sept, r = 0.31, $p = 0.01$) and right ventricular diastolic function (e´t, r = −0.29, $p = 0.02$; E/e´t, r = 0.31, $p = 0.02$). The 5-year average value of HbA1c weakly correlated with the Doppler index of left ventricular filling pressure E/e´sept (r = 0.27, $p = 0.04$). We found no significant correlations of fasting glucose, diabetes duration, HbA1c trend, GFR, serum cholesterol, and triglycerides with the observed echocardiographic parameters (Table 3 and 4).

In the multiple linear regression model after adjusting for age, diabetes duration and the 5-year average value of HbA1c, BMI remained significantly associated with LVM, left atrial volume, and the mitral inflow Doppler ratio E/A (Table 5). The association of BMI with e´t and E/e´t met borderline significance ($p = 0.050$ for e´t and $p = 0.047$ for E/e´t).

DISCUSSION

In our study, BMI was the only variable consistently associated with early changes in cardiac structure and function in asymptomatic normotensive middle-aged patients with T1DM. Average 5-year glycemic control was weakly associated with the noninvasive Doppler index of left ventricular filling pressure E/e´.

In studies including patients with T1DM left ventricular hypertrophy was an inconsistent finding and was more prevalent in patients with microalbuminuria [8,17]. On the other hand, left ventricular hypertrophy has been much more frequently observed in patients with T2DM, as supported by a considerable amount of evidence [18,19]. Less myocardial hypertrophy in T1DM compared with T2DM might be at least partly explained by the reduced insulin secretion capacity in T1DM, since insulin stimulates growth and hypertrophy of myocardial cells [20]. While chronic hyperglycemia promotes accumulation of advanced glycation end products and

TABLE 2. Echocardiographic parameters of patients (N=61)

Parameter	Mean±SD
2D parameters	
Left ventricular mass indexed to BSA (g/m^2)	74.2±13.2
Left ventricular relative wall thickness	0.41±0.05
Left atrial volume indexed to BSA (mL/m^2)	29.6±3.7
Right atrial area indexed to BSA (cm^2/m^2)	8.0±1.0
Left ventricular ejection fraction (%)	64.9±6.0
Interventricular septal thickness (mm)	9.0±1.0
Left ventricular end-diastolic diameter indexed to BSA (mm/m^2)	24.0±2.0
Left ventricular posterior wall thickness (mm)	9.0±1.0
Right ventricular basal end-diastolic diameter indexed to BSA (mm/m^2)	18.0±2.0
Pulsed wave Doppler — mitral inflow velocities	
Early inflow velocity wave E (m/s)	0.8±0.2
Late inflow velocity wave A (m/s)	0.7±0.1
Ratio E/A	1.2±0.3
Pulsed wave Doppler — tricuspid (t) inflow velocities	
Early inflow velocity Et (m/s)	0.5±0.1
Late inflow velocity At (m/s)	0.4±0.1
Ratio E/At	1.3±0.3
Tissue Doppler — mitral and tricuspid (t) annular velocities	
s'sept (cm/s)	8.6±1.2
e'sept (cm/s)	8.9±1.9
a'sept (cm/s)	9.7±1.9
E/e'sept	9.2±1.9
s't (cm/s)	14.4±2.4
e't (cm/s)	13.4±2.9
a't (cm/s)	13.9±3.7
E/e't (cm/s)	4.0±1.1
IVA_{LV} (cm/s^2)	235.2±71.7
IVA_{RV} (cm/s^2)	283.4±79.4

SD: Standard deviation; BSA: Body surface area; s'sept: Peak systolic mitral annular velocity at the septal part of mitral annulus; e'sept: Peak early diastolic mitral annular velocity at the septal part of mitral annulus; a'sept: Peak late diastolic mitral annular velocity at the septal part of mitral annulus; s't: Peak systolic tricuspid annular velocity; e't: Peak early diastolic tricuspid annular velocity; a't: Peak late diastolic tricuspid annular velocity; IVA_{LV}: Myocardial isovolumetric acceleration of the left ventricle; IVA_{RV}: Myocardial isovolumetric acceleration of the right ventricle

subsequent myocardial stiffening, in T2DM insulin resistance and hyperinsulinemia predominantly increase LVM [20,21]. Since left ventricular structural changes evaluated by imaging studies were often mild in patients with T1DM, some authors even questioned the existence of type 1 diabetes-specific cardiomyopathy [22,23]. However, more recent studies confirmed left ventricular diastolic dysfunction in up to 30.7% of middle-aged patients with T1DM, which is comparable with the 15 years older general population [8,10,17,24]. Furthermore, recent observational data confirmed a higher incidence of heart failure and mortality in patients with T1DM compared with the general population, but little is known about early predictors of cardiac abnormalities in these patients [25,26].

Recently published Swedish registry-based data have demonstrated an increased mortality of patients with T1DM compared with matched controls even in patients with HbA1c below 6.9% [26]. It seems that, besides glycemic control, other potentially even more important and poorly recognized contributors to adverse outcome exist in these patients. In the echocardiography-based study of Wai et al. increasing age and BMI were suggested as the two most important predictors of cardiac dysfunction progression in patients with T1DM, while the mean observational time was 3.8 years [27]. Epidemiological data also revealed a link between obesity and hospitalizations for heart failure in patients with diabetes mellitus [28,29]. Due to the volume overload and metabolic derangements, obesity has been linked to left ventricular hypertrophy and dysfunction even in non-diabetic populations [30]. Similarly, in our patients, BMI was associated with LVM and left atrial volume, both of which have been proven to predict adverse cardiac events [29,31].

Few imaging studies evaluated the impact of long-term glycemic control on cardiac function in patients with T1DM. Some of them demonstrated the reduction of LVM as well as the reversal of the left ventricular diastolic dysfunction by improved glycemic control [11,12]. On the other hand, in a subpopulation of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study (DCCT/EDIC) only a mild effect of long-term glycemic control on LVM and volume was demonstrated by cardiac magnetic resonance over years [32]. Similarly, we found no significant effect of 5-year glycemic control on cardiac structure,

TABLE 3. Correlation analysis of clinical and laboratory parameters with cardiac chamber size

Parameter	LAVI	LVEDDI	LVMI	RWT	RAAI	RVDDI
DM duration						
r	–0.10	–0.14	–0.21	–0.10	–0.30	–0.12
p	0.46	0.27	0.10	0.43	0.02*	0.35
HbA1c-5y						
r	0.17	0.05	–0.01	–0.01	–0.23	–0.08
p	0.18	0.70	0.97	0.94	0.07	0.56
Kendall's tau for HbA1c trend						
r	0.08	0.14	0.23	–0.01	–0.01	0.01
p	0.53	0.28	0.07	0.94	0.93	0.94
Fasting glucose						
r	0.12	0.04	–0.05	–0.05	–0.01	0.02
p	0.34	0.75	0.69	0.69	0.92	0.86
GFR						
r	0.26	0.07	0.14	0.00	0.28	0.00
p	0.04*	0.58	0.27	0.98	0.03*	0.98
Cholesterol						
r	–0.06	0.23	0.16	–0.06	0.14	–0.01
p	0.65	0.08	0.21	0.65	0.27	0.93
Triglycerides						
r	0.01	–0.20	0.04	0.28	–0.04	0.03
p	0.97	0.12	0.76	0.03*	0.77	0.80
	LAV	LVEDD	LVM	RWT	RAA	RVDD
Body mass index						
r	0.47	0.27	0.42	0.32	0.19	0.20
p	<0.01*	0.04*	<0.01*	0.01*	0.15	0.14

r: Pearson's correlation coefficient; LAVI: Left atrial volume indexed to body surface area; LVEDDI: Left ventricular end-diastolic diameter indexed to body surface area; LVMI: Left ventricular mass index; RWT: Left ventricular relative wall thickness; RAAI: Right atrial area indexed to body surface area; RVDDI: Right ventricular basal end-diastolic diameter indexed to body surface area; LAV: Left atrial volume; LVEDD: Left ventricular end-diastolic diameter; RAA: Right atrial area; RVDD: Right ventricular basal end-diastolic diameter; DM: Diabetes mellitus; HbA1c-5y: 5-year average value of glycated hemoglobin; GFR: Glomerular filtration rate. *Statistically significant correlations

but we confirmed a weak association of glycemic control with the Doppler index of left ventricular filling pressure E/e´. Furthermore, we found no significant correlation of diabetes duration and the 5-year trend of HbA1cwith left ventricular size and function. This might be due to the good average long-term glycemic control achieved by the frequent use of continuous subcutaneous insulin infusion and the absence of an overall trend in HbA1c over years (mean Kendall's tau = 0.0 ± 0.4). Based on our results and previous findings, we assume that in well-controlled T1DM chronic hyperglycemia *per se* induces only mild structural and functional cardiac changes, but makes the heart more vulnerable and susceptible to further and more extensive injury due to obesity and other noxious stimuli. This might be the reason for a better association of BMI than diabetes duration and HbA1c with cardiac remodeling in our patients. However, our results may not be applied to patients with poor glycemic control. An increased susceptibility of diabetic heart to more extensive damage has already been demonstrated in case of ischemic and reperfusion injury, which resulted in a significantly larger ischemic area in patients with diabetes compared with the non-diabetic controls [33].

Although autoantibodies in T1DM were assumed to cause dilated phenotype with eccentric left ventricular remodeling and systolic dysfunction, convincing evidence is lacking [8,34]. As left ventricular ejection fraction has low sensitivity to detect early left ventricular systolic impairment, we also used IVA as a relatively novel and less load-dependent TDI-derived parameter of systolic function [35]. Consistent with the results of most previous studies, we found no significant correlation of observed variables with the parameters of left and right ventricular systolic function [24,36]. Recently, few small-sized studies have demonstrated impaired global longitudinal deformation of the left ventricle in patients with T1DM analyzed by the speckle tracking echocardiography [37]. However, left ventricular deformation imaging might be an even more sensitive echocardiographic technique to detect early changes in systolic function than TDI-derived IVA.

Cardiac steatosis is a common finding in diabetes mellitus due to metabolic derangements. The uptake of fatty acids by myocardial cells exceeds the capacity of mitochondrial oxidation. The myocardial lipid overload produces lipotoxic intermediates that increase the production of reactive oxygen species and promote myocardial cell apoptosis [38]. In our patients, serum triglycerides and total cholesterol levels were not significantly associated with cardiac structure and function. This might be explained by the relatively normal lipid profile, especially low serum triglycerides.

TABLE 4. Correlation analysis of clinical and laboratory parameters with echocardiographic functional parameters

Parameter	E/A	s'sept	e'sept	E/e'sept	s't	e't	E/e't	LVEF	IVA_{LV}	IVA_{RV}
DM duration										
r	–0.12	0.01	0.07	0.03	–0.02	0.01	0.02	–0.08	0.12	–0.03
p	0.33	0.96	0.57	0.81	0.86	0.93	0.88	0.51	0.37	0.86
BMI										
r	–0.39	0.05	–0.31	0.31	0.05	–0.29	0.31	–0.14	0.22	0.19
p	<0.01*	0.73	0.02*	0.01*	0.73	0.02*	0.02*	0.25	0.10	0.17
Fasting glucose										
r	0.09	0.07	–0.02	0.14	–0.12	–0.05	0.01	0.04	0.13	0.05
p	0.48	0.61	0.90	0.29	0.34	0.72	0.96	0.74	0.32	0.70
HbA1c-5y										
r	–0.02	–0.19	–0.21	0.27	–0.28	–0.09	0.12	–0.04	0.12	0.02
p	0.89	0.15	0.11	0.04*	0.02*	0.51	0.39	0.73	0.37	0.89
HbA1c trend										
r	0.04	–0.04	–0.18	0.17	–0.16	0.02	–0.10	0.00	–0.11	0.03
p	0.76	0.78	0.16	0.19	0.23	0.89	0.45	0.98	0.40	0.85
GFR										
r	0.23	–0.00	0.08	0.05	0.16	0.12	–0.12	–0.10	0.07	0.14
p	0.09	0.10	0.54	0.73	0.23	0.37	0.37	0.45	0.62	0.31
Cholesterol										
r	0.05	0.04	0.15	–0.15	0.08	0.21	–0.12	0.15	–0.06	0.13
p	0.73	0.76	0.27	0.28	0.55	0.13	0.40	0.26	0.68	0.35
Triglycerides										
r	–0.04	0.17	–0.12	0.26	0.01	–0.01	–0.11	0.10	–0.07	0.02
p	0.77	0.22	0.38	0.06	0.96	0.93	0.44	0.46	0.63	0.89

r: Pearson's correlation coefficient; DM: Diabetes mellitus; BMI: Body mass index; HbA1c-5y: 5-year average value of glycated hemoglobin; HbA1c trend: Kendall's tau for 5-year HbA1c measurements; GFR: Glomerular filtration rate; s'sept: Peak systolic mitral annular velocity at the septal part of mitral annulus; e'sept: Peak early diastolic mitral annular velocity at the septal part of mitral annulus; s't: Peak systolic tricuspid annular velocity; e't: Peak early diastolic tricuspid annular velocity; LVEF: Left ventricular ejection fraction; IVA_{LV}: Myocardial isovolumetric acceleration of the left ventricle; IVA_{RV}: Myocardial isovolumetric acceleration of the right ventricle. *Statistically significant correlations

TABLE 5. Association of BMI with cardiac chamber size and function after adjustment for age, diabetes duration, and 5-year average value of glycated hemoglobin

Independent variable	Dependent variable	B	SE	95% CI for B	*p*
Body mass index	LV mass	4.14	1.12	(1.89, 6.38)	<0.01*
	Left atrial volume	1.28	0.34	(0.60, 1.96)	<0.01*
	LVEDD	0.03	0.01	(0.00, 0.05)	0.04*
	LV relative wall thickness	0.02	0.01	(0.00, 0.05)	0.08
	E/A	–0.02	0.01	(–0.04, –0.01)	<0.01*
	e'sept	–0.11	0.06	(–0.24, 0.01)	0.08
	E/e'sept	0.11	0.06	(–0.02, 0.24)	0.09
	e't	–0.20	0.10	(–0.40, 0.00)	0.050
	E/e't	0.07	0.04	(0.00, 0.15)	0.047*

B: Regression coefficient; SE: Standard error; CI: Confidence interval; LV: Left ventricle; LVEDD: Left ventricular end-diastolic diameter; E: Early mitral inflow velocity; A: Late mitral inflow velocity; e'sept: Peak early diastolic mitral annular velocity at the septal part of mitral annulus; e't: Peak early diastolic tricuspid annular velocity. *Statistically significant correlations

In the observational study of Vestberg et al., advanced chronic kidney failure was related to increased hospitalizations for heart failure in patients with T1DM [39]. We found a weak association of glomerular filtration rate with left and right atrial size but no correlation with observed functional parameters. The reason might be the exclusion of patients with advanced renal disease (GFR <60 mL/min/1.73 m^2).

There are limitations of our study. The number of eligible patients was limited due to the restrictive exclusion criteria. However, we decided to select patients with T1DM without major comorbidities influencing cardiac chamber size and function. Coronary angiography was not performed to exclude coronary artery disease due to ethical issues. We excluded all symptomatic patients and patients with a history of ischemic heart disease, resting ECG changes or left ventricular wall motion abnormalities. Although the threshold of T1DM duration for the study entry was 5 years, the time of T1DM diagnosis was quite variable. Furthermore, we could not provide reliable data of weight stability and duration of obesity. Only selected laboratory data were collected as the emphasis of the study was to identify potentially reversible factors for the development of diabetic cardiomyopathy. For

instance, inflammatory parameters which might accelerate the development of diabetic heart disease were not studied. Another important limitation of the study is the use of non-corrected multiple testing in a relatively small sample. The study was cross-sectional and generated hypotheses, which warrant further research. The Doppler assessment of diastolic parameters has limitations, especially the biphasic distribution of the Doppler index E/A as well as the non-linear correlation of E/e´ with the invasive measurements of left ventricular filling pressure.

CONCLUSION

In our study, only BMI was associated with early structural and functional changes in the heart of middle-aged asymptomatic patients with T1DM. Long-term glycemic control was associated with the noninvasive Doppler index of left ventricular filling pressure, but not with cardiac chamber size. Based on our results, we hypothesize that overweight and obese middle-aged patients with T1DM might be more prone to the development of cardiomyopathy and that screening of this subset of patients with echocardiography should be recommended. However, as our study is cross-sectional and hypothesis-generating, further studies are needed to confirm the causal relationship between obesity and cardiac dysfunction in patients with T1DM.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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