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Association of antithyroid peroxidase antibodies with cardiac function in euthyroid women with type 1 diabetes mellitus — assessment with two-dimensional speckle-tracking echocardiography

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Abstract

Introduction: The presence of diabetes is associated with loss of cardioprotection in premenopausal women; however, the mechanisms involved remain unknown. Autoimmune factors are suspected to play a role in cardiovascular complications, especially in type 1 diabetes (T1DM). The aim of this pilot study was to explore whether antithyroid peroxidase antibody (aTPO) as a marker of increased immune activity is related to cardiac dysfunction in young, asymptomatic women with T1DM.

Material and methods: Eighty-eight euthyroid women (59 with T1DM and 29 healthy controls) underwent physical examination, laboratory tests, thyroid ultrasound, and two-dimensional speckle-tracking echocardiography. According to the antiperoxidase antibodies (aTPO) titre, the T1DM women were divided into an aTPO positive (T1DM aTPO+) (n = 34) and an aTPO negative (T1DM aTPO–) (n = 25) group. The relationship between thyroid autoimmunity parameters and echocardiographic parameters was evaluated.

Results: Global longitudinal strain (GLS) was slightly reduced in the T1DM aTPO+ group compared to T1DM aTPO– and significantly compared to controls (p = 0.051 and p = 0.015, respectively). Although, the lower values of longitudinal strain of left ventricular were found in the majority of segments in the T1DM aTPO+ group in comparison to T1DM aTPO– and controls, significant differences were only found in the two-chamber view (specifically in the anterior segments) between the T1DM aTPO+ and T1DM aTPO– groups (p = 0.030) and in the four-chamber view (specifically in the anterolateral segments) between the T1DM aTPO+ group and controls (p = 0.021). Echocardiographic parameters of diastolic and systolic function of both ventricles were significantly correlated with parameters of thyroid autoimmunity. A logistic regression analysis showed that Hashimoto's thyroiditis (HT) duration [odds ratio (OR): 0.997, 95% confidence interval (CI): 0.995-0.999, p = 0.008), the dose of levothyroxine (OR: 0.814, 95% CI: 0.689–0.960, p = 0.013), and reduced echogenicity on thyroid ultrasound (OR: 0.309, 95% CI: 0.120–0.793, p = 0.013) had a significant influence on reduced GLS.

Conclusions: Our results suggest that coexistence of aTPO with T1DM was associated with poorer myocardial function, particularly in the anterior and anterolateral segments, which may be related to an autoimmune factor. The impaired function of these segments is probably the first sign of myocardial systolic dysfunction in women with T1DM, which needs to be confirmed in further studies. **(Endokrynol Pol 2022; 73 (5): 812–822)**

Key words: *type 1 diabetes mellitus; thyroid autoimmunity; speckle tracking echocardiography; diabetic cardiomyopathy; heart failure*

Introduction

Cardiovascular (CV) complications comprise the most challenging problem in clinical practice in patients with diabetes because they develop more rapidly and are associated with a significantly worse course in this group of patients [1]. On the basis of preclinical and clinical evidence, it is hypothesized that autoimmunity may be a determinant factor in their development, especially in type 1 diabetes mellitus (T1DM) [2–4].

Recently, a meta-analysis including more than 12 million individuals showed that the excess risk of heart failure (HF) associated with diabetes is significantly greater in women than in men, with T1DM increasing by 47% and in type 2 diabetes by about 9% [5]. Hashimoto's thyroiditis (HT) is the most com-

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mon autoimmune concomitant disease with T1DM and is more prevalent in women [6]. Previous studies demonstrated that subclinical hypothyroidism is associated with impaired systolic and diastolic function of the left ventricle (LV), but some adverse changes can be reversed by levothyroxine therapy [7]. Despite the known effects of thyroid hormones on the CV system [8], the number of studies evaluating the effects of thyroid autoimmunity on cardiac function is limited. Antithyroid peroxidase antibodies (aTPO) are frequently detected in T1DM patients (up to 50%), but their importance during euthyroidism has not been sufficiently studied [9]. On the basis of our knowledge, to date, whether the presence of aTPO in asymptomatic young euthyroid women with T1DM is associated with myocardial dysfunction has not been investigated. This assessment seems even more appropriate because, in children and young adults with T1DM, cardiac dysfunction has been demonstrated despite short disease duration, good metabolic control, and the absence of other complications [10, 11]. Given that premenopausal women with T1DM present increased incidence of CV disease than diabetic men [12] and are also more at risk of developing autoimmune conditions [6], we hypothesized that autoimmunity specifically may contribute to the development of HF in this group of patients.

Accordingly, the aim of this pilot study was to determine whether aTPO and other parameters associated with thyroid autoimmunity are associated with echocardiographic signs of subclinical cardiac dysfunction in young, asymptomatic, euthyroid women with T1DM using tissue Doppler and speckle tracking echocardiography (STE).

Materials and methods

Participants and study design

For this prospective pilot study, we enrolled 59 females with T1DM aged 20 to 35 years and 29 age- and sex-matched healthy controls. Participants of study group were recruited from the patient population attending the Diabetes Outpatient Clinic of the Central Clinical Hospital of the Ministry of Internal Affairs and Administration in Warsaw, while the control group was recruited from hospital employees and their relatives between May 2018 and October 2020. The study protocol was approved by the local medical Ethics Committee (permit No. 22/2018 of 09.05.2018) and was prepared in accordance with the Declaration of Helsinki. All subjects signed informed consent papers before participation.

Exclusion criteria for all participants were as follows: history of any CV disease (especially hypertension, coronary artery disease, cardiac arrhythmia, congenital heart disease), smoking, known renal disease, or any other chronic disease. All patients who were taking drugs other than insulin and levothyroxine were excluded from the study.

Inclusion criteria for the study group were as follows: diagnosed T1DM, glycosylated haemoglobin A_{1c} (HbA_{1c}) < 10%, age between 20 and 35 years, female, and current euthyreosis status in laboratory tests. Patients were qualified on the basis of the results of previous medical records indicating an autoimmune background of the T1DM (presence of diabetes-specific autoantibody) or a typical clinical picture based on the National Institute for Health and Clinical Excellence (NICE) recommendations for the diagnosis of T1DM in adults [13]. The diagnosis of Hashimoto's thyroiditis (HT) was based on the demonstration of circulating antibodies to thyroid antigens (aTPO and/or antithyroglobulin antibody [aTG]) and reduced echogenicity on thyroid ultrasound [14]. For the control group, a negative history of diabetes or thyroid disorders was required.

All women meeting the inclusion and exclusion criteria for the study were surveyed concerning the duration of diabetes, daily insulin dose, the presence of microangiopathy complications, duration of HT, levothyroxine dose per week, and comorbidity with other autoimmune diseases. The data on the presence of microangiopathy complications and the duration of HT were assessed on the basis of past medical records (all patients qualified for the study with T1DM were under regular care of a hospital outpatient clinic). Body mass index (BMI) was determined as the weight in kilograms divided by the square of height in metres. The systolic and diastolic blood pressures were measured during echo analysis using a standard mercury sphygmomanometer after 10 minutes of rest. Heart rate was estimated by measurement from standard 12-lead electrocardiography (ECG). The data of the study population were collected on a computerized data sheet.

Laboratory evaluation and thyroid assessment

Serum total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglyceride (TG), glycosylated haemoglobin A_{1c} (HbA_{1c}), thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), aTPO, and aTG were measured for all patients using standard methods in the hospital laboratory. The range of normal values for fT4 was between 0.93 and 1.7 (ng/dL), for fT3, it was between 2 and 4.4 (pg/mL), and for TSH, it was between 0.27 and 4.2 (μIU/mL). The positive values for antibodies were > 34 IU/mL for aTPO and > 115 (IU/mL) for aTG. Thyroid ultrasonography using a 5 to 12 MHz linear array transducer was performed in all patients by the same experienced sonographer using a high-definition echograph (Aplio a, Canon Medical System) according to the guidelines presented by the Polish Ultrasonography Society [15].

Echocardiography

A complete echocardiographic study was performed on each patient and control using an EPIQ system (version 7C/CVx, Philips Medical Systems, Best, Netherlands) by a single experienced echocardiographer, blinded to the examined group. It included a detailed conventional, tissue Doppler and two-dimensional (2D) STE imaging evaluation. All measurements were made in accordance with the recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography [16, 17].

Using 2D imaging in the parasternal long-axis view LV dimension, the interventricular septum (IVS), the posterior wall dimensions (PWD) in systole and diastole, and the right ventricular dimension in diastole (RVDd) were measured. The left atrial volume index (LAVI) was calculated by dividing the left atrium volume by the body surface area (BSA). The LV mass index was calculated according to the formulae of Devereux at al. [18]. Tricuspid plane systolic excursion (TAPSE) was obtained from the four-chamber (4CH) view as the difference between end-diastolic and end-systolic positions of the tricuspid annulus. The LV ejection fraction (EF) was assessed with Simpson's method from the apical 4CH and two-chamber (2CH) views [17].

Using pulsed-wave Doppler imaging, the mitral early diastolic flow (E), late diastolic flow (A) velocities and E/A ratios were calculated. The deceleration time (DT) of the E-wave was also determined. The isovolumic relaxation time (IVRT) was calculated from the end of the maximal systolic myocardial velocity until the beginning of the early diastolic myocardial velocity wave.

Using the tissue Doppler peak, the early (Emed') and late (Amed') diastolic velocity of the septal mitral annulus were measured. Mitral E/Emed' and E/Amed' ratios were calculated. Speckle tracking analyses were performed on standard images from apical 4-, 3-, and 2-CH views for LV longitudinal strain (LS). We used the automatic global longitudinal strain (GLS) evaluation software AutoStrain, which eliminates manual errors, providing efficient and reproducible results [19]. Strain values of LV were assessed in 18 segments, and the mean value of each strain was calculated as the GLS.

Statistical analysis

Analysis was performed using Statistica 13. Continuous variables were examined through the Shapiro–Wilk test for normality. To assess differences between the 2 groups, we used Student's t test for variables with a normal distribution and the Mann-Whitney U test for variables with a non-normal distribution. To assess differences between the 3 groups, we used the analysis of variance with Tukey's post hoc RIR test for unequal numbers for variables with a normal distribution or the ANOVA rang Kruskal-Wallis test and the pairwise Mann-Whitney U tests with Bonferroni correction for variables with a nonnormal distribution. Categorical variables were presented as percentages and compared using Fisher's exact test. The degree of association between thyroid data and echocardiography measurements was demonstrated using the Spearman test. Univariate logistic regression analyses were performed to identify clinical predictors of abnormal LVGLS in the whole group. The LVGLS threshold for pathology was adopted at a level of –18% [LVGLS ≥ –18% (LVGLS ≤ 18% in absolute values) was calculated as pathology]. Odds ratios (ORs) with 95% confidence interval (95% CI) were calculated. The statistical significance level was set at $p < 0.05$.

Results

Clinical characteristics

This study included 59 women with T1DM (mean age, 26 ± 4.5 years; diabetes duration 13.1 ± 6.2 years, HbA_{1c} 7.8 ± 1.3%) and 29 age- and sex-matched healthy controls (mean age, 26.8 ± 3.8 years). All patient with T1DM use an insulin pump or multiple daily insulin injections. None of our patients had nephropathy, but 5 had a history of diabetic retinopathy and 3 had chronic sensorimotor peripheral neuropathy. According to the antithyroid peroxidase antibody (aTPO) titre, the T1DM women were divided into an aTPO positive (T1DM aTPO+) (n = 34) and an aTPO negative (T1DM aTPO–) (n = 25) group. Diabetes duration, daily insulin dose, presence of microangiopathy complications, HbA_{1c}, TSH, fT4, and fT3 were similar in both groups of T1DM (aTPO+ and aTPO–), whereas aTPO, aTG, ultrasound features of HT, HT duration, and levothyroxine dose per week were significantly higher in the T1DM aTPO+ group than in the T1DM aTPO– group. No significant differences were detected between the T1DM subgroups and the healthy controls with regard to age, BMI, lipid parameters, TSH, fT4, heart rate, and systolic and diastolic blood pressure. FT3 was significantly lower in patients with T1DM aTPO– than in the control group ($p < 0.05$) (Tab. 1).

There were no significant differences between groups in terms of BSA, LVEDd, PWS, PWD, IVSD, RVDd, LAVI, LVMI, E, A, E/A, E/Emed', E'/Amed', and DT of LVEF. Table 2 shows the echocardiographic parameters in the study groups and the results of the comparative analysis.

Within cardiac chamber size, we found significant differences only in the IVS in systole, in both the T1DM

Table 1. ***Characteristics of the studied subgroups of type 1 diabetes mellitus (T1DM): with positive antiperoxidase antibody titre (T1DM aTPO+) and negative antiperoxidase antibody titre (T1DM aTPO–) and healthy controls (p value of the analysis of variance or the ANOVA Kruskal-Wallis test)***

	T1DM aTPO+ (n = 34)	T1DM aTPO– (n = 25)	Controls (n = 29)	p
Age [years]	26 (23–30)	24 (23–27)	26 (24–29)	0.355
BMI ± [kg/m²]	22.5 (20.8–24.9)	22.0 (20.3–24.5)	22.0 (20.3–23.0)	0.397
Diabetes duration [years]	13 (8–19)	11 (9–16)	–	0.291*
daily insulin dose [units]	36 (30–46)	41 (25–45)	–	0.699*
microangiopathy (%)	4 (11.7)	4 (16.0)	–	0.711*
HbA_{1c} (%)	7.8 (7.0–9.2)	7.4 (6.8–8.0)	–	0.080*
TC [mg/dL]	174 (160–196)	173 (151–196)	173 (153–191)	0.848
LDL [mg/dL]	89 (72–117)	83 (67–104)	83 (66–104)	0.685
HDL [mg/dL]	66 (57–78)	71 (51–82)	67 (1–85)	0.904
TG [mg/dL]	67 (58–86)	76 (60–108)	77 (61–109)	0.368
TSH [μIU/mL]	2.1 ± 1.1	2.0 ± 1.1	2.4 ± 1.0	0.285
fT4 [ng/dL]	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.2 (1.1–1.2)	0.345
fT3 [pg/mL]	3.2 (2.8–3.2)	3.0 (2.6–3.2)	3.2 (3.0–3.4)	0.019
aTPO [IU/mL]	185 ± 203	12 ± 8	11 ± 9	< 0.001
aTG [IU/mL]	179 (57–388)	12 (11–33)	11 (5–70)	< 0.001

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Table 1. *Characteristics of the studied subgroups of type 1 diabetes mellitus (T1DM): with positive antiperoxidase antibody titre (T1DM aTPO+) and negative antiperoxidase antibody titre (T1DM aTPO–) and healthy controls (p value of the analysis of variance or the ANOVA Kruskal-Wallis test)*

	T1DM aTPO+ (n = 34)	T1DM aTPO– (n = 25)	Controls (n = 29)	p
Reduced echogenicity of the thyroid gland on ultrasound (%)	(31) 91.2%	0	0	< 0.001
Presence of connective tissue echoes on thyroid ultrasound (%)	(21) 61.8%	0	0	< 0.001
HT duration [years]	7.2 ± 6.5	0	0	< 0.001
L-thyroxine dose per week [μg]	336.4 ± 338.4	91.0 ± 220.9	0	0.029*
Heart rate	72 (63–78)	69 (65–85)	72 (55–90)	0.970
Systolic blood pressure [mm Hg]	115 ± 7	117 ± 6	115 ± 4	0.163
Diastolic blood pressure [mm Hg]	73 ± 7	75 ± 6	76 ± 4	0.252

*p of Mann-Whitney U test for variables with nonparametric distribution or Student's t-test for variables with parametric distribution or Fisher's exact test for categorical variables between T1DM aTPO+ *vs*. T1DM aTPO–; data presented as median (interquartile range) or mean ± SD (standard deviation) or number (percentage); aTG — anti-thyroglobulin antibody; aTPO — anti-thyroid peroxidase antibody; BMI — body mass index; fT3 — free triiodothyronine; fT4 — free thyroxine; HbA_{1c} — glycated haemoglobin; HDL — high-density lipoprotein; HT — Hashimoto's thyroiditis; LDL — low-density lipoprotein; SD — standard deviation; TC — total cholesterol; TG — triglyceride; TSH — thyroid-stimulating hormone

aTPO+ and T1DM aTPO– groups compared to controls (p = 0.007 and p = 0.030, respectively).

In certain parameters describing diastolic function, we found significant differences in the Emed', with the lowest values in the T1DM aTPO+ group (p = 0.025 in comparison to controls) and in the IVRT group, with the highest values in the T1DM aTPO+ group (p < 0.0001 in comparison to controls). Emed'

Table 2. *Echocardiography parameters in women with type 1 diabetes mellitus (T1DM) and positive antiperoxidase antibody titres (T1DM aTPO+) vs. women with T1DM and negative aTPO titres (T1DM aTPO) vs. the control group (p value of the analysis of variance or the ANOVA Kruskal-Wallis test)*

	T1DM aTPO+ (n = 34)	T1DM aTPO– (n = 25)	Controls (n = 29)	p value
BSA [m^2]	1.71 (1.65–1.78)	1.69 (1.61–1.78)	1.67 (1.59–1.79)	0.597
Cardiac chamber size				
LVEDd [mm]	43.0 (41.0–46.0)	44.5 (42.0–46.0)	45.0 (43.0 - 46.0)	0.368
IVSD [mm]	9.0 (8.0–9.0)	8.0 (8.0–9.0)	9.0 (8.0–9.0)	0.263
PWD [mm]	9.0 (8.0–10.0)	8.5 (8.0–9.0)	9.0 (8.0–9.0)	0.151
LVSDd [mm]	32.0 (29.0–34.0)	30.0 (27.0–32.0)	31.0 (29.0–33.0)	0.221
IVSS [mm]	11.0 (10.0–12.0)	10.5 (9.0–12.0)	12.0 (11.0–13.0)	0.021[A]
PWS [mm]	12.0 (11.0–13.0)	11.0 (10.0–13.0)	12.0 (12.0–13.0)	0.129
RVDd [mm]	26.0 (24.0–29.0)	26.5 (23.0–28.0)	27.0 (25.0–28.0)	0.801
LAVI [mL/m^2]	21.0 (17.8–25.0)	26.0 (22.0–28.6)	24.0 (19.0–26.0)	0.094
LVMI [g/m^2]	70.0 (60.5–80.0)	67.9 (61.0–77.0)	73.9 (71.0–79.3)	0.076
Diastolic function				
E [cm/s]	88.3 (80.0–96.0)	94.1 (84.9–106.0)	94.0 (82.0–99.0)	0.594
A [cm/s]	58.0 (53.0–63.5)	49.0 (43.7–67.4)	55.0 (48.0–69.0)	0.289
E/A	1.53 (1.3–1.7)	1.72 (1.4–2.1)	1.50 (1.1–2.0)	0.350
Emed' [cm/s]	11.8 (10.7–13.1)	12.9 (12.1–13.6)	13.8 (11.5–14.8)	0.031[B]
E/Emed'	7.4 (6.4–8.6)	7.2 (6.7–8.1)	6.8 (6.4–7.5)	0.173
E/Amed'	1.7 (1.6–2.0)	1.9 (1.6–2.5)	1.8 (1.4–2.3)	0.313
DT [ms]	211.0 (180.0–236.0)	218.0 (197.0–250.0)	211.0 (194.0– 243.0)	0.490
IVRT [ms]	98.0 (90.0–104.0)	91.5 (85.0–99.0)	81.0 (79.0–85.0)	< 0.0001[C]

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Table 2. *Echocardiography parameters in women with type 1 diabetes mellitus (T1DM) and positive antiperoxidase antibody titres (T1DM aTPO+) vs. women with T1DM and negative aTPO titres (T1DM aTPO) vs. the control group (p value of the analysis of variance or the ANOVA Kruskal-Wallis test)*

	T1DM aTPO+ (n = 34)	T1DM aTPO– (n = 25)	Controls (n = 29)	p value
Systolic function				
TAPSE [mm]	22.0 (20.0–24.0)	22.0 (20.0–24.0)	26.0 (23.0–27.0)	p =0.0001[D]
LV GLS [%]	17.1 (16.20–18.15)	18.3 (17.4–19.6)	18.5 (17.1–20.0)	p =0.031[E]
LV ejection fraction [%]	62.5 ± 3.1	62.6 ± 3.9	63.3 ± 2.4	p = 0.570

Data presented as median (interquartile range) or mean ± standard deviation (SD); in A, B, C, D below, we present the significant differences that came out between groups:

- [A]T1DM aTPO+ *vs*. controls, p = 0.007; T1DM aTPO– *vs*. controls, p = 0.030;
- [B]T1DM aTPO+ *vs*. controls, p = 0.025; T1DM aTPO+ *vs*. T1DM aTPO–, p = 0.047;
- [C]T1DM aTPO+ *vs*. controls, p< 0.0001; T1DM aTPO– *vs*. controls, p = 0.0002;
- [D]T1DM aTPO+ *vs*. controls, p = 0.0002; T1DM aTPO– *vs*. controls, p = 0.0001;
- [E]T1DM aTPO+ *vs*. controls, p = 0.015.

A — mitral inflow peak late velocity; BSA — body surface area; DT — deceleration time; E—mitral inflow peak early velocity; E/A — mitral E-wave velocity divided by mitral A-wave velocity; Emed' — early diastolic velocity of the septal mitral annulus; E/Amed' — mitral E-wave velocity divided by late diastolic velocity of the septal mitral annulus; E/Emed' — mitral E-wave velocity divided by early diastolic velocity of the septal mitral annulus; IVRT — isovolumic relaxation time; IVSD — interventricular septum end-diastolic diameter; IVSS — interventricular septum end-systolic diameter; LAVI — left atrial volume index; LVEDd — left ventricle end-diastolic diameter; LVESd — left ventricle end-systolic diameter; LV GLS — left ventricular global longitudinal strain; LVMI — left ventricular mass index; PWD — posterior wall thickness at end-diastole; PWS — posterior wall thickness at end-systole; RVDd — right ventricular dimension in diastole; TAPSE — tricuspid annular plane systolic excursion

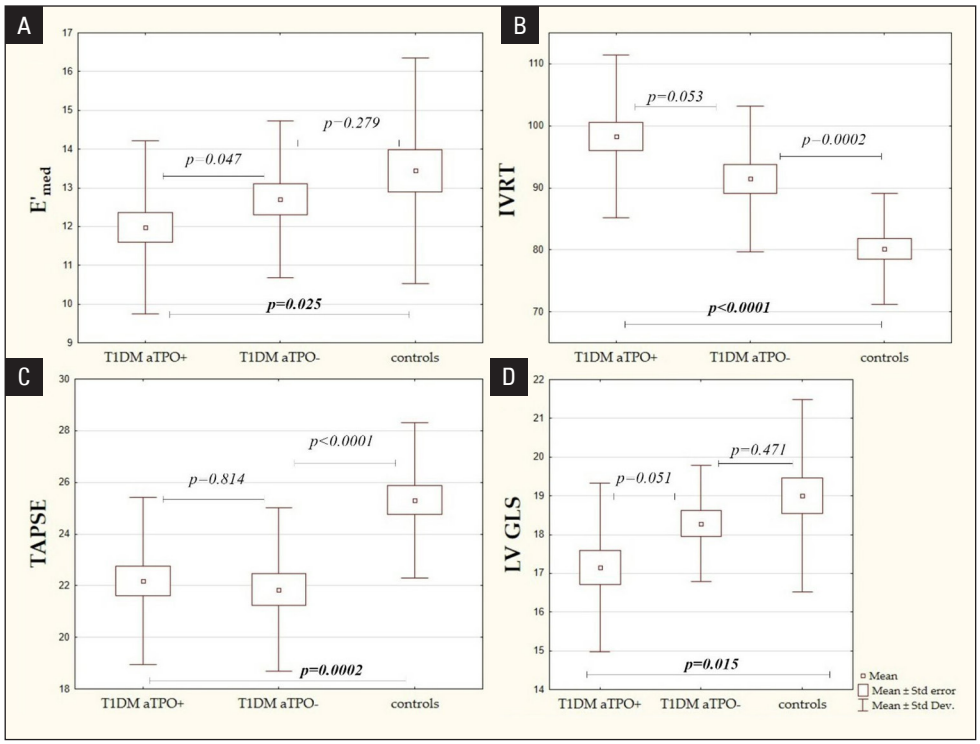

Figure 1. *Comparison of selected echocardiographic parameters.* **A.** *Early diastolic velocity of the septal mitral annulus (Emed');* **B.** *Isovolumic relaxation time (IVRT);* **C.** *tricuspid annular plane systolic excursion (TAPSE);* **D.** *Left ventricular global longitudinal strain (LV GLS) in absolute values between groups*

was also significantly different (p = 0.047), while IVRT was similar (p = 0.053) between the T1DM aTPO+ and T1DM aTPO– groups (Fig. 1AB).

Within systolic function, we found significant differences in TAPSE (RV systolic function), with the lowest values in the T1DM aTPO+ group (p = 0.0002 in comparison to controls), and in GLS (LV systolic function), with the lowest values in the T1DM aTPO+ group (p = 0.015 in comparison to controls). However, when comparing the T1DM aTPO+ and T1DM aTPO– groups, the difference for TAPSE was nonsignificant (p = 0.814), while for GLS was borderline insignificant (p = 0.051) (Fig. 1CD).

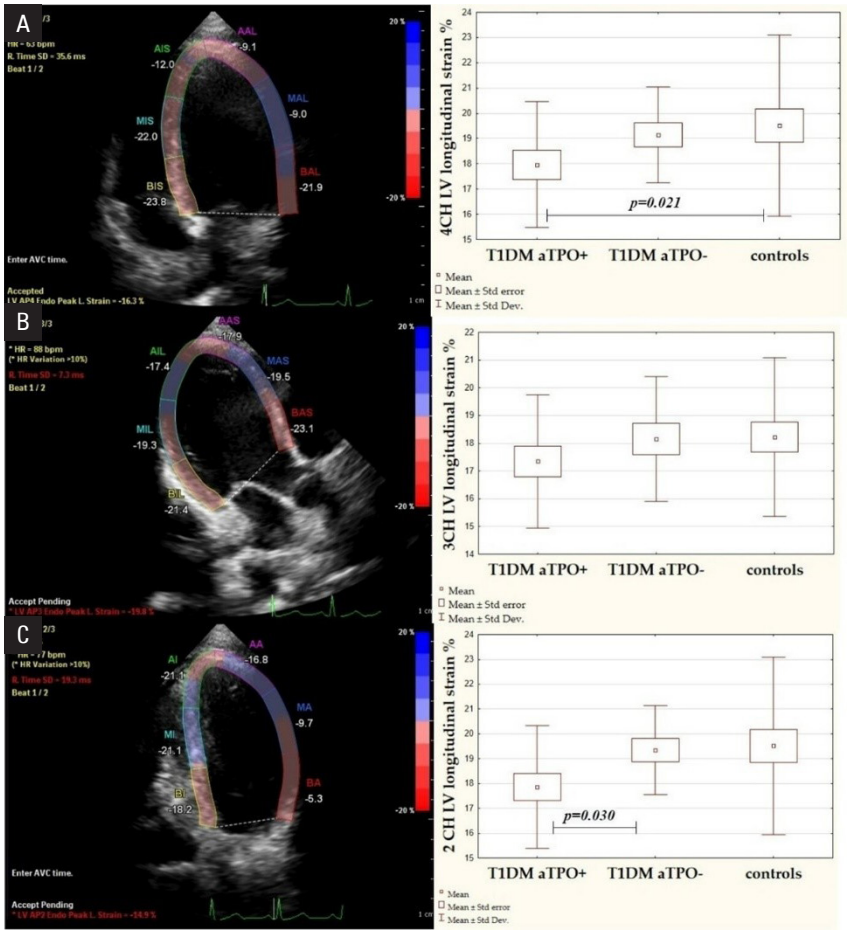

Figure 2. *Images of left ventricular longitudinal strain (LV LS) from apical views.* **A.** *Four-chamber (4CH) inferoseptal and anterolateral segments;* **B.** *Three-chamber (3CH) inferolateral and anteroseptal segments;* **C.** *Two-chamber (2CH) inferior and anterior segments. The graphs next to images show that the lowest longitudinal strain values were in the group of women with type 1 diabetes and positive antithyroid peroxidase antibodies (T1DM aTPO+). However, significant differences were found only in 4CH LV LS between the T1DM aTPO+ group and controls (p = 0.021) and in 2CH LV LS between the T1DM aTPO+ and T1DM aTPO– groups (p = 0.03). LS in the graphs is presented in absolute values*

We also performed a comparative analysis of LS from 3 apical views: 4CH, reflecting the function of inferoseptal and anterolateral segments; 3CH, showing the function of inferolateral and anteroseptal segments; and 2CH, presenting the function of inferior and anterior segments of LV. The lowest values of LS were found in most segments in the T1DM aTPO+ group. However, significant differences were only found in the 4CH view between the T1DM aTPO+ and control groups (p = 0.021) and in the 2CH view between the T1DM aTPO+ and T1DM aTPO– groups (p = 0.030) (Fig. 2).

When assessing the differences between segmental LV LS, we found that both the T1DM aTPO+ and T1DM aTPO– groups had significantly lower anterolateral wall strain as compared to controls (p = 0.016 and p = 0.014, respectively) and only the T1DM aTPO+ group exhibited significantly lower anterior wall strain as compared to controls (p = 0.017) (Tab. 3).

Our results may contribute to the identification of characteristics for the development of diabetic cardiac dysfunction. Figure 3 shows an example of the LS bull's eye plot in women with T1DM.

We performed correlation analyses between thyroid parameters and selected echocardiographic parameters, which were significantly different in the comparative analysis. IVSS was significantly negatively correlated with aTPO levels (r = 0.26, p = 0.02). Figure 4 shows the results of the most significant correlation between thyroid parameters and selected echocardiographic parameters.

In the univariate regression analyses, the risk factors for GLS in all women (n = 88) were HT duration, levothyroxine dose per week, and reduced echogenicity on thyroid ultrasound (Tab. 4). The remaining thyroid-related parameters, such as fT3, fT4, aTPO, aTG, and the presence of connective tissue echoes on ultrasound were not significantly associated with GLS.

Table 3. *Comparison of left ventricular longitudinal strain (LV LS) from apical views in women with type 1 diabetes mellitus and positive antiperoxidase antibody (T1DM aTPO+) versus women with type 1 diabetes mellitus and negative antiperoxidase antibody (T1DM aTPO–) versus control group. LS presented in absolute values (p value of the ANOVA Kruskal-Wallis test)*

	T1DM aTPO+ (n = 34)	T1DM aTPO– (n = 25)	Controls (n = 29)	p value
LV LS 4CH strain %	17.3 (16.0–19.0)	17.7 (15.6–20.4)	19.5 (17.5–20.5)	0.057[A]
Anterior lateral	16.8 (14.6–18.5)	17.2 (15.3–18.6)	19.2 (17.4–20.3)	0.014[B]
Inferior septal	18.1 (16.6–20.2)	19.2 (15.5–19.9)	19.2 (17.8–21.2)	0.321
LV LS 3CH strain %	17.4 (16.1–18.9)	17.7 (16.6–19.6)	17.1 (16.5–19.2)	0.619
Inferior lateral	16.9 (15.4–18.6)	17.4 (15.4–19.4)	18.4 (16.5–21.9)	0.154
Anterior septal	17.5 (16.2–19.2)	17.7 (16.5–21.2)	17.1 (14.5–19.3)	0.447
LV LS 2CH strain %	17.3 (16.2–19.7)	19.9 (17.4–21.1)	19.2 (17.5–21.3)	0.093[C]
Anterior	15.7 (14.5–18.2)	17.7 (15.5–19.7)	18.3 (16.2–19.7)	0.056[D]
Inferior	19.7 (17.8–20.5)	19.6 (18.4–22.0)	19.9 (17.6–21.7)	0.629

In A, B, C, D below, we present the significant differences that came out between groups:

- [A]T1DM aTPO+ vs. controls, p = 0.021;
- [B]T1DM aTPO+ vs. controls, p = 0.016; T1DM aTPO– vs. controls, p = 0.014;
- [C]T1DM aTPO+ vs. T1DM aTPO–, p = 0.030;
- [D]T1DM aTPO+ vs. controls, p = 0.017.

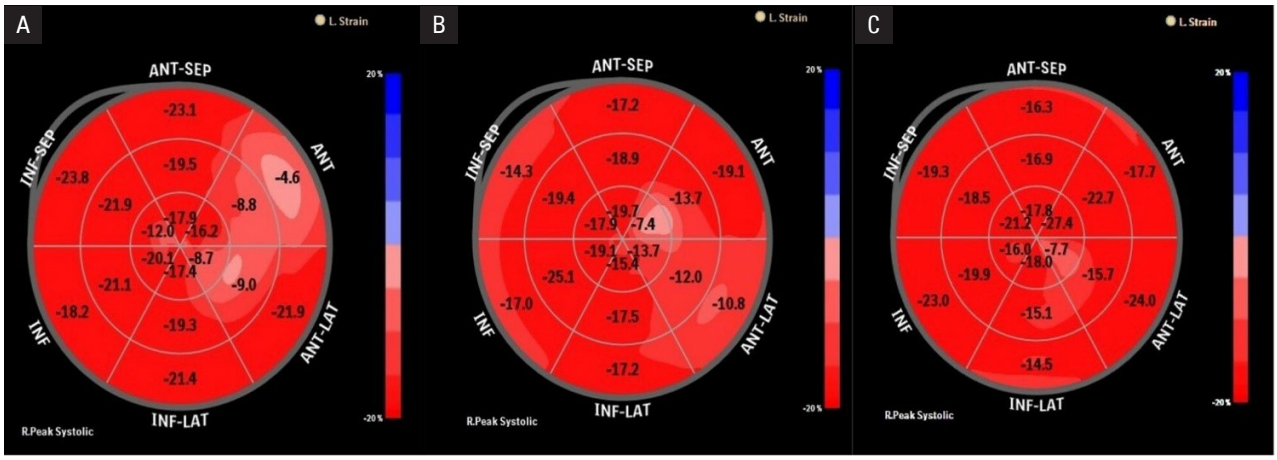

Figure 3. *Examples of the longitudinal strain bull's eye plot derived from 2D speckle tracking imaging in the study population of women with type 1 diabetes mellitus (T1DM).* **A.** *29-year-old female with positive antiperoxidase antibody (T1DM aTPO+) with a 15-year duration of T1DM and Hashimoto's thyroiditis (HT).* **B.** *23-year-old female with positive antiperoxidase antibody (T1DM aTPO+) with an 8-year duration of T1DM and 5 years of HT.* **C.** *31-year-old female with negative antiperoxidase antibody (T1DM aTPO–) with a 16-year duration of T1DM.*

Discussion

On the basis of our knowledge, this is the first report to evaluate echocardiographic parameters in euthyroid women with T1DM in relation to aTPO and other thyroid autoimmunity parameters in such detail. The strength of this study is the use of the STE, which is an accurate and angle-independent technique that allows an objective analysis of myocardial deformation [20]. Importantly, among different types of strain assessment, GLS allows precise evaluation of subendocardial longitudinal fibre damage, which is the most vulnerable and affected even in subclinical disease stages [21]. It has been proven that GLS can be a biomarker of diabetic cardiomyopathy in patients with preserved ejection fraction [22]. Although imaging patterns of LF systolic function using STE provide valuable insight into the characteristics of various cardiomyopathies [23], the current literature does not contain comprehensive data on the typical "bull's eye" pattern in patients with diabetes. Our results suggest that coexistence of aTPO with T1DM was associated with worse strain function specifically in anterior and anterolateral segments, which may be related to the autoimmunity factor. We

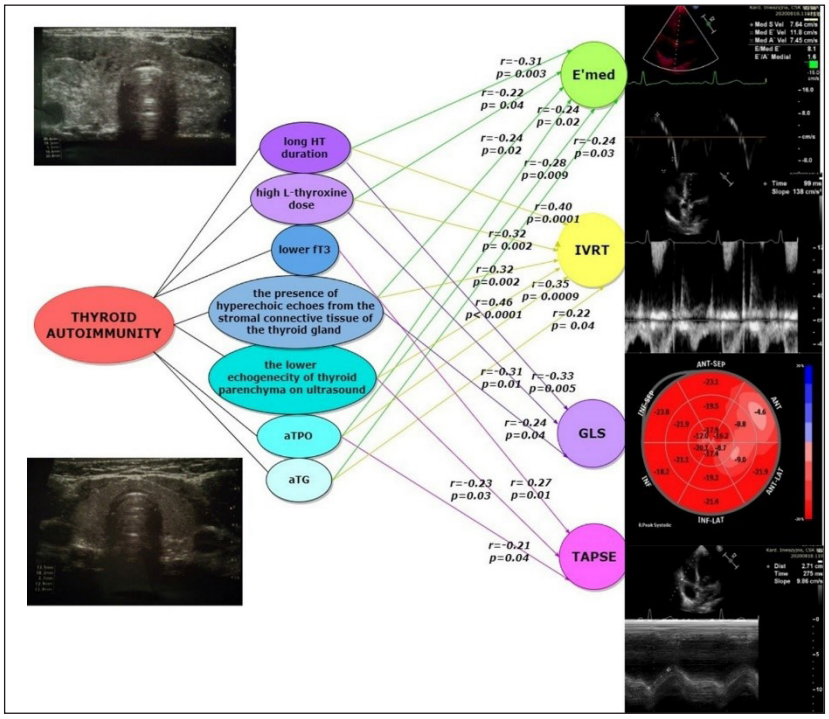

Figure 4. *The correlation analyses between parameters related to thyroid autoimmunity and echocardiographic parameters of diastolic and systolic function. HT — Hashimoto's thyroiditis; aTPO — anti-thyroid peroxidase antibody; aTG — anti-thyroglobulin antibody; E'med — early diastolic velocity of the septal mitral annulus; IVRT — isovolumic relaxation time; GLS — global longitudinal strain; TAPSE — tricuspid annular plane systolic excursion*

Table 4. ***Univariate logistic regression analyses of thyroid risk factors for global longitudinal strain (GLS)***

Dependent variable	Predictors	Odds ratio	95% CI	p value
GLS	HT duration	0.997	0.995–0.999	0.008
	L-thyroxine dose per week	0.814	0.689–0.960	0.013
	Reduced echogenicity on thyroid Ultrasound	0.309	0.120–0.793	0.013

HT — Hashimoto's thyroiditis; CI — confidence interval

are led to this conclusion by the fact that autoimmunity probably participates in the development of cardiac complications in T1DM, and the presence of antithyroid antibodies indicates increased activity of the immune system. The impairment of the function of these segments probably appears in the early development of diabetic cardiac dysfunction. Our results are the first to contribute to the identification of characteristic strain "bull's eye" plot patterns in women with diabetes or coexisting diabetes and aTPO, which may be of great value in early cardiac diagnosis. Nevertheless, studies on a larger group of patients are needed.

We found that Emed' values were significantly lower in the T1DM aTPO+ group as compared with the T1DM aTPO– group and controls, which suggests greater predisposition to diastolic dysfunction [24]. Other parameters suggestive of worse myocardial diastolic function, such as a prolongation of IVRT, a reduction in mitral E velocity, and an increase in E/Emed' ratio, were also present in the T1DM aTPO+ group in comparison with the T1DM aTPO– group, but without statistical significance. In turn, comparing the T1DM aTPO+ group with the control group, a statistical difference was found between 2 parameters reflecting diastolic function (Emed' and IVRT). These findings are consistent with previous results related to diastolic dysfunction at very early stages of diabetes in asymptomatic patients with T1DM [25, 26]. Interestingly, we demonstrated that both Emed' and IVRT were correlated with the presence of antithyroid antibodies (aTPO, aTG), and the features of thyroid autoimmunity on ultrasound, levothyroxine dose, and the duration of HT. Whereas, the most significant effects on GLS were the duration of HT and the severity of HT as reflected by levothyroxine dose and ultrasound features of HT, but not the pres-

ence of antithyroid antibodies. It may be that, already in the early stages of thyroid autoimmunity, there are processes that promote myocardial dysfunction, which develops as the HT disease progresses and includes successively diastolic and systolic dysfunction. In accordance with this assumption, there are recent reports that suggest that hyperglycaemia in T1DM may induce autoimmunity, which leads to the development of long-term CV complications, possibly through inflammatory pathways [27]. In fact, both T1DM and HT exhibit immune dysfunction associated with infiltration of CD4+ cells involved in the stimulation of effector cell cytotoxicity and humoral responses, implying CV complications [28, 29]. This is evidenced by anticardiac antibodies being identified in T1DM patients with cardiac abnormalities, which was not observed in type 2 diabetes [30]. Importantly, cardiac autoantibody production correlated with lymphocytic infiltration and myocardial destruction, inducing the development of HF [31]. Thus, it cannot be excluded that processes resulting from autoimmunity in the thyroid gland, leading to parenchymal destruction and fibrosis, also occur in myocardial tissue. Indeed, in both autoimmune thyroiditis and HF in diabetes, there is increased transforming growth factor-β expression associated with increased fibrotic processes [32, 33]. Our results showed a significant positive correlation between the presence of connective tissue echoes in thyroid on ultrasound and echocardiographic parameters reflecting systolic and diastolic function of LV. The possible mechanisms associated with this relationship are the activation of the inflammatory process and oxidative stress connected with thyroid autoimmunity, which may have a systemic effect [34–36]. Indeed, it has recently been shown that early myocardial dysfunction may be related to sirtuin 1 and interleukin 27, the serum concentrations of which were higher in women with T1DM and HT than in women with T1DM alone and correlated significantly with several echocardiographic parameters [37]. This is a new insight into the development of HF in women with T1DM and needs to be verified in further research.

In addition to the importance of IVRT in the assessment of diastolic function, this parameter also proved to be a good tool for differentiating between types of cardiac remodelling, e.g. concentric cardiac hypertrophy in pressure overload with decreased IVRT and eccentric hypertrophy in LV volume overload with increased IVRT [38]. Interestingly, clinical studies on HF in diabetes mainly describe two phenotypes: a dilated phenotype with eccentric LV remodelling, more frequently observed in T1DM, and a restrictive phenotype with concentric LV remodelling, characteristic of patients with type 2 diabetes [39]. A significantly longer IVRT time was observed in the T1DM aTPO+ and T1DM aTPO– groups compared to controls, supporting the eccentric nature of myocardial hypertrophy. Nevertheless, all our study participants had normal myocardial dimensions and normal EF, showing only discrete differences in echocardiographic parameters. Surprisingly, LVMI and IVSS were lower in patients with T1DM as compared to controls. This may be explained by the fact that the autophagy process is enhanced in T1DM, which may precede cardiomyocyte hypertrophy [40]. In fact, in an animal model of T1DM, heart weights were reduced, and cardiac fibrosis developed in parallel with changes in cardiac diastolic function, although cardiomyocyte size remained unchanged [41]. This observation from preclinical rodent studies could explain our results, although this requires further investigation.

TAPSE reflects the longitudinal function of the right ventricle (RV) and appears to signal early systolic dysfunction and vascular stiffness [42]. In all study groups, TAPSE was within the normal range; however, when comparing groups with T1DM, significant differences were found as compared to the controls. These findings suggest that metabolic disturbances associated with diabetes can influence right ventricular function, which is consistent with previous studies conducted in type 1 [43, 44] and type 2 diabetes [45, 46]. This may be due to systemic effects of glucotoxicity, lipotoxicity, and epigenetic or immunological factors underlying heart failure in diabetes [47]. Although there were no significant TAPSE differences between the T1DM aTPO+ and T1DM aTPO– groups, the correlation analysis showed a significant negative association with aTPO and the presence of reduced echogenicity of the thyroid parenchyma on ultrasound. These findings are coherent with previous results showing impaired RV and LV function in euthyroid HT patients when compared with controls [48–50].

Our study had several limitations. Firstly, data on the presence of microangiopathies were assessed on the basis of medical diagnoses in the history and there was a lack of cardiac autonomic neuropathy assessment; thus, we cannot exclude the possibility of misclassification. Secondly, considering the demonstration of only minor differences between groups in terms of cardiac function, there is the possibility of a chance finding due to the relatively small group of patients. Given that the precise immunological mechanisms linking thyroid autoimmunity and cardiac dysfunction in T1DM women could be used to improve prevention and even to develop sex- and immune-targeted therapies, further exploration on a larger group of patients in this area is critical.

Conclusions

Although our data do not allow us to conclude a direct link between the presence of aTPO and cardiac dysfunction in women with T1DM, they indicate an association of thyroid autoimmunity parameters with several echocardiographic parameters of right and left ventricular diastolic and systolic function. Our results are the first to suggest that the anterior and anterolateral segments are likely to be primarily affected in the early stages of cardiac dysfunction in women with T1DM; although these data need to be confirmed in a larger group of patients, they may have important implications in early cardiac diagnosis.

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Conflict of interests
None of the authors have any potential conflicts of interest associated with this research.

Authors contribution
M.Ł.T. contributed to the conception and design of the study, date collection, researched and analysed the data, and wrote the manuscript. A.P. contributed to the data collection and critical revision of the manuscript, J.Z. contributed to the conception and statistical data analysis and the critical revision of the manuscript. B.M.R., E.F., and L.C. contributed to the conception and design of the study and the critical revision of the manuscript. All approved the final version of the manuscript.

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Ethical approval
The study was approved by the Ethics and Surveillance Committee for Research in Human and Animal Sciences at the Central Clinical Hospital of the Ministry of Internal Affairs (No. 22/2018 of 09.05.2018).

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