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The association of IL-1β, IL-1α, IL-6, and E-selectin with the diastolic dysfunction in patients with type 2 diabetes mellitus and preserved ejection fraction

Povezanost IL-1β, IL-1α, IL-6 i E-selektina sa dijastolnom disfunkcijom kod obolelih od dijabetesa melitusa tipa 2 sa očuvanom ejekcionom frakcijom

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Abstract

Background/Aim. The importance of chronic inflammation, endothelial dysfunction, certain cytokines, and selectins in the development of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVDs) is increasingly evident and supported by evidence. However, the role of chronic inflammation in the development of diastolic dysfunction (DD) in the early stages of cardiomyopathy in T2DM patients is insufficiently studied. The aim of this study was to examine the possible association of interleukin (IL)-1β, IL-1α, IL-6, and E-selectin with DD in T2DM patients with still preserved ejection fraction (EF). **Methods.** The research included a total of 74 subjects divided into two groups: a group with proven T2DM, i.e., diabetes group (DG) (n = 45), and a healthy control group (HCG) (n = 29). Echocardiographic parameters of DD and serum levels of IL-1β, IL-1α, IL-6 and E-selectin were compared between the two groups, and the correlation of echocardiographic parameters of DD and serum biomarkers was examined in both groups. **Results.** Subjects with T2DM had significantly different values of DD parameters compared to HCG but also higher values of IL-6 (19 pg/mL vs. 12 pg/mL, $p = 0.002$), E-selectin (2,036 pg/mL vs. 1,522 pg/mL, $p < 0.001$), and IL-1α (46 pg/mL vs. 37 pg/mL, $p = 0.003$). The majority of subjects who met the echocardiographic criteria of DD were from DG. In subjects with proven DD, significantly higher values of IL-6 (20.5 pg/mL vs. 16 pg/mL, $p = 0.003$) and IL-1β (15.0 pg/mL vs. 11.4 pg/mL, $p = 0.036$) were verified compared to subjects without DD. **Conclusion.** The results of our study indicate the presence of a connection between chronic inflammation and echocardiographic parameters with the onset of DD in the phases of preserved cardiac EF in patients with T2DM.

Key words:
biomarkers; cardiomyopathies; cardiovascular diseases; cytokines; diabetes mellitus, type 2; echocardiography; heart failure.

Apstrakt

Uvod/Cilj. Značaj hronične inflamacije, endotelne disfunkcije, određenih citokina i selektina u razvoju dijabetesa melitusa tipa 2 (DMT2) i kardiovaskularnih bolesti (KVB) je sve očigledniji i potkrepljeniji dokazima. Međutim, uloga hronične inflamacije u razvoju dijastolne disfunkcije (DD) u ranim fazama kardiomiopatije kod obolelih od DMT2 je nedovoljno proučena. Cilj rada bio je da se ispita moguća povezanost interleukina (IL)-1β, IL-1α, IL-6 i E-selektina sa DD kod obolelih od DMT2 kod kojih je ejekciona frakcija (EF) srca još uvek očuvana. **Metode.** Istraživanjem je obuhvaćeno ukupno 74 ispitanika podeljenih u dve grupe: grupu sa dokazanim DMT2, odnosno dijabetes grupu (DG) (n = 45), i kontrolnu grupu (KG) (n = 29) zdravih ispitanika. Upoređivani su ehokardiografski parametri DD i nivoi IL-1β, IL-1α, IL-6 i E-selektina u serumu između dve grupe i ispitana je korelacija ehokardiografskih parametara DD i serumskih biomarkera u obe grupe. **Rezultati.** Kod ispitanika obolelih od DMT2 utvrđene su statistički značajno različite vrednosti parametara DD u poređenju sa KG, ali i više vrednosti IL-6

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(19 pg/mL vs. 12 pg/mL, $p = 0{,}002$), E-selektina (2 036 pg/mL vs. 1 522 pg/mL, $p < 0{,}001$) i IL-1α (46 pg/mL vs. 37 pg/mL, $p = 0{,}003$). Većina ispitanika koji su ispunjavali ehokardiografske kriterijume DD bila je iz DG. Kod ispitanika sa dokazanom DD utvrđene su statistički značajno više vrednosti IL-6 (20,5 pg/mL vs. 16 pg/mL, $p = 0{,}003$) i IL-1β (15,0 pg/mL vs. 11,4 pg/mL, $p = 0.036$) u odnosu na ispitanike bez DD. **Zaključak.** Rezultati našeg istraživanja ukazuju da postoji povezanost hronične upale i ehokardiografskih parametara sa nastankom DD u fazama očuvane srčane EF kod obolelih od DMT2.

Ključne reči:
biomarkeri; kardiomiopatije; kardiovaskularne bolesti; citokini; dijabetes melitus, tip 2; ehokardiografija; srce, insuficijencija.

Introduction

Type 2 diabetes mellitus (T2DM) and numerous cardiovascular diseases (CVDs) majorly contribute to the total morbidity, mortality, the number of hospitalizations, and overall medical costs in healthcare systems worldwide [1]. CVDs are one of the primary causes of death in patients with T2DM [1, 2]. T2DM is a major risk factor for the development of atherosclerosis and CVDs, including coronary artery disease and heart failure (HF) [1–3]. CVDs, stroke, and peripheral vascular disease are the main macrovascular complications of T2DM [4]. The mutual relationship and overall significance of T2DM and CVDs give high priority to better understanding their pathophysiology and correlation. Results of previous epidemiological, genetic, preclinical, and clinical studies pointed to the connection of aberrant inflammatory processes to both the progression from prediabetes to diabetes and the onset of late cardiovascular complications [1–8]. There is growing evidence of the involvement of chronic inflammation and certain pro-inflammatory cytokines in the development of HF in patients with T2DM [9, 10]. T2DM may significantly impact the heart, resulting in the clinical presentation of coronary artery disease or diabetic cardiomyopathy (DCM) [11]. Although different, they may progress to the same condition, clinical HF [12]. At the beginning of a typical metabolic but still specific cardiac muscle dysfunction, known as DCM, there is an early yet very long asymptomatic period designated as the subclinical period of the disease [13, 14]. During that initial phase, structural changes occur gradually leading to its remodeling and consequent diastolic dysfunction (DD) [15]. DD is viewed as an impaired left ventricular (LV) relaxation, with increased LV stiffness at its advanced stages and elevated filling pressures at more advanced ones [16]. Possible further deterioration of DD results in a decrease in relaxation and extensibility of the myocardium, which then leads to an increase in chamber filling pressure even with the smallest increase in volume. Finally, as the disease progresses, signs of LV systolic dysfunction develop, as well as first clinical manifestations. Those are a direct consequence of HF with preserved ejection fraction (EF) – HFpEF. If the disease continues to progress, the following conditions develop: HF with moderately reduced EF (HFmrEF), then HF with reduced EF (HFrEF), dilated LV of the heart, shortened ejection period, and increased ventricular filling pressure [17]. Gradually, pulmonary congestion starts manifesting more strongly as well as the development of a typical clinical picture of the final stage of HF [18].

The importance of pro-inflammatory cytokines, chronic inflammation, and endothelial dysfunction in the development of DD in the early stages of cardiomyopathy in patients with T2DM is not nearly as sufficiently studied. The potential correlation between inflammation and DD is of great significance for the early selection of T2DM patients for the echocardiographic assessment. An echocardiographic exam done during that period allows us to gather important information about LV diastolic function in the absence of valvular, ischemic, or uncontrolled hypertensive disease. Early diagnosis of DCM and intensive therapy in the primary asymptomatic stages of the disease is every clinician's imperative.

The aim of this study was to examine and identify the association of interleukin (IL)-1α, IL-1β, IL-6, and E-selectin with the LV DD in patients with T2DM.

Methods

Study population and design

Our study included a total of 74 participants, categorized into two groups: patients with T2DM, already known or newly diagnosed, i.e., diabetes group (DG) (n = 45), and age- and sex-matched healthy control group (HCG) (n = 29). The participants were selected during their regular visits or as a part of the outpatient clinic systematic examination of the Department of Endocrinology of the Military Medical Academy (MMA), Belgrade, Serbia. All participants were over 18 years of age. Patients' demographic and clinical data were gathered through patient interviews, medical records, blood test results, and echocardiographic examination. None of the participants had valvular or ischemic heart disease or uncontrolled hypertension. In inconsistent situations, the diagnosis of T2DM was defined using a two-hour oral glucose tolerance test according to official recommendations [19]. Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of height (in meters). Systolic blood pressure (BP) > 140 mmHg and diastolic BP > 90 mmHg, treated or not, was considered uncontrolled arterial hypertension. Exclusion criteria were as follows: diagnosed prediabetes, T1DM, ischemic cardiomyopathy, prior myocardial infarction, atrial fibrillation or other severe arrhythmias, LV EF < 50%, existing chronic kidney disease [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2], acute inflammation, malignant or systemic autoimmune diseases, pregnancy,

people older than 70 years. Serum levels of biochemical parameters and inflammatory cytokines were analyzed from the morning venous blood sample: C-reactive protein (CRP) [reference range (RR): 0.0–4.0 mg/L], fibrinogen (RR: 2.1–4.0 g/L), D-dimer [RR: < 0.50 mg/L fibrinogen equivalent units (FEU)], fasting plasma glucose (FPG) (RR: 4.1–5.9 mmol/L), glycosylated hemoglobin (HbA1c) (RR: < 6.0 %), serum triglyceride (TG) (RR: < 1.7 mmol/L), total cholesterol (TC) (RR: < 5.2 mmol/L), low-density lipoprotein (LDL) (RR: < 3.5 mmol/L), high-density lipoprotein (HDL) (RR: > 1.3 mmol/L), IL-1β, IL-1α, IL-6, and E-selectin.

Echocardiography was performed in all included participants, with obtained values of LV EF, lateral wall diameter (LWD), posterior wall diameter (PWD), interventricular septum diameter (IVSD), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and left atrial volume (LAV). We used diagnostic criteria for DD assessment in patients with preserved LV EF mainly based on six parameters: tricuspid regurgitation peak velocity (TRpV), E wave, E/A ratio [the mitral inflow pattern is obtained with the peak of passive filling (E wave) and the peak of active filling (A wave)], septal e′, average E/e′, and left atrial volume index (LAVI). If the patients fulfilled more than two positive criteria (peak E velocity > 50 cm/s with adequate mitral E/A ratio, LAVI > 34 mL/m^2, TRpV > 2.8 m/s, average E/e′ > 14, septal e′ velocity < 7 cm/s), DD was diagnosed. For a more accurate DD assessment, we also measured isovolumic relaxation time (IVRT), a time delay between aortic valve closure and mitral valve opening, and E wave deceleration time (DT). The combination of E/A > 1, enlarged left atrial, IVRT > 100 ms, DT > 200 ms, and abnormal LV intrinsic relaxation (reduced e′) strongly suggests DD [20].

The study was approved by the Ethics Committee of the Faculty of Medicine of the MMA (No. 462-1, from February 02, 2023), and every patient provided a signed consent form.

Data collection

Patient's medical history, anthropometric measurements [waist circumference (WC), body height and weight, BMI], physical examination (BP, heart rate), and blood sampling (after a minimum of 15 minutes of rest) were done at the Department of Endocrinology of MMA. Standard laboratory analyses were measured on the same day at the Institute of Medical Biochemistry, MMA. The cytokine concentrations were measured at the Institute for Medical Research, MMA. A peripheral blood sample was submitted to the Institute for Medical Research MMA immunology laboratory within one hour of sampling, where serum was separated and stored at -70° C until analysis. All collected serum samples were analyzed in the same act. The cytokine concentrations (IL-1α, IL-1β, IL-6, and E-selectin) were measured in the patient's sera using a Premixed Multiplex Kit-Human Custom 10 Plex (N. Orange Grove Ave., Pomona, CA 91767, USA) and by bead-based multiplex immunoassays, performed according to the manufacturer's instructions (flow cytometer Beckman Coulter Navios EX). Detection kits were produced by AimPlex Biosciences, Inc. Echocardiography for the diagnosis of DD was performed at the Clinic for Cardiology, MMA, on a General Electric Vivid 7 PRO Ultrasound System machine.

Statistical analysis

The differences in demographic, clinical characteristics, and laboratory analyses between patients with diabetes and the control group were compared using the Chi-square test for categorical variables, the *t*-test for continuous variables with normal distribution, and the Mann-Whitney *U* test for non-normally distributed variables. Association between variables was tested using Pearson's or Spearman's correlation, where appropriate, according to the normality distribution. Statistical analyses were performed using IBM SPSS Statistics version 25 for Windows (IBM Corporation, Armonk, NY, USA). The level of statistical significance was set at $p < 0.05$.

Results

Basic clinical and biochemical parameters

The average age of the 74 study participants was 50.1 ± 10.5 years, with 60.8% of the study population being male. The mean BMI in the study cohort was 28.5 ± 5.6 kg/m^2. The mean WC was 100.8 ± 18.3 cm. Clinical characteristics of all the included participants were presented within the two given groups, DG and HCG. Patients in DG had significantly higher levels of BMI, WC, systolic BP, diastolic BP, FPG, HbA1c, and serum TG than the HCG patients. There were no significant differences between the two groups for heart rate, TC, HDL, LDL, CRP, fibrinogen, and D-dimer (Table 1).

Cytokines

Median IL-6 levels in DG subjects were significantly higher compared to HCG subjects (19 pg/mL vs. 12 pg/mL, $p = 0.002$), including E-selectin levels (2,036 pg/mL vs. 1,522 pg/mL, $p < 0.001$) and median IL-1α levels (46 pg/mL vs. 37 pg/mL, $p = 0.003$). Comparing serum levels of IL-1β between the groups showed no statistical significance (Table 2).

Echocardiographic parameters

No significant differences in LV EF mean value were shown between the two subject groups. Patients with T2DM had significantly higher LVESD (median: 3.3 mm vs. 3.0 mm, $p = 0.041$), wall thickness (IVSD – median 1.1 cm vs. 0.9 cm, $p < 0.001$; LWD – median: 1.0 cm vs. 0.9 cm, $p < 0.001$; PWD – median: 1.0 cm vs. 0.9 cm, $p < 0.001$), LAV (median: 36 mL vs. 31 mL, $p = 0.004$), A wave (median: 0.77 m/s vs. 0.65 m/s, $p < 0.001$), as well as septal a' (median: 0.10 m/s vs. 0.09 m/s, $p = 0.001$) compared to HCG (Table 3).

Table 1

Baseline subject characteristics of study participants

Parameters	HCG (n = 29)	DG (n = 45)	*p*-value
Body mass index (kg/m^2)	26.5 ± 4.8	29.8 ± 5.8	**0.014**
Waist circumference (cm)	93 (78.6–105.7)	108.5 (96.2–117)	**0.01**
Systolic BP (mmHg)	120 (110–130)	130 (120–140)	**< 0.001**
Diastolic BP (mmHg)	80 (70–85)	85 (80–85)	**0.041**
Heart rate (bpm)	70 (65–85)	75 (65–85)	0.676
C-reactive protein (mg/L)	1.03 (0.40–3.22)	1.13 (0.49–5.10)	0.508
Fibrinogen (g/L)	3.4 ± 0.7	3.7 ± 0.8	0.229
D-dimer (mg/L FEU)	0.31 (0.22–0.41)	0.28 (0.20–0.37)	0.142
Fasting plasma glucose (mmol/L)	4.9 (4.7–5.4)	6.9 (5.9–8.6)	**< 0.001**
HbA1c (%)	5.1 (4.8–5.4)	6.3 (5.7–7.3)	**< 0.001**
Triglyceride (mmol/L)	1.15 (0.81–1.56)	1.78 (1.11–2.62)	**< 0.001**
Total cholesterol (mmol/L)	5.19 ± 0.90	5.32 ± 1.22	0.624
Low-density lipoprotein (mmol/L)	3.02 ± 0.80	3.03 ± 1.02	0.977
High-density lipoprotein (mmol/L)	1.56 ± 0.41	1.40 ± 0.37	0.082

HCG – healthy control group; DG – diabetes group; BP – blood pressure; bpm – beats *per* minute; FEU – fibrinogen equivalent units; HbA1c – glycosylated haemoglobin.
Results are given as mean ± standard deviation or median (interquartile range).
Bold values indicate the significance level of $p < 0.05$.

Table 2

Levels of serum biomarkers in the healthy control group (HCG) and the diabetes group (DG)

Biomarkers	HCG (n = 29)	DG (n = 45)	*p*-value
IL-1ß (pg/mL)	10.3 ± 7.1	13.1 ± 5.5	0.068
IL-6 (pg/mL)	12 (10–18)	19 (14–24)	**0.002**
IL-1α (pg/mL)	37 (16.5–49)	46 (38–57)	**0.003**
E-selectin (pg/mL)	1,522 (1,219–1,970.5)	2,036 (1,766–2,584.5)	**< 0.001**

IL – interleukin. Results are given as mean ± standard deviation or median (interquartile range).
Bold values indicate the significance level of $p < 0.05$.

Table 3

Echocardiographic characteristics of study participants

Parameters	HCG (n = 29)	DG (n = 45)	*p*-value
LVEF (%)	67 (61–70)	64 (61–66)	0.138
LVEDD (mm)	5.0 ± 0.5	5.1 ± 0.4	0.199
LVESD (mm)	3.0 (2.8–3.3)	3.3 (3.1–3.5)	**0.041**
IVSD (cm)	0.9 (0.9–1.1)	1.1 (1.0–1.1)	**< 0.001**
LWD (cm)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	**< 0.001**
PWD (cm)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	**< 0.001**
E wave (m/s)	0.77 (0.59–0.84)	0.70 (0.61–0.81)	0.626
A wave (m/s)	0.65 (0.56–0.66)	0.77 (0.66–0.89)	**< 0.001**
E/A ratio	1.24 (0.92–1.49)	0.84 (0.72–1.15)	**< 0.001**
Septal e′ (m/s)	0.10 (0.07–0.11)	0.07 (0.06–0.09)	**< 0.001**
Septal a′ (m/s)	0.09 (0.08–0.09)	0.10 (0.09–0.11)	**0.001**
E/e′ ratio	8.2 ± 1.4	9.6 ± 1.7	**0.001**
LAVI	16.5 ± 3.0	18.7 ± 3.9	**0.014**
LAV (mL)	31 (27–37)	36 (32–42.25)	**0.004**
DT (m/s)	200.2 ± 47.6	223.8 ± 40.9	**0.030**
IVRT (ms)	91.1 ± 12.9	100.8 ± 15.0	**0.007**
TRpV (m/s)	2.58 ± 0.25	2.62 ± 0.26	**0.024**

HCG – healthy control group; DG – diabetes group; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; IVSD – interventricular septum diameter; LWD – lateral wall diameter; PWD – posterior wall diameter; LAVI – left atrial volume indexed; LAV – left atrial volumen; DT – deceleration time; IVRT – isovolumic relaxation time; TRpV – tricuspid regurgitation peak velocity.

Results are given as mean ± standard deviation or median (interquartile range).

Bold values indicate the significance level of $p < 0.05$.

Patients with diabetes had significantly higher levels of DD parameters: E/e′ ratio (mean: 9.6 vs. 8.2, $p = 0.001$), LAVI (mean: 18.7 vs. 16.5, $p = 0.014$), IVRT (mean: 100.8 ms vs. 91.1 ms, $p = 0.007$), TRpV (mean: 2.62 m/s vs. 2.58 m/s, $p = 0.024$), and DT (mean 223.8 m/s vs. 200.2 m/s, $p = 0.030$), compared to HCG. However, levels of E/A ratio (median: 0.84 vs. 1.24, $p < 0.001$) and septal e′ (median: 0.07 m/s vs. 0.10 m/s, $p < 0.001$) were significantly lower in patients with diabetes (Table 3).

Correlation between echocardiographic parameters and pro-inflammatory cytokines

There was no significant correlation between analyzed cytokines and diastolic function parameters in HCG. However, some significant correlations were revealed between E-selectin and septal a′ ($p = 0.014$), E-selectin and A wave ($p = 0.041$), and IL-1α and septal a′ ($p = 0.028$) (Table 4).

When talking about the parameters essential for the assessment of DD in DG, there was a statistically significant positive correlation between IL-6 level and E/e′ ratio (r = 0.424, $p = 0.028$), IL-6 and LAVI (r = 0.248, $p = 0.037$), IL-1β and E/e′ ratio (r = 0.265, $p = 0.026$), and between IL-1α and LAVI (r = 0.241, $p = 0.043$). There was also a significant negative correlation between IL-6 level and E/A ratio (r = -0.281, $p = 0.018$), E-selectin and E/A ratio (r = -0.245, $p = 0.040$), and IL-6 and septal e′ (r = -0.301, $p = 0.011$) (Table 4).

There was a statistically significant positive correlation between IL-6 and LVEDD ($p = 0.004$), IL-6 and LVESD ($p < 0.001$), and IL-6 and wall thickness [IVSD ($p = 0.006$), LWD ($p = 0.010$), PWD ($p = 0.007$)]. A significant positive correlation was found between IL-1α and septal a′ ($p = 0.003$) and between IL-1α and wall thickness [LWD ($p = 0.049$), PWD ($p = 0.041$)] as well. Moreover, there is a significant positive correlation between E-selectin and septal a′ ($p < 0.001$) and between E-selectin and wall thickness [IVSD ($p = 0.039$), LWD ($p = 0.013$), PWD ($p = 0.006$)]. There was a significant negative correlation between IL-6 level and LV EF ($p < 0.001$) (Table 4).

In the exploratory analysis, out of 16 patients with echocardiographic signs of DD, 14 were from DG and only 2 were from HCG. Those participants with LVDD [16 (21.6%)] had significantly higher IL-6 (median: 20.5 vs. 16 pg/mL, $p = 0.003$) and IL-1β (mean: 15.0 vs. 11.4 pg/mL, $p = 0.036$) compared to the ones with normal diastolic function [58 (78.4%)] (Table 5). There was no statistically significant difference in E-selectin and IL-1α between DG and HCG.

Table 4

Correlation coefficients between inflammatory markers and echocardiographic parameters between the healthy control group (HCG) and the diabetes group (DG)

Parameters	HCG (n = 29) / DG (n = 45)			
	IL-β	IL-6	IL-1α	E-selectin
LVEF	-0.130/0.218	-0.354/-0.433*	-0.191/-0.183	-0.124/-0.33
LVEDD	-0.104/0.027	0.341/0.355*	0.098/0.130	0.020/0.103
LVESD	-0.011/0.227	0.348/0.453*	0.093/0.196	0.033/0.105
IVSD	-0.137/0.059	0.026/0.324*	0.142/0.232	-0.055/0.245*
LWD	-0.059/0.001	0.226/0.302*	0.303/0.235*	0.054/0.293*
PWD	-0.089/-0.011	0.250/0.318*	0.313/0.243*	0.107/0.322*
E/A ratio	0.211/-0.075	0.103/-0.281*	-0.170/-0.152	-0.158/-0.245*
DT	0.024/0.018	-0.015/0.177	0.190/0.068	-0.093/-0.020
E/e′ ratio	0.146/0.265*	0.031/0.424*	0.071/0.151	-0.141/0.171
LAV	-0.094/0.119	0.022/0.069	0.101/-0.012	0.018/-0.203
IVRT	-0.131/0.065	0.011/0.158	0.168/0.066	0.145/0.131
LAVI	-0.027/0.160	0.170/0.248*	0.225/0.241*	0.110/0.031
Septal e′	0.118/-0.184	0.091/-0.301*	-0.096/-0.115	0.046/-0.100
Septal a′	0.128/0.068	0.167/0.271	0.424*/0.343*	0.468*/0.433*
E wave	0.069/-0.141	-0.040/-0.209	-0.214/0.160	-0.008/0.256
A wave	-0.012/0.084	0.141/0.131	0.206/-0.030	0.382*/0.229
TRpV	0.068/0.100	-0.204/-0.187	-0.138/-0.202	0.040/-0.188

For abbreviations, see Tables 2 and 3.
Units of measurement of all presented parameters are given in Tables 2 and 3. *$p < 0.05$.

Table 5

Levels of serum biomarkers in participants with and without diastolic dysfunction (DD)

Biomarkers	Without DD (n = 58)	With DD (n = 16)	Values
IL-1β (pg/mL)	11.4 ± 6.0	15.0 ± 5.9	t = -2.135, **p = 0.036**
IL-6 (pg/mL)	16 (11–19.5)	20.5 (15.0–33.5)	U = 239.5, **p = 0.003**
IL-1α (pg/mL)	40.9 ± 15.0	47.9 ± 14.4	t = -1.757, p = 0.083
E-selectin (pg/mL)	1,929 (1,507–2,331)	1,766 (1,541.5–2,599.5)	U = 456.5, p = 0.922

IL – interleukin.
Results are given as mean ± standard deviation or median (interquartile range).
Bold values indicate the significance level of $p < 0.05$.

Discussion

The connection between T2DM, chronic inflammation, and cardiomyopathy has been known for many decades. Some pro-inflammatory cytokines, chemokines, selectins, and specific adhesive molecules were exceedingly discussed among scientific and professional circles as likely significant. They were studied as potential diagnostic and prognostic markers or even therapeutic targets. It is a common fact that low-grade chronic inflammation precedes T2DM and that the immune system is connected to every single stage of its development in various ways [21–23]. It is known that chronic hyperglycemia with hyperinsulinism, as a main characteristic of these disorders, is followed by changes in serum levels of different cytokines [5]. Additionally, inflammation is implicated in the process of remodeling myocardium with consequent HF in patients with T2DM [11, 24–31]. The estimated prevalence of DCM in the diabetic population is approximately 16.9% [32]. Nowadays, DCM is defined as a specific cardio-muscular dysfunction in patients with T2DM, characterized by the development of myocardial interstitial fibrosis, cardiomyocyte hypertrophy, and apoptosis, occurring independently of arterial hypertension, coronary artery disease, valvular heart disease, and other structural ones [33]. The subclinical period of the disease is long and asymptomatic, and it is characterized by the presence of LV DD, a precursor of systolic HF in DCM [25–28]. Evaluation of systolic function is usually implied in cardiac mechanics, but DD has proven to be its essential element [34]. Over the past decades, inflammation stood out as one of the principal features in the pathogenesis of systolic heart disease [9, 11, 29]. However, there has not been much data on the role of inflammation in the development of DD.

Our results showed a significant difference among many parameters (anthropometric, biochemical, and echosonographic) and the monitored cytokines and selectin between DG and HCG. Patients with T2DM had higher BMI, WC, BP values, morning glycemia, HbA1c, and TG, which is in accordance with previous research [35–37]. They are considered a manifestation of a poorly led lifestyle and depict not only the consequences of T2DM but also its causes. Moreover, many studies indicate that similar differences in the mentioned parameters were noticed much earlier, even in the prediabetes stage [22, 35, 36, 38]. Our examination also revealed that DG had significantly higher levels of IL-6, IL-1α, and E-selectin than HCG. Such results unequivocally indicate the importance of the pro-inflammatory factor in the development of T2DM and are partially in agreement with earlier research [5, 9, 36, 39]. IL-6 is a pro-inflammatory cytokine produced by numerous cells such as activated leukocytes, macrophages, monocytes, endothelial cells, vascular smooth muscle cells, fibroblasts, and adipocytes [30, 39]. Statistically higher values of IL-6 in DG in our study are in agreement with many known results [40–44]. This cytokine was proved to incite hyperglycemia and compensatory hyperinsulinemia in murine models and humans [40]. Spranger et al. [41] noted that the IL-6 plasma levels are associated with the development of T2DM. In a study published in 2019, the authors suggested a connection between HbA1c and serum levels of IL-6 in patients with T2DM [42]. Tuttolomondo et al. [43] explained the positive correlation between IL-6 and vascular complications of T2DM. Direct connection was found among IL-6, IL-1β, HbA1c, and FPG [44].

In our research, the IL-1α values were significantly higher in DG than HCG ($p = 0.003$), with IL-1β showing a trend towards higher values ($p = 0.068$). Similar results were obtained in previously published data [45–51]. The IL-1 family of cytokines is primarily connected to innate immunity and contains pro-inflammatory components but also has elements that antagonize and regulate inflammation [45, 46]. Innate immunity is manifested by inflammation, which functions as a host defense mechanism but can also be detrimental to survival if uncontrolled. There is also evidence proving the key role of the innate system in the process of destroying pancreatic β-cells and impaired insulin secretion [47, 48]. There is a small number of studies that have dealt with the correlation between IL-1α and T2DM. Physiologically, IL-1α is expressed in epithelial and mesenchymal cells (including cardiomyocytes) and is released upon injury or cell death. When released from necrotic cells, IL-1α triggers a large amount of inflammatory reactions [49]. On the other hand, even though IL-1β is the most researched member of the IL-1 family, the results of the studies that dealt with its connection with T2DM were very inconsistent [45]. A meta-analysis from 2022 showed that patients with T2DM have non-significantly higher values of IL-1β than healthy controls, thus excluding this cytokine as a significant T2DM marker [50]. A recent meta-analysis from 2024 stated a clear connection between elevated levels of IL-6 and IL-1β with T2DM and its complications [51].

There is a lack of evidence confirming that elevated E-selectin values accelerate T2DM. Increased levels of E-selectin have been previously associated with insulin resistance and hyperinsulinemia [52]. Previous studies claimed that E-selectin and other specific adhesion molecules had been connected to microvascular complications of T2DM as markers of endothelial dysfunction [53, 54]. Furthermore, higher E-selectin values in circulation had been interpreted as early markers of the forthcoming microvascular (neuropathic and retinopathic) T2DM complications [36, 55]. Ekelund et al. [56] indicated that the levels of E-selectin may serve as a predictive biomarker for the development of diabetic retinopathy in patients with T2DM.

The prevalence of HF in diabetic patients is very high (~30%) [57]. It is also the main cause of hospitalization and an important predictor of increased mortality [58]. The results of our study, observing only echocardiographic parameters, are all in agreement with the listed epidemiological data [57, 58]. Echocardiographic parameters, such as wall thickness (IVSD, LWD, PWD), LVESD, LAV, A wave, and septal a′, had statistically higher values in DG patients. Usually, the four phases of diastole include isovolumic relaxation, rapid filling (E wave), slow filling (diastasis), and active filling (A wave) [20]. The main pathophysiological consequence of advanced DD is elevated filling pres-

sure [59]. In our study, values of almost every followed DD parameter had a statistically significant difference between the followed groups. TRpV, E/e′ ratio, LAVI, IVRT, and DT were significantly higher in DG, while E/A ratio and septal e′ had much lower levels compared to HCG. Since all patients had preserved LV EF, it is important to underline that the majority of subjects with DD were from DG. However, when interpreting these results, apart from the existence of T2DM, we must take into account the fact that the subjects had higher BMI and WC, higher BP values, and TG.

The results of our study indicate several significant correlations between the analyzed biomarkers and many myocardial indices in DG, which were not detected in the HCG. The correlations between the monitored cytokines and echosonographic parameters of DD strongly point out the important role of inflammation in the process of DCM formation (positive correlations: between IL-6 and LAVI, IL-6 and E/e′ ratio, IL-1β and E/e′ ratio, IL-1α and LAVI; negative correlations: between IL-6 and E/A ratio, IL-6 and septal e′, E-selectin and E/A).

A very strong correlation between the IL-6 values and the DD parameters in DG is not surprising. IL-6 is a significant cytokine with an important role in numerous heart diseases and a spectrum of functions [2]. Some authors pointed out a connection between IL-6 and many myocardial indices [PWD, IVSD, left ventricle mass (LVM), LVM index (LVMI), relative wall thickness (RWT), and LVEDD] [9]. What might have served as a predictive marker for HF were higher IL-6 levels associated with reduced systolic function in apparently healthy individuals [60]. By infusing IL-6 in rats, both DD and clinically consequential HFpEF can be induced [61]. According to the observations, HFpEF patients have a higher circulating IL-6 level compared with the ones with asymptomatic hypertension, and patients with HF have a higher IL-6 level compared with the healthy [62, 63]. Circulating IL-6 levels were connected to the escalating severity of congestive HF [63]. In their study, Toczylowski et al. [64] reported a connection between the high level of IL-6 with LV hypertrophy and systolic dysfunction. In patients with acute HF, higher IL-6 levels were detected at 30 days. Such values were connected to all-cause mortality at 48–72 hrs [65]. Physical exercise has been noticed to reduce IL-6 and improve overall function in patients with HF [66]. The signal transducing receptor subunit glycoprotein 130 (gp130) levels for IL-6 have been connected to total, cardiovascular, and HF-induced mortality [67]. There is a positive correlation between IL-6 and systolic and diastolic functions of the heart, which increase the functional and structural morbidity of the cardiac muscles, according to Zhuravlyova and Sokolnikova [68].

We also detected a positive correlation between IL-1β and E/e' ratio and between IL-1α and LAVI, as well as a negative correlation between E-selectin and E/A in DG patients. IL-1α and IL-1β are primarily pro-inflammatory cytokines and are dominantly involved in the pathophysiology of heart diseases [69, 70]. IL-1β is one of the most studied cytokines as a possible therapeutic target for a number of heart diseases. However, IL-1β levels are in general affected by many factors such as age or BMI, but also many genetic, hormonal, and environmental ones [50]. The results of the study of the IL-1 receptor blocker (anakinra) effect on the heart are significant. A study on animal models found that IL-1 receptor blockade after myocardial infarction prevents deterioration of systolic and diastolic function [71]. In D-HART Pilot Study, a two-week anakinra treatment was used on patients with stable HFpEF and proved systematic inflammation. The treatment resulted in statistically significant reduction in sistematic inflammation and an increase in aerobic exercise tolerance [72]. In the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), using canakinumab (the anti-IL-1β monoclonal antibody) caused a decrease of 15% in mortality risk [73], as well as a decrease in the percentage of HF-related hospitalization [74].

Conclusion

The results of our study can be summarized by highlighting the following four facts. The values of IL-6, E-selectin, and IL-1α, as well as the echocardiographic parameters of DD, were statistically significantly higher in participants with T2DM. The absolute majority of participants who met the criteria for DD were from diabetes group. A correlation was detected between the monitored cytokine and selectin values and the parameters of DD in diabetes group, as well as the absence of such correlation in the healthy control group. Statistically significantly higher IL-6 and IL-1β levels have been detected in participants with proven DD.

This information suggests a mutual relationship between heart diastolic function disorders and chronic inflammation in individuals with T2DM and normal left ventricular systolic function. There is a clear possibility of using the elevated values of certain cytokines or selectins as non-invasive tests in the early selection of patients with T2DM for echocardiographic examination. Further clinical and experimental research is necessary to fully explain the relationship between DD and inflammation in patients with T2DM, but also the pro- and anti-inflammatory role of cytokines in the earliest stages of the disease and their interaction with metabolic and immune elements.

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