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(Citation)

International Journal of Cardiovascular Imaging, 38(9):1991-1998

(Issue Date)

2022-09-01

(Resource Type)

journal article

(Version)

Accepted Manuscript

(Rights)

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(URL)

<https://hdl.handle.net/20.500.14094/0100476441>



Association between diabetic nephropathy and left ventricular longitudinal myocardial function in type 1 diabetes mellitus patients with preserved ejection fraction

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Abstract

Purpose: Left ventricular (LV) longitudinal myocardial dysfunction can be observed even in type 2 diabetes mellitus (DM) (T2DM) patients with preserved LV ejection fraction (LVEF), and is considered the earliest marker of DM-related cardiac dysfunction. Furthermore, diabetic nephropathy (DN), a common complication in DM, is strongly associated with LV longitudinal myocardial function in T2DM patients, but its association with type 1 DM (T1DM) has not been fully investigated.

Methods: We studied 125 asymptomatic T1DM patients with preserved LVEF, and 75 age-, gender-, LVEF-matched non-diabetic healthy controls. Two-dimensional speckle-tracking strain LV was used to assess longitudinal myocardial function as global longitudinal strain (GLS).

Results: GLS of T1DM patients was significantly lower than that of normal controls ($19.7 \pm 3.6\%$ vs. $20.6 \pm 1.8\%$, $P=0.049$). GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN ($17.3 \pm 3.7\%$ vs. $20.2 \pm 3.5\%$, $P<0.001$), but that of T1DM patients without DN was similar compared to normal controls ($20.6 \pm 1.8\%$ vs. $20.2 \pm 3.5\%$, $P=0.37$). Moreover, multiple regression analysis identified DN the independent determinant parameters for GLS of T1DM patients also correlated significantly with duration of T1DM.

Conclusions: Impaired LV longitudinal myocardial function was observed in asymptomatic T1DM patients with preserved LVEF, and DN was associated with LV longitudinal myocardial dysfunction. These findings are clinically useful for better management of T1DM patients to prevent impending development of cardiovascular disease.

Keywords: Type 1 diabetes mellitus; LV longitudinal myocardial dysfunction; global longitudinal strain; diabetic nephropathy; echocardiography

Introduction

It is well known that diabetes mellitus (DM) is an important risk factor for Stage A heart failure (HF). The association of DM with HF is the result of structural, metabolic, and functional impairment. Hyperglycemia may cause left ventricular (LV) structural alterations, including microvascular remodeling and LV myocardial fibrosis, a finding hypothesized to be secondary to the accumulation of advanced glycation end products [1]. Identification of high-risk patients among Stage A HF patients is therefore important because of possible eventual progression to overt HF such as Stages B, C and D HF as well as Stage B HF. LV longitudinal myocardial dysfunction was already observed even in DM patients with preserved LV ejection fraction (LVEF) without overt coronary artery stenosis or HF, and this subclinical LV dysfunction is considered the first marker of a preclinical form of DM-related cardiac dysfunction in DM patients [2-6]. The DM-related major microvascular diseases, such as neuropathy, retinopathy, or nephropathy, have been found to be associated with a higher risk of developing HF [7-9], with diabetic nephropathy (DN) being the most common manifestation of microvascular involvement [9, 10]. Moreover, DM patients with DN are at high risk of developing cardiovascular complications, which are the leading cause of death for DM patients undergoing hemodialysis [11]. Investigations into the association of DM with HF have mostly focused on type 2 DM (T2DM) patients, although type 1 DM (T1DM) has also been found to be associated with HF incidence rates compared to those of a 10-year-older background population, with a 6- to 12-fold increase in the risk of death due to cardiovascular [12, 13]. However, details of LV longitudinal myocardial function in T1DM patients with preserved LVEF and its association with DN remain unclear. The purpose of this study was therefore to investigate LV longitudinal myocardial function in asymptomatic T1DM patients with preserved LVEF in comparison with age-, gender- and LVEF-matched non-diabetic healthy volunteers. We also investigated the association between DN and LV longitudinal myocardial function in such patients.

Materials and Methods

Study population

A total of 125 asymptomatic T1DM patients with preserved LVEF ($\text{all} \geq 55\%$) and without overt HF, who were admitted to Kobe University Hospital between September 2013 and November 2019, were retrospectively studied. Their mean age was 46 ± 19 years, 36 patients (29%) were men, and their mean LVEF was $66\% \pm 5\%$ ($\text{all} \geq 55\%$). All enrolled patients underwent an exercise stress screening test, such as a treadmill exercise or a stress myocardial perfusion scintigraphy, during hospitalization, and patients with an ischemic response were excluded. The preliminary exclusion criteria were: (1) history of coronary artery disease; (2) previous history of open-heart surgery or congenital heart disease; (3) uncontrolled hypertension with blood pressure $> 180/100$ mmHg; (4) more than moderate valvular heart disease; and (5) atrial fibrillation. The diagnosis of T1DM was based on World Health Organization criteria [14]. For comparison, a control group including 75 age-, sex-, and LVEF-matched normal subjects were randomly chosen from our database by observers who were not involved in echocardiographic analysis. All normal subjects did not have any history of either T1DM or T2DM, or of cardiovascular disease. DN was defined as albuminuria at least ≥ 30 mg/day (but glomerular filtration rate > 30 mL/min/1.73 m²) [15]. This study was approved by the local ethics committee of our institution (No. B210244) and was conducted in accordance with the Declaration of Helsinki.

Standard echocardiographic examination

All T1DM patients and normal controls underwent transthoracic echocardiography, and echocardiographic data were obtained with a commercially available echocardiographic system. Digital routine grayscale two-dimensional cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from standard parasternal and apical views. The sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging [16].

Speckle-tracking strain analysis

Speckle-tracking strain analysis was performed for each patient with the aid of a single dedicated software to evaluate LV longitudinal function, which was measured by means of GLS (AutoSTRAIN; TOMTEC-ARENA, TOMTEC Imaging Systems GmbH, Munich, Germany). Briefly, apical 4-, 2- and long-axis views, obtained as Digital Imaging and Communications in Medicine (DICOM) formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated by means of an automated contouring detection algorithm, and manual adjustments of regions of interest were performed if necessary. Longitudinal strain results were visualized as color-coded in individual clips and combined in a bull's eye plot. GLS was then determined as the averaged peak longitudinal strain of 18 LV segments, and, in accordance with current guidelines, was expressed as an absolute value [16].

Statistical analysis

Continuous variables were expressed as mean values with standard deviation for normally distributed data and as median values with interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared using Student's t-test or the Mann-Whitney U test, as appropriate. Proportional differences were evaluated using Fisher's exact test. Independent associations of GLS with clinical and echocardiographic parameters in T1DM patients were evaluated by means of multiple regression analysis. For all steps, a P-value<0.05 was considered statistically significant. All analyses were performed using commercially available software (MedCalc, version 19.6; MedCalc Software, Mariakerke, Belgium).

Results

Comparison of baseline characteristics of patients with T1DM and normal controls

The baseline clinical and echocardiographic characteristics of the 125 patients with T1DM

and 75 normal controls are summarized in Table 1. Clinical data showed that patients with T1DM were more likely to have a higher prevalence of dyslipidemia (26.4% vs. 9.3%, $P<0.05$), while echocardiographic data showed that patients with T1DM were more likely to have a larger E/e' (9.6 ± 3.9 vs. 7.2 ± 3.7 , $P<0.001$) and lower e' (8.6 ± 3.3 cm/s vs. 10.0 ± 3.0 cm/s, $P=0.005$) compared to normal controls.

Comparison of GLS of patients with T1DM and normal controls

GLS of T1DM patients was significantly lower than that of normal controls ($19.7 \pm 3.6\%$ vs. $20.6 \pm 1.8\%$, $P=0.049$; Figure 1). In addition, GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN ($17.3 \pm 3.7\%$ vs. $20.2 \pm 3.5\%$, $P<0.001$), but GLS of T1DM patients without DN was similar compared to that of normal controls ($20.6 \pm 1.8\%$ vs. $20.2 \pm 3.5\%$, $P=0.37$) as shown in Figure 2. GLS in T1DM patients also correlated significantly with duration of T1DM ($r=0.33$, $P<0.001$; Figure 3).

Comparison of baseline characteristics of T1DM patients with and without DN

The baseline clinical and echocardiographic characteristics of the T1DM patients with and without DN are summarized in Table 2. Clinical data showed that T1DM patients with DN were more likely to have a longer duration of DM (21.7 years vs. 10.9 years, $P<0.001$), lower estimated glomerular filtration rate (60.8 ± 42.9 mL/min/1.73 m² vs. 91.0 ± 25.9 mL/min/1.73 m², $P<0.001$), a higher prevalence of hypertension (47.6% vs. 14.4%, $P<0.001$) and a higher prevalence of prescription of calcium channel blockers (38.1% vs. 13.0%, $P=0.007$), while echocardiographic data showed that T1DM patients with DN were more likely to have LV hypertrophy (LV septal wall: 9.3 ± 2.2 mm vs. 7.5 ± 1.8 mm, $P<0.001$; LV posterior wall: 9.8 ± 2.1 mm vs. 8.0 ± 1.7 mm, $P<0.001$; LV mass index: 30.8 ± 9.9 g/m² vs. 25.6 ± 9.0 g/m², $P<0.001$), and have a lower E/A (1.1 ± 0.6 vs. 1.5 ± 0.7 , $P=0.049$), lower e' (6.8 ± 2.8 cm/s vs. 9.0 ± 3.3 cm/s, $P=0.006$), and higher E/e' (11.9 ± 2.4 vs. 9.1 ± 3.6 , $P=0.002$).

Association of DN with GLS for T1DM patients

The multiple regression analysis for the association of GLS with clinical and echocardiographic parameters for T1DM patients is shown in Table 3. It was noteworthy that DN was an independent determinant parameter for GLS as well as age, duration of T1DM, dyslipidemia, LVEF and e'.

Figure 4 shows the representative cases of polar plot longitudinal strain mapping for a normal control, a T1DM patient without DN and that with DN.

Discussion

This study found that GLS of asymptomatic T1DM patients with preserved LVEF was significantly lower than that of age-, gender- and LVEF-matched non-diabetic normal controls, and GLS of T1DM patients correlated significantly with duration of T1DM. Furthermore, GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN, but GLS of T1DM patients without DN was similar compared to that of normal controls. DN was also independently associated with GLS of T1DM patients as determined with multivariate regression analysis.

LV longitudinal myocardial function in T1DM patients

Although the survival of HF has improved, the mortality remains as low as roughly 50% within 5 years from diagnosis [17]. A population cohort study showed that 5-year survival rates for Stages A, B, C, and D HF were 97%, 96%, 75%, and 20%, respectively [18]. Screening for comorbid diseases should pay closer attention because of the growing interest in addressing Stage A HF as the best means of preventing eventual progression to overt HF such as Stages B, C and D. Previous prospective epidemiologic studies have identified risk factors and risk markers for HF development, while identification of individuals with Stage A HF can be potentially useful for the implementation of the prevention strategies for HF. Thus, patients with Stage A HF at high risk of developing HF should be screened using serial non-invasive assessment for detection of the onset of structural LV dysfunction such as seen in Stage B HF. LV longitudinal myocardial dysfunction assessed as low GLS

alters in patients with Stage A HF and can be an early marker of LV myocardial dysfunction, and therefore may indicate possible progression to cardiovascular morbidity and mortality [19].

It is well known that diabetes mellitus (DM) is an important risk factor for Stage A heart failure (HF). DM control is an important as a predictor of the new onset of HF, with every 1% increase in HbA1c and an 8%-19% increase in HF incidence [20, 21]. T2DM is also a major cause of HF with preserved LVEF (HFpEF) as well as hypertension, and HFpEF is usually presenting as LV diastolic dysfunction. Previous investigators have shown that LV longitudinal myocardial dysfunction, rather than LV diastolic dysfunction, is considered the first marker of DM-related LV dysfunction in T2DM patients with preserved LVEF without overt HF [2-5]. Ernande et al. showed that LV longitudinal myocardial dysfunction of GLS<18% was observed even in T2DM patients with preserved LVEF and normal LV diastolic function [2]. The presence of LV longitudinal myocardial dysfunction in T2DM patients with preserved LVEF is well known, whereas, that in T1DM patients with preserved LVEF has not yet been fully investigated. Zairi et al. identified GLS in T1DM patients with a mean age of 11.2 years (5-15 years), and showed that their preserved LVEF was significantly lower than that of age-, gender-, and LVEF-matched healthy children [22]. Our study showed GLS of asymptomatic T1DM patients with preserved LVEF was significantly lower than that of age-, gender- and LVEF-matched non-diabetic normal controls, and GLS of T1DM patients correlated significantly with duration of T1DM.

Impact of DN on LV longitudinal myocardial function of T1DM patients

The major contributor to morbidity and mortality in both T1DM and T2DM is related to direct or indirect effects of hyperglycemia on the vascular system. The major DM-related microvascular disease in both T1DM and T2DM patients is commonly recognized as the presence of neuropathy, retinopathy, or nephropathy, and such DM-related microvascular complications are associated with a higher risk of developing HF [7, 8]. Furthermore, a DM-related microvascular disease is related to a worse quality of life of DM patients with HFpEF than of those with HFrEF [9]. Thus, these

microvascular complications can be an important screening marker for cardiac evaluation. Among major DM-related microvascular diseases, DN is the most common manifestation of microvascular involvement [9, 10]. Moreover, DM patients with DN are at high risk of developing cardiovascular complications, which are the leading cause of death for diabetic patients undergoing hemodialysis [11]. DM patients with DN show a high incidence of cardiovascular disease because of abnormal glucose metabolism, insulin resistance, vascular endothelial damage, and toxin accumulation in the body [23]. Ronco et al. reported that cardiac damage, especially LV diastolic dysfunction, occurs earlier in DM patients with DN [24]. Our group previously found that DN was independently associated with GLS in 144 asymptomatic DM patients (104 T2DM patients and 40 T1DM patients) with preserved LVEF [4].

Previous studies regarding the effect of DN on LV function in DM patients mostly focused on T2DM patients so that the impact of DN on LV longitudinal myocardial function of T1DM patients with preserved LVEF remains unclear. Some investigators demonstrated that the presence of albuminuria is a major risk factor for the development of heart disease in T1DM patients, and that such presence is associated with increased mortality [25-27]. Jansen et al. reported that GLS of T1DM patients was significantly lower than that of healthy control subjects [10]. They also showed that GLS of T1DM patients with normoalbuminuria was significantly higher than that of T1DM patients with albuminuria, but that their GLS was similar to that of healthy controls. Unlike our study, this study by Jansen et al. included T1DM patients with reduced LVEF of <50%, which was significantly lower than that of healthy controls. We showed GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN, but that GLS of T1DM patients without DN was similar to that of normal controls. Our study used asymptomatic T1DM patients with preserved LVEF and age-, gender, LVEF-matched non-diabetic healthy controls. Moreover, multivariate regression analysis showed DN was independently associated with GLS of T1DM patients.

Clinical implications

The identification of high-risk Stage A HF patients is potentially useful for the implementation of HF prevention strategies. Low GLS can be an early marker of subclinical LV dysfunction in patients, and may indicate cardiovascular morbidity and mortality. Since we showed that asymptomatic T1DM patients with preserved LVEF showed lower GLS, and those with DN much lower GLS, the optimal management of asymptomatic T1DM patients with preserved LVEF may require the inclusion of screening for microvascular complications for the detection of subclinical LV dysfunction and prevention of development of HF in the future. Thus, our findings suggest that careful observation or early therapeutic intervention with established cardioprotective medications may avoid or limit the progression of Stage A HF to Stage B HF for asymptomatic T1DM patients with preserved LVEF.

Study limitations

There are some limitations in this study. First, this study was a single-center retrospective study, so that further longitudinal-based cohort studies with larger populations are required to validate our findings. Second, the evaluation of GLS after treatment of T1DM and outcome data were not part of this study because only a small number of patients are available for follow-up. Finally, age-, gender-, LVEF-matched non-diabetic healthy controls had some confounding factors which could affect GLS such as hypertension and dyslipidemia though GLS in this group was within normal range.

Conclusion

Asymptomatic T1DM patients with preserved LVEF showed significantly lower GLS than did age-, gender- and LVEF-matched non-diabetic normal controls. GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN, but GLS of T1DM patients without DN was similar to that of normal controls. Our findings should provide new insights into the management of T1DM patients.

Compliance with Ethical Standards

Conflict of interest:

Hidekazu Tanaka is a consultant for AstraZeneca plc and Ono Pharmaceutical Company, Limited.

Yushi Hirota is a consultant for Eli Lilly and Company.

Wataru Ogawa is a consultant for Sumitomo Dainippon Pharma Co., Ltd. Wataru Ogawa has received research funding from Sumitomo Dainippon Pharma Co., Ltd., Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk A/S, TEIJIN PHARMA LIMITED., and Takeda Pharmaceutical Company Limited.

Ken-ichi Hirata has received research funding from Daiichi Sankyo Company, Limited, Actelion Pharmaceuticals Japan, Terumo Corporation, Abbott Vascular Japan, Otsuka Pharmaceutical Company, Limited, Kowa Company, Limited, Takeda Pharmaceutical Company Limited, Nihon Medi-Physics Company Limited, Novartis Pharma Company Limited, Bayer Company Limited, Biotronic Japan Company Limited, FUJIFILM Toyama Chemical Company Limited, Medtronic Japan Company Limited, Sysmex Company Limited.

The remaining authors have no conflicts of interest to declare.

Ethical approval: This article does not contain any studies with human participants or animals.

Figure Legends

Figure 1: Comparison of GLS between asymptomatic T1DM patients with preserved LVEF and normal controls, showing significant lower GLS in asymptomatic T1DM patients with preserved LVEF.

Figure 2: Comparison of GLS between normal controls, T1DM patients with and without DN, showing that GLS of T1DM patients with DN was significantly lower than that of T1DM patients without DN, but GLS of T1DM patients without DN was similar compared to normal controls.

Figure 3: Dot plots of duration of T1DM in relation to GLS show a significant negative correlation.

Figure 4: Representative cases of the polar plot longitudinal strain mapping in a normal control, a T1DM patient with and without DN.

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Table 1
Baseline characteristics of T1DM patients and normal controls

Variables	T1DM patients (n=125)	Normal controls (n=75)	P value
<u>Clinical Characteristics</u>			
Age, years	46.1 ± 18.5	46.2 ± 13.6	0.800
Gender (male), n (%)	36 (28.8)	21 (28.0)	0.904
DM duration, years	13 (0-45)	-	-
Body mass Index, kg/m ²	21.8 ± 3.4	22.6 ± 4.3	0.151
eGFR, mL/min/1.73 m ²	85.7 ± 31.9	81.7 ± 24.7	0.417
HbA1c, %	8.71 ± 2.08	-	-
<u>Comorbidities, n (%)</u>			
Hypertension	25 (20.0)	8 (10.7)	0.086
Dyslipidemia	33 (26.4)	7 (9.3)	0.003
<u>Antidiabetic drugs, n (%)</u>			
Insulin	122 (97.6)	-	-
DPP-4I	2 (1.6)	-	-
GLP-1 RA	2 (1.6)	-	-
SU	1 (0.8)	-	-
α-GI	13 (10.4)	-	-
Thiazolidine	2 (1.6)	-	-
Metformin	11 (8.8)	-	-

SGLT2 inhibitors	0 (0)	-	-
Statins	30 (24.0)	7 (9.3)	0.001
Calcium channel blockers	18 (14.4)	5 (6.7)	0.098
β-blockers	7 (5.6)	3 (4.0)	0.617
ACE inhibitor/AT II antagonists	22 (17.6)	4 (5.3)	0.012
<u>Echocardiographic Parameters</u>			
LVEF, %	66.1 ± 4.6	65.5 ± 4.7	0.366
LV diastolic diameter, mm	42.5 ± 3.9	44.3 ± 4.7	0.005
LV systolic diameter, mm	26.5 ± 3.8	27.2 ± 3.9	0.207
LV septal wall, mm	7.8 ± 2.0	7.38 ± 1.4	0.103
LV posterior wall, mm	8.3 ± 1.9	8.4 ± 1.4	0.550
LVMI, g/m ²	67.6 ± 18.1	68.5 ± 16.7	0.727
LAVI, mL/m ²	26.5 ± 9.5	24.8 ± 7.3	0.178
E/A	1.4 ± 0.7	1.4 ± 0.7	0.974
e', cm/s	8.6 ± 3.3	10.0 ± 3.0	0.005
E/e'	9.6 ± 3.9	7.2 ± 3.7	<0.001
GLS	19.7 ± 3.6	20.6 ± 1.8	0.049

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; DPP-4I, Dipeptidyl Peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptors agonists; SU, Sulfonylureas, α-GI α-glucosidase inhibitors; SGLT2, sodium glucose transporter type 2; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LAVI, left atrial volume index; e', spectral pulsed-wave Doppler-

derived early diastolic velocity from the septal mitral annulus; E, peak early diastolic mitral flow velocity; GLS, global longitudinal strain.

Table 2
Baseline characteristics of T1DM patients with and without DN

Variables	T1DM patients <u>with</u> DN (n=21)	T1DM patients <u>without</u> DN (n=104)	P value
<u>Clinical Characteristics</u>			
Age, years	52.0 ± 19.0	44.3 ± 18.2	0.086
Gender (male), n (%)	9 (42.9)	27 (26.0)	0.121
DM duration, years	21.7 (0-45)	10.9 (0-39)	<0.001
Body mass Index, kg/m ²	21.0 ± 2.6	22.0 ± 3.5	0.257
eGFR, mL/min/1.73 m ²	60.8 ± 42.9	91.0 ± 25.9	<0.001
HbA1c, %	9.11 ± 3.12	8.63 ± 1.85	0.334
<u>Comorbidities, n (%)</u>			
Hypertension	10 (47.6)	15 (14.4)	<0.001
Dyslipidemia	5 (23.8)	28 (26.9)	0.770
<u>Antidiabetic drugs, n (%)</u>			
Insulin	20 (95.2)	102 (98.0)	0.442
DPP-4I	0 (0)	2 (1.9)	1.0
GLP-1 RA	0 (0)	2 (1.9)	1.0
SU	0 (0)	1 (1.0)	1.0
α-GI	3 (14.3)	10 (9.6)	0.526
Thiazolidine	0 (0)	2 (1.9)	1.0
Metformin	0 (0)	14 (10.6)	0.124

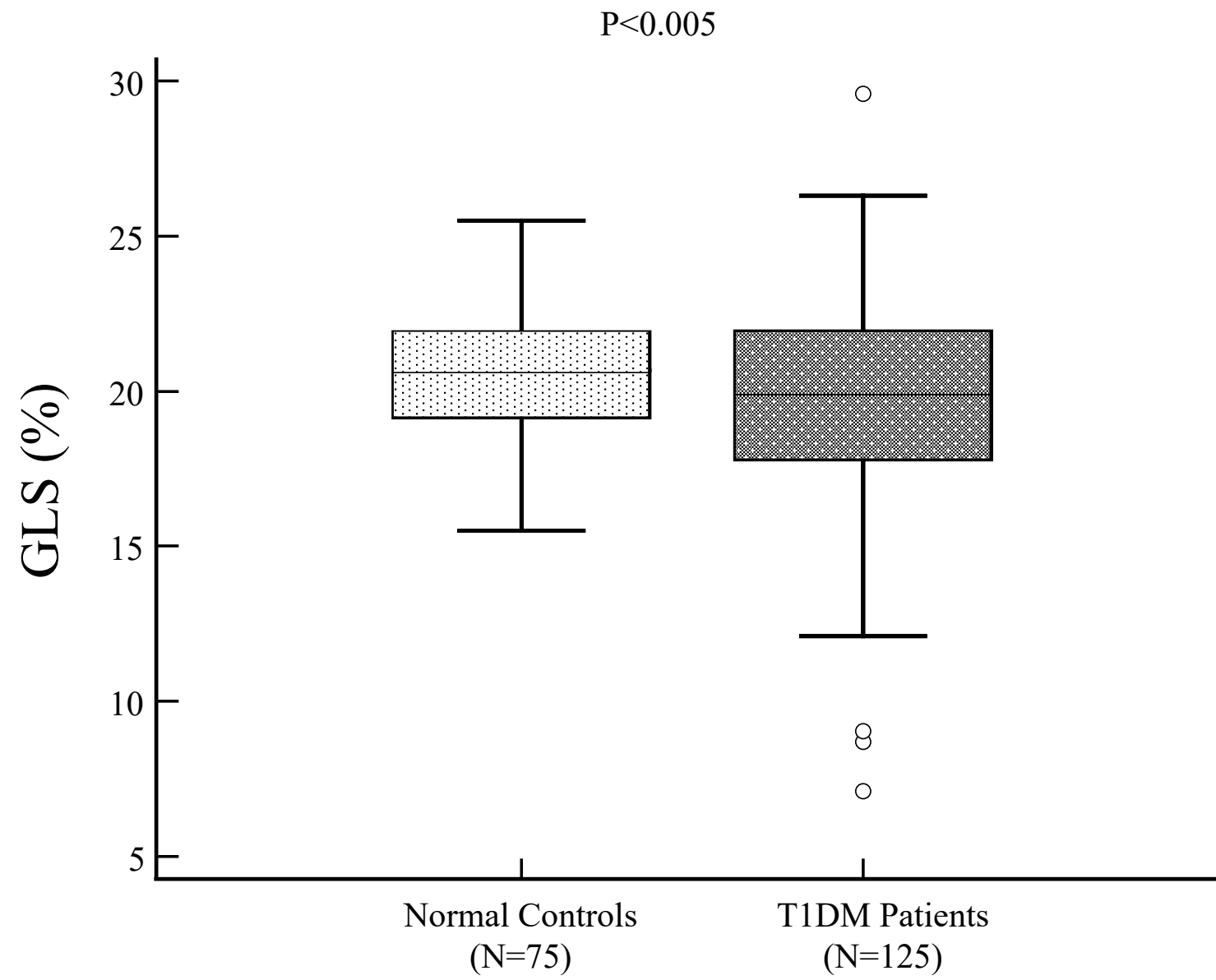
SGLT2 inhibitors	0 (0)	0 (0)	1.0
Statins	5 (23.8)	25 (24.0)	0.982
Calcium channel blockers	8 (38.1)	10 (9.6)	<0.001
β-blockers	4 (19.0)	3 (2.9)	0.003
ACE inhibitor/AT II antagonists	8 (38.1)	14 (13.0)	0.007
<u>Echocardiographic Parameters</u>			
LVEF, %	66.6 ± 4.3	66.0 ± 4.6	0.594
LV diastolic diameter, mm	41.9 ± 2.5	42.6 ± 4.2	0.445
LV systolic diameter, mm	26.1 ± 3.4	26.6 ± 3.9	0.588
LV septal wall, mm	9.3 ± 2.2	7.5 ± 1.8	<0.001
LV posterior wall, mm	9.8 ± 2.1	8.0 ± 1.7	<0.001
LVMI, g/m ²	83.6 ± 24.7	64.4 ± 14.7	<0.001
LAVI, mL/m ²	30.8 ± 9.9	25.6 ± 9.0	0.491
E/A	1.1 ± 0.6	1.5 ± 0.7	0.049
e', cm/s	6.8 ± 2.8	9.0 ± 3.3	0.006
E/e'	11.9 ± 2.4	9.1 ± 3.6	0.002
GLS	17.3 ± 3.7	20.2 ± 3.3	<0.001

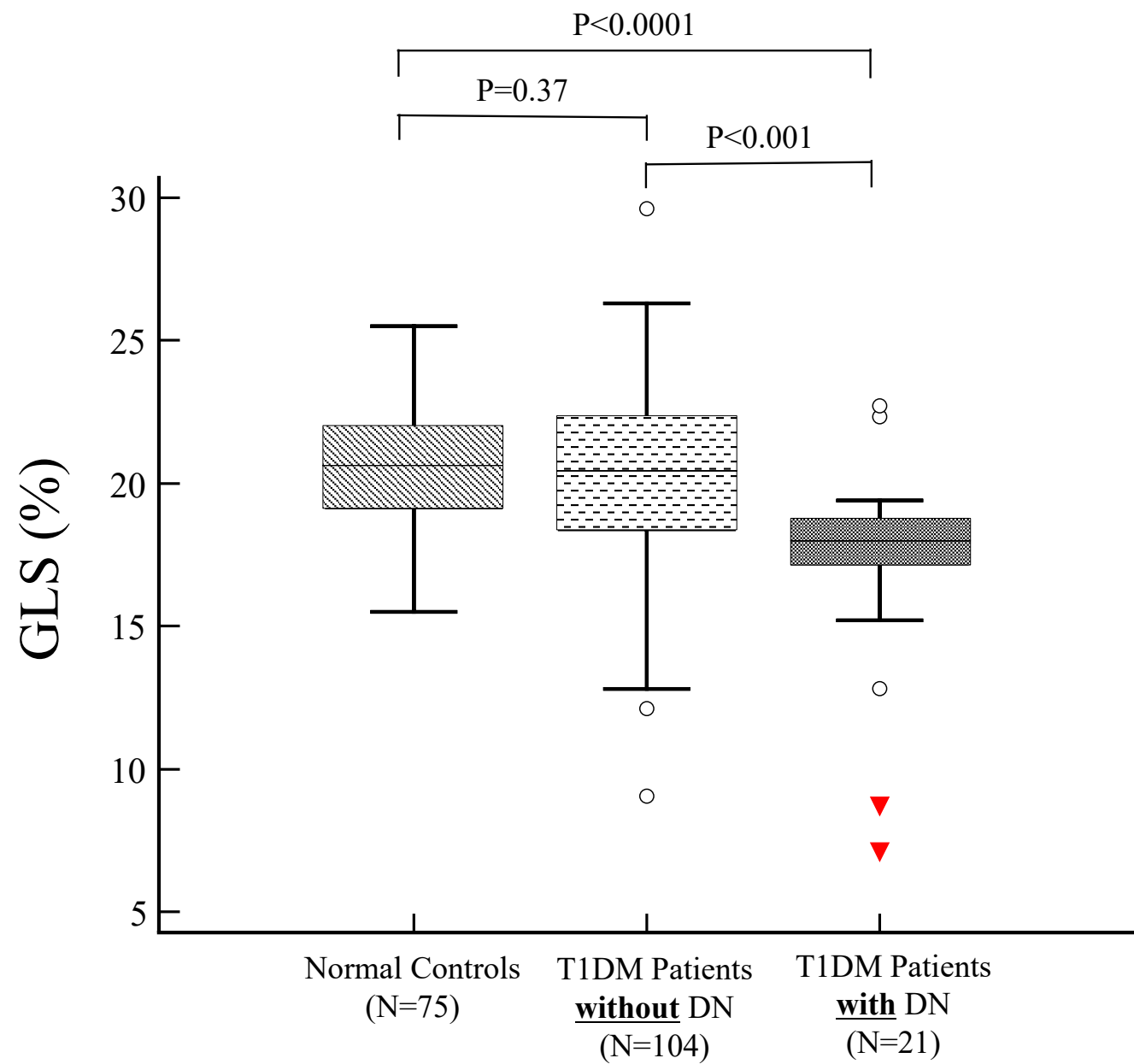
Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).
DN, diabetic nephropathy. Other abbreviations as in Table 1

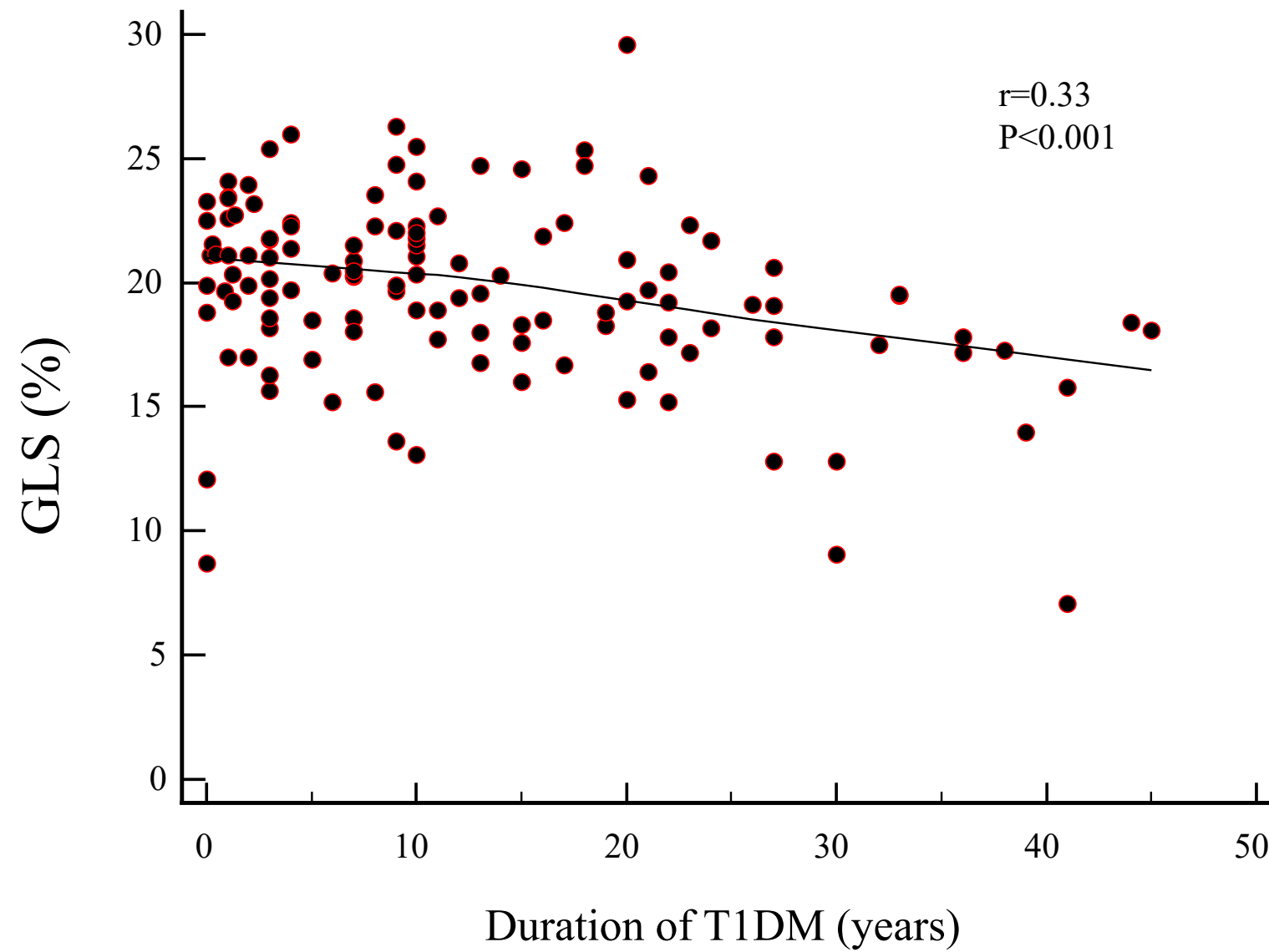
Table 3
Multiple regression analysis for GLS in T1DM patients

	Standardizing coefficient	t value	P value
Age	0.05	0.0023 - 0.11	< 0.05
Male	0.52	-0.99 - 2.034	0.49
Body mass index	-0.02	-0.20 - 0.16	0.83
Duration of T1DM	-0.33	-0.48 - -0.16	< 0.05
LVEF	0.16	0.025 - 0.29	< 0.05
LVMI	-0.04	-0.083 - 0.012	0.14
LAVI	0.07	-0.0014 - 0.14	0.054
e'	0.53	0.21 - 0.84	< 0.05
Hypertension	0.93	-0.90 - 2.77	0.32
Dyslipidemia	-2.66	-4.16 - -1.15	< 0.05
Diabetic neuropathy	1.50	-0.26 - 3.27	0.094
Diabetic retinopathy	-0.72	-2.22 - 0.79	0.35
Diabetic nephropathy	-3.27	-5.24 - -1.29	< 0.05

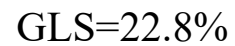
All abbreviations as in Table 1



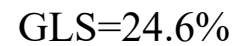




✓ 49-year-old female
✓ LVEF=69.8 %



- ✓ 30-year-old female
- ✓ LVEF=62%



- ✓ 55-year-old male
- ✓ LVEF=64%

