Original Article

Left Ventricular Global Longitudinal Strain: an Early Marker of Diabetic Cardiomyopathy

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Abstract

Background: Diabetic cardiomyopathy (DCM) leads to abnormal myocardial structure and function in the absence of cardiac risk factors. Screening in the pre-clinical phase is not well established. Global longitudinal strain (GLS) has been measured as an important echocardiography parameter in asymptomatic patients.

Objective: To describe the presence of early parameters of DCM in patients with type 2 diabetes (T2DM) without cardiovascular disease and to compare results against 2 control groups (CT groups).

Methods: A total of 58 patients were divided into the following 3 groups: T2DM (n = 20); heart failure (HF) with preserved ejection fraction (HFpEF) without T2DM (n = 19); and control without T2DM or HFpEF (n = 19). Patients with cardiovascular disease and those using SGLT2 inhibitors, pioglitazone or saxagliptin were excluded.

Results: The mean overall prevalence of GLS was 16% (standard deviation [SD] ± 2.9), and 41% of participants had abnormal values, comprising 10 (50%) patients from the T2DM, 11 (58%) from the HFpEF, and 3 (16%) from the CT groups (p = 0.019). Mean GLS values in the T2DM, HFpEF, and CT groups were 16.1%, 14.8%, and 17.5%, respectively (p = 0.015). There was a negative moderate association between HbA1c levels and GLS values in the T2DM group (p = 0.043).

Conclusions: GLS proved to be a potential early marker of left ventricular (LV) cardiac changes in patients with T2DM, given the similarity between this patient group and the HFpEF group studied.

Keywords: Diabetes Mellitus; Diabetic Cardiomyopathies; Echocardiography; Ventricular Dysfunction.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic heterogeneous disease characterized by persistent hyperglycemia caused by metabolic disturbances, resulting in impaired insulin secretion and/or action.[1] The condition is increasingly recognized as a complex cardio-renal-metabolic disease, promoted by a positive energy balance.[2]

Persistent hyperglycemia is associated with a host of cardiovascular complications.[1] Even in the absence of valvulopathies or coronary heart diseases, T2DM alone can cause structural and functional cardiac changes, generally referred to as diabetic cardiomyopathy (DCM)[3-5] (Central Figure).

The pathogenesis of DCM is multifactorial and not yet fully elucidated. Several elements appear to play a role in cardiac dysfunctions in this patient group: mitochondrial dysfunction, activation of the renin-angiotensin-aldosterone system, oxidative stress, myocardial fibrosis, microangiopathy, inflammatory cytokines, and the underlying hyperglycemia.[3] These patients can consequently develop relaxation difficulties, changes in left ventricular (LV) pressure and stiffness and left atrial enlargement.[4]

These alterations are referred to as diastolic dysfunction (DD), an echocardiographic finding recognized as an early marker of DCM that can be associated with preserved or reduced fraction ejection (FE). Screening for DD in the pre-clinical stage is important given the benefits of early intervention in these individuals, with the aim of preventing progression to the symptomatic form of the disease.

Mechanisms for diagnosing patients with DCM in the asymptomatic stage are inadequate owing to the clinical complexity of the condition. The use of imaging scans allows monitoring and/or stratifying the degree of ventricular dysfunction.[5] Tissue Doppler echocardiogram is a highly accessible, relatively non-invasive imaging method that provides early detection of structural and functional cardiac dysfunctions in patients at risk of heart failure (HF), the symptomatic progression of DCM.[6]

Useful parameters for assessing the presence of ventricular remodeling include indexed LV mass, indexed left atrial volume, and the ratio of early diastolic transmitral inflow to early diastolic mitral annular velocity (E/E' mitral), which aid

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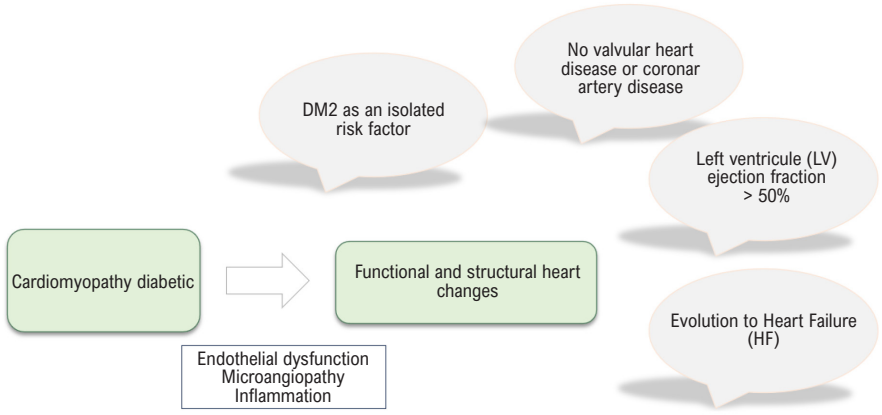
Central Illustration: Left Ventricular Global Longitudinal Strain: an Early Marker of Diabetic Cardiomyopathy



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diagnosis and offer high specificity for characterizing elevated LV diastolic pressures.[7]

However, the emergence of new echocardiographic methods, such as LV global longitudinal strain (GLS), can offer even greater sensitivity for early DCM diagnosis. GLS constitutes a measure of myocardial deformity and provides greater diagnostic sensitivity, particularly in asymptomatic patients. Currently, GLS is considered a better predictor of risk than EF.[8]

Thus, this raises the possibility of using LV GLS as an echocardiographic marker of changes present in DCM (not widely recognized by health professionals) which manifest early in patients with T2DM in the absence of known cardiovascular disease. Therefore, this study sought to establish a potential association between clinical characteristics of patients with T2DM and LV GLS, in addition to similarities and differences on comparisons with 2 control groups (CT groups) of patients without T2DM.

Materials and methods

A cross-sectional study was conducted of patients recruited from the Endocrinology Outpatient Clinic, with clinically confirmed diagnosis of T2DM, as defined by the 2023 criteria of the American Diabetes Association.[1] Control subjects, matched for age, body mass index (BMI), and comorbidities, were recruited from the Endocrinology, Cardiology and/or Internal Medicine Outpatient Clinics to form 2 CT groups: patients without T2DM or suspected symptoms of HF with preserved ejection fraction (HFpEF); and patients without T2DM investigated for HFpEF, as per the criteria of the European Society of Cardiology.[9] In conjunction with medical chart review, participants underwent clinical examination, imaging scans and laboratory tests.

Patients with history of previous ischemic or hemorrhagic stroke, cardiovascular disease, confirmed infectious cardiomyopathies, collagen disorders, and/or granulomatous diseases were excluded. Patients using SGLT-2 inhibitors, pioglitazone, or saxagliptin for more than 1 month and patients with atrial fibrillation, LVEF < 50%, or severe valve disease as classified by the criteria of the American Society of Echocardiography (ASE) were also excluded.[10]

A Doppler transthoracic echocardiogram was performed and assessed by the same physician assistant of the cardiology sector, blinded to participants´ clinical data. Echocardiographic assessments and reports were based on the 2016 ASE Guidelines,[10] using a Vivid™ iq Ultra Edition GE HealthCare device. GLS was analyzed by 2D speckle tracking, using the software Echo-PAC, version 113, with 3 apical standard views. Apical images were divided into 6 standard deformation segments and times, yielding corresponding deformation curves. The cutoff point defined for LV GLS was < 16%.

Blood samples were collected from participants to test glycated hemoglobin (HbA1c) by turbidimetry, levels of natriuretic peptide using chemiluminescence, and kidney function (urea and creatine, automated glomerular filtration rate calculated using the CKD-EPI equation at ml/min/1.73 m^2). Only patients with T2DM underwent triage for nephropathy screening based on microalbuminuria in a spot sample using immunoturbidimetry (positivity defined as > 30 mg albumin/gram of creatinine) and diabetic retinopathy.

A retinography scan was carried out using a Phelcon Eyer NM Top device with photographic documentation and classified according to the international 2018 ETDRS (Early Treatment Diabetic Retinopathy Study) classification[11] by a vitreoretinal specialist ophthalmologist. The study was approved by the Research Ethics Committee (CAAE permit number: 26182819.5.0000.5479).

A total of 104 patients with clinically confirmed T2DM were randomly selected from the Endocrinology Outpatient Clinic.

Retrospective analysis of patient electronic medical records and application of the inclusion and exclusion criteria led to the assignment of 20 participants into the group with T2DM (T2DM group).

The CT group comprised an initial 20 patients randomly selected from the Internal Medicine Outpatient Clinic, with 1 subject subsequently excluded for EF < 50% on echocardiogram, resulting in 19 participants. For the group with suspected HFpEF (HFpEF group), an initial 24 patients were recruited from the Cardiology Outpatient Clinic, with subsequent exclusion of 5 patients for EF < 50% on the echocardiogram, resulting in 19 patients. Thus, a final total of 58 patients were analyzed. The study design is depicted in Figure 1.

For descriptive analysis, categorical variables were expressed as frequencies and percentages, and continuous variables as measures of central tendency (mean, standard deviation [SD], minimum and maximum).

For inferential analysis, categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were assessed using Student's t test, or by the Mann-Whitney non-parametric test when data had a non-normal distribution. A 5% level of significance was adopted for all tests. All statistical analyses were performed using the software IBM SPSS Statistics for Windows, version 25.0.

Results

Of the total 58 participants, 64% were female, and groups had a similar sex distribution. For the overall sample, mean age was 56 (SD ± 12) years and 97% had preserved renal function (creatinine clearance > 60 ml/min). Regarding BMI, 51.8% of participants had some degree of obesity (BMI > 30 kg/m^2), with the highest prevalence in the T2DM group. The demographic characteristics of the population analyzed are presented in Table 1.

T2DM group

Mean age of patients in the T2DM group was 62 (SD ± 7.5) years, and 65% were female. With respect to disease duration, 11 patients had been diagnosed more than 10 years prior, and 45% were using insulin. Mean HbA1c level was 7.6% (SD ± 1.8). Of the patients assessed, 30% had microalbuminuria, and 35% had some degree of retinopathy.

Among the comorbidities assessed, systemic arterial hypertension and dyslipidemia were more prevalent in the T2DM group. The characteristics of the T2DM group are given in Table 2.

Echocardiographic data

Overall, mean GLS in the groups was 16% (SD ± 2.9; median 17%). Of all patients analyzed, 24 had abnormal strain (41%), comprising 10 (50%) from the T2DM group, 11 (58%) from the HFpEF group, and 3 (16%) from the CT group (p = 0.019). Median strain by group was 16.5% in the T2DM group, 15% in the HFpEF group, and 17.9% in the CT group (p = 0.015), with the largest statistical difference occurring between the HFpEF and CT groups (p = 0.012).

In the T2DM group, a negative association was found between HbA1c levels and strain. Patients with higher HbA1c levels had GLS < 16% (p = 0.043), as shown in Figure 2.

Regarding the association of microvascular complications and abnormal LV GLS, 4 (40%) patients testing positive for microalbuminuria (p = 0.628) and 5 patients (50%) with retinopathy (p = 0.350) had strain < 16%. Among patients with some degree of obesity, 90% had abnormal LV GLS values (p = 0.087). The results of the subanalyses of the T2DM group are presented in Table 3. The mean and SD for the variables investigated are given in Table 4.

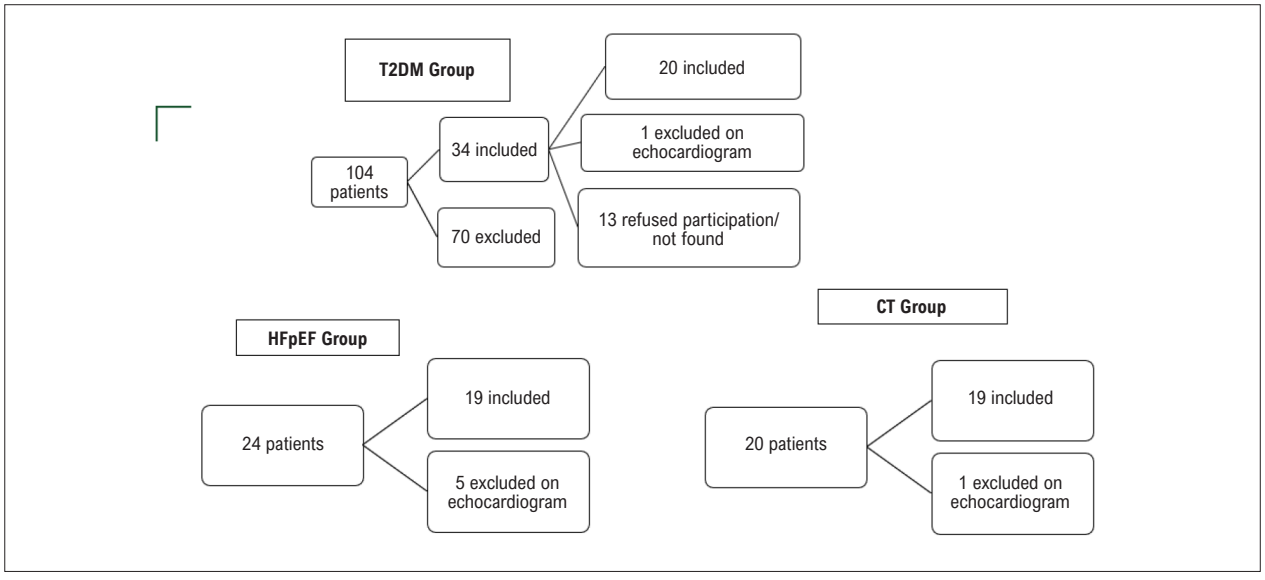

Figure 1 – *Study design CT: control; HFpEF: heart failure with preserved ejection fraction; T2DM: type 2 diabetes mellitus.*

Table 1 – Main demographic characteristics of overall study population and by group

Characteristics	Total	T2DM	HFpEF	Control	p value
n	58	20	19	19	
Sex					
Female	37 (64%)	13 (65%)	11 (58%)	13 (68%)	0.789
Male	21 (36%)	7 (35%)	8 (42%)	6 (32%)	
Age range (years)					0.001
≤ 40	6 (10%)	0 (0%)	1 (5%)	5 (26%)	
41 to 50	10 (17%)	0 (0%)	6 (32%)	4 (21%)	
51 to 60	18 (31%)	10 (50%)	2 (11%)	6 (32%)	
61 to 70	18 (31%)	6 (30%)	8 (42%)	4 (21%)	
> 70	6 (10%)	4 (20%)	2 (11%)	0 (0%)	
BMI					0.404
Normal	10 (17%)	4 (20%)	4 (21%)	2 (11%)	
Overweight	18 (31%)	2 (10%)	7 (37%)	9 (47%)	
Obese	30 (52%)	14 (70%)	8 (42%)	8 (42%)	
Tobacco use					0.015
No	50 (86%)	18 (90%)	13 (68%)	19 (100%)	
Yes	8 (14%)	2 (10%)	6 (32%)	0 (0%)	
SAH					<0.001
No	26 (45%)	4 (20%)	6 (32%)	16 (84%)	
Yes	32 (55%)	16 (80%)	13 (68%)	3 (16%)	
Dyslipidemia					<0.001
No	31 (53%)	3 (15%)	13 (68%)	15 (79%)	
Yes	27 (47%)	17 (85%)	6 (32%)	4 (21%)	
CrCl					0.006
≥ 60	47 (81%)	12 (60%)	16 (84%)	19 (100%)	
60 a 30	9 (16%)	6 (30%)	3 (16%)	0 (0%)	
30 a 15	2 (3%)	2 (10%)	0 (0%)	0 (0%)	
< 15	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

BMI: body mass index; CrCl: creatinine clearance; HFpEF: heart failure with preserved ejection fraction; SAH: systemic arterial hypertension; T2DM: type 2 diabetes mellitus.

Discussion

T2DM is one of the most prevalent diseases worldwide, and not only represents a risk factor for the development of HF but can exacerbate the progression of the existing disease.[12] Studies involving patients with T2DM and HF have shown the positive impact of treatment on disease progression.[13-15] The 2015 EMPAREG study, comparing the use of empagliflozin against placebo, found a 35% reduction in the number of hospital admissions for HF.[14] A similar result was seen in the 2017 CANVAS study, which reported a 33% decrease in hospitalizations for decompensated HF.[15] Some of these patients were unaware that they hard HFpEF.[13]

It is believed that, through early diagnosis of DCM in the asymptomatic stage, early damage can be reversed and progression to the symptomatic disease averted. Currently, specific therapies are available which can improve the prognosis of the disease.[16]

The characteristics of patients with DD secondary to diabetes, in the early stages, are both complex and challenging to diagnose. Currently, there is no consensus on screening or when to start treatment in asymptomatic patients, although several factors can be considered, including disease duration, insulin use, glycemic control, and presence of microvascular complications.[17]

The physiopathology of DCM is not fully understood, and one of the main hypotheses is the progression of diastolic to systolic dysfunction, concomitant with LV remodeling and hypertrophy. Metabolic changes secondary to hyperglycemia and insulin resistance begin to promote

Table 2 – Main demographic characteristics of T2DM group

	T2DM (n = 20)
Disease duration (years)	
≤ 5	2 (10%)
5 to 10	7 (35%)
> 10	11 (55%)
Insulin use	
No	11 (55%)
Yes	9 (45%)
HbA1c	
< 6.5%	7 (35%)
6.5% to 7.5%	5 (25%)
7.5% to 9.0%	3 (15%)
9.0% to 11%	3 (15%)
> 11%	2 (10%)
MAB (> 30 mg)	
No	14 (70%)
Yes	6 (30%)
Retinopathy	
Absent	12 (60%)
Mild non-proliferative	3 (15%)
Moderate non-proliferative	2 (10%)
Severe non-proliferative	1 (5%)
Proliferative	1 (5%)
Inconclusive	1 (5%)
Post-laser	0 (0%)

HbA1c: glycated hemoglobin; MAB: microalbuminuria; T2DM: type 2 diabetes mellitus.

gradual changes in the heart, and, owing to compensatory adaptation, changes are evident only at a structural and cellular level.[17]

LV GLS serves as a predictor of hospitalization for HF and cardiovascular death, correlating strongly with LV stiffness and biomarkers.[18] Strain is believed to be the best marker of subclinical DD in DCM.[8]

In a systematic review, da Silva et al.[8] reported that around 40% of asymptomatic T2DM patients exhibited abnormal strain values. Mirroring the present findings, the study by Karagöz et al.,[19] comparing T2DM patients with control subjects, observed lower strain results in the T2DM group.

The relationship between microvascular complications and low GLS is also well established. Many studies have demonstrated the association of diabetic retinopathy, for example, with the development of DD and HF.[8,20] By contrast, Karagöz et al.[19] failed to identify this association. Although the present study was unable to confirm this association in the sample assessed, a tendency towards a greater incidence of abnormal strain values among patients testing positive for microalbuminuria was evident. The mean HbA1c of 7.6% and lower prevalence of microvascular complications in the patient sample might explain the absence of this association in the study.

The association between T2DM duration and LV GLS is controversial.[21] Silverii et al.[21] assessed patients with T2DM and was unable to establish this relationship. In the present analysis, although the association could not be confirmed, 60% of patients with GLS < 16% had T2DM for more than 10 years. Moreover, the cited study also established an inverse correlation of HbA1c with GLS, a finding corroborated by the current results in the T2DM group.

Obesity is associated with abnormal GLS values, irrespective of the concomitant presence of T2DM. In the series by Mochizuki et al.,[20] patients with T2DM concomitant with obesity had abnormal GLS values, a correlation also observed in the present analysis.

Study limitations

The research was initially planned to assess at least 30 patients for each group to provide a significant confidence interval for the variables investigated. However, the start of data collection and patient recruitment coincided with the COVID-19 outbreak. The pandemic led to delays in data collection and problems inviting patients due to the lockdown and social distancing measures, where most patients were deemed a high-risk group.

Notably, patients in the T2DM group had HbA1c values averaging 7.6% The low number of echocardiographic abnormalities observed in the present study may have been attributed to the apparently better controlled T2DM in the patient population studied.

Lastly, given that the tertiary hospital handled cases of greater complexity, factors such as systemic arterial hypertension and obesity were more prevalent in the patient group compared to the CT groups, representing factors which also correlate with cardiac dysfunctions.

Conclusion

LV relaxation abnormalities are important echocardiographic findings in patients with T2DM and a diagnostic component of the early stages of DD.

LV GLS proved a valuable early marker of LV abnormalities, where the results obtained for T2DM group were similar to those of the HFpEF group, yet differed from the control population. Further, these abnormalities were also more prevalent in patients with diabetes, obesity, and associated microvascular complications. However, the limiting factors of the study may have had a statistical impact on the results obtained.

Thus, future studies involving a larger patient sample and fewer confounding factors are needed for a more accurate assessment of the impact of employing LV GLS as an early marker of DCM in the pre-clinical phase.

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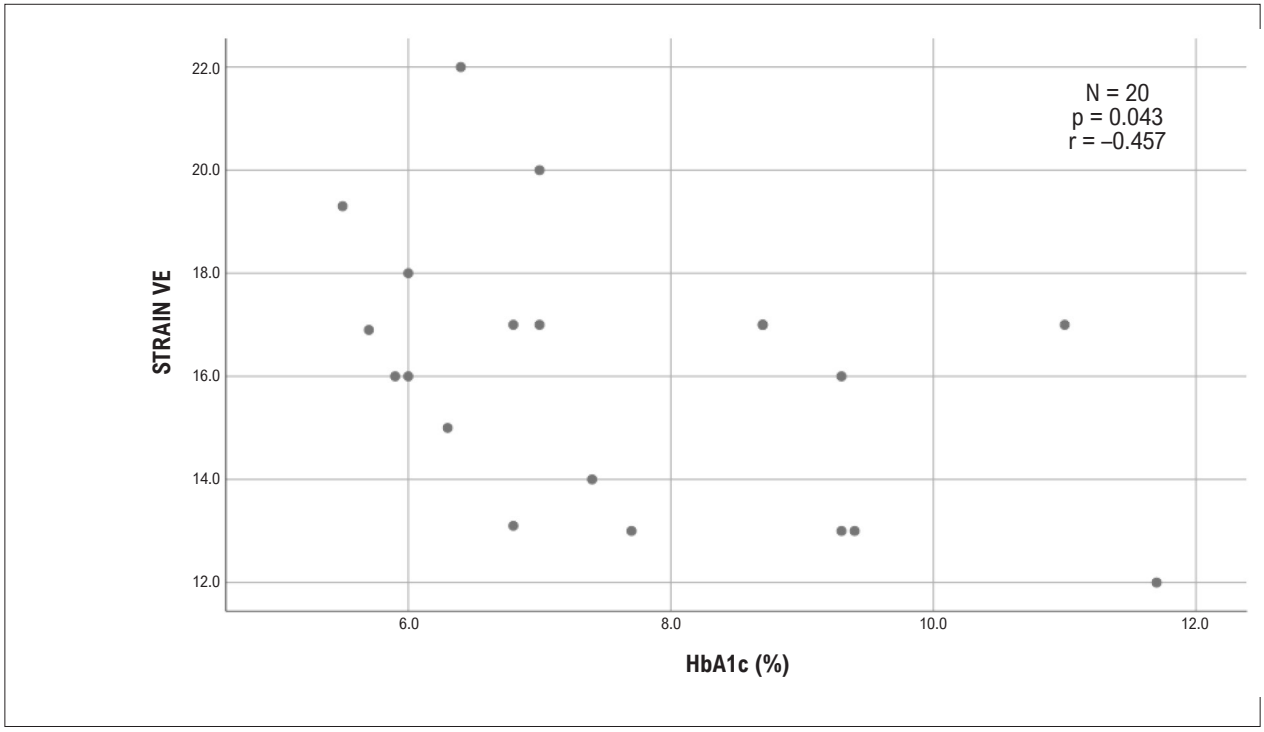

Figure 2 – *Dot plots of negative moderate correlation between LV GLS and HbA1c. HbA1c: glycated hemoglobin; LV GLS: left ventricular global longitudinal strain.*

Table 3 – Descriptive analysis of T2DM group and association with LV GLS

	LV GLS			p value	Test used
	Total	> 16%	< 16%		
n	20	10	10	-	-
Insulin				1.000	Fisher's exact
No	11 (55%)	5 (50%)	6 (60%)		
Yes	9 (45%)	5 (50%)	4 (40%)		
MAB				0.628	Fisher's exact
No	14 (70%)	8 (80%)	6 (60%)		
Yes	6 (30%)	2 (20%)	4 (40%)		
Retinopathy				0.350	Fisher's exact
Absent	12 (60%)	7 (70%)	5 (50%)		
Present	7 (35%)	2 (20%)	5 (50%)		
Inconclusive	1 (5%)	1 (10%)	0 (0%)		
BMI				0.087	Fisher's exact
Normal	4 (20%)	4 (40%)	0 (0%)		
Overweight	2 (10%)	1 (10%)	1 (10%)		
Obese	14 (70%)	5 (50%)	9 (90%)		
Disease duration (years)				1.000	Fisher's exact
≤ 5	2 (10%)	1 (10%)	1 (10%)		
5 to 10	7 (35%)	4 (40%)	3 (30%)		
> 10	11 (55%)	5 (50%)	6 (60%)		

BMI: body mass index; LV GLS: left ventricular global longitudinal strain; MAB: microalbuminuria in spot sample; T2DM: type 2 diabetes mellitus.

Table 4 – Mean and SD of variables analyzed

Variable	Total (n = 58)	T2DM (n = 20)	HFpEF (n = 19)	Control (n = 19)	p value
Age	55.9 (± 11.6)	61.6 (± 7.5)	57.2 (± 12.2)	48.8 (± 11.6)	0.001
CrCl (value)	72.22 (± 25)	-	-	-	
BNP (value)	27.9 (± 32.8)	33.5 (± 40)	34.9 (± 33.7)	13.6 (± 13.2)	0.048
LAV	26.6 (± 8.3)	29.4 (± 9.5)	25.8(± 7.9)	24.6 (± 7.1)	0.176
E/e'	8.6 (± 2.5)	9.1 (± 2.3)	8.8 (± 2.5)	7.5 (± 2.7)	0.274
LV GLS	16 (± 2.9)	16.1 (± 2.6)	14.8 (± 3.2)	17.5 (± 2.5)	0.015
LV mass	87.5 (± 20)	92 (± 17.7)	89.3 (± 20.6)	80.4 (± 21.9)	0.185

BNP: natriuretic peptide; CrCl: Creatinine clearance; E/e': ratio of E diastolic mitral inflow velocity to e' diastolic mitral annulus velocity (abnormal > 14); HFpEF: heart failure with preserved ejection fraction; LAV: indexed left atrial volume (abnormal > 34 ml/²); LV GLS: left ventricular global longitudinal strain; LV mass: left ventricular mass (abnormal > 95 g/m² in females and > 115 g/m² in males); T2DM: type 2 diabetes mellitus.

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Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Saran AC, Tormin SC, Krakauer R, Salles JEN; acquisition of data: Saran AC, Tormin SC, Vogel J, Krakauer R; analysis and interpretation of the data: Saran AC, Tormin SC, Vogel J, Krakauer R, Salles JEN; statistical analysis and writing of the manuscript: Saran AC, Tormin SC, Vogel J, Krakauer R, Salles JEN.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Santa Casa de São Paulo under the protocol number 26182819.5.0000.5479. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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