



# Negative synergism of diabetes mellitus and obesity in patients with heart failure with preserved ejection fraction: a cardiovascular magnetic resonance study

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## Abstract

In patients with heart failure with preserved ejection fraction (HFpEF), diabetes mellitus (DM) and obesity are important comorbidities as well as major risk factors. Their conjoint impact on the myocardium provides insight into the HFpEF aetiology. We sought to investigate the association between obesity, DM, and their combined effect on alterations in the myocardial tissue in HFpEF patients. One hundred and sixty-two HFpEF patients ( $55 \pm 12$  years, 95 men) and 45 healthy subjects ( $53 \pm 12$  years, 27 men) were included. Patients were classified according to comorbidity prevalence (36 obese patients without DM, 53 diabetic patients without obesity, and 73 patients with both). Myocardial remodeling, fibrosis, and longitudinal contractility were quantified with cardiovascular magnetic resonance imaging using cine and myocardial native  $T_1$  images. Patients with DM and obesity had impaired global longitudinal strain (GLS) and increased myocardial native  $T_1$  compared to patients with only one comorbidity (DM + Obesity vs. DM and Obesity; GLS,  $-15 \pm 2.1$  vs  $-16.5 \pm 2.4$  and  $-16.7 \pm 2.2\%$ ; native  $T_1$ ,  $1162 \pm 37$  vs  $1129 \pm 25$  and  $1069 \pm 29$  ms;  $P < 0.0001$  for all). A negative synergistic effect of combined obesity and DM prevalence was observed for native  $T_1$  ( $np^2 = 0.273$ ,  $p = 0.002$ ) and GLS ( $np^2 = 0.288$ ,  $p < 0.0001$ ). Additionally, severity of insulin resistance was associated with GLS ( $R = 0.590$ ,  $P < 0.0001$ ), and native  $T_1$  ( $R = 0.349$ ,  $P < 0.0001$ ). The conjoint effect of obesity and DM in HFpEF patients is associated with diffuse myocardial fibrosis and deterioration in GLS. The negative synergistic effects observed on the myocardium may be related to severity of insulin resistance.

**Keywords** Cardiovascular magnetic resonance · Heart failure with preserved ejection fraction · Obesity · Diabetes mellitus · Myocardial fibrosis

## Introduction

Heart failure with preserved ejection fraction (HFpEF) affects approximately half of all clinical HF patients and leads to greater morbidity and mortality than HF with reduced ejection fraction (HFrEF) [1, 2]. Coupled with its complex pathophysiology, HFpEF is considered a

heterogeneous syndrome linked to several comorbidities, such as diabetes mellitus (DM) and obesity [1–7].

Obesity is a growing worldwide health burden and strongly associated with HFpEF [8–11]. Its effects on the cardiovascular system are multifaceted. Specifically, changes in volume status, altered cardiac loading, reduced energy substrate utilization, abnormal tissue metabolism, and systemic inflammation are all factors considered to promote HFpEF progression [8–12]. Additionally, increased body mass is independently associated with symptom severity in HFpEF patients [9–14]. Similarly, diabetes mellitus (DM) is present in ~40% of HFpEF patients, and its prevalence is increasing in patients with new-onset HFpEF [5, 15, 16]. DM is generally associated with left ventricular (LV) function decline through increased myocardial stiffness, fibrosis, and deterioration in longitudinal contractility. Prognostically, DM is associated with a nearly twofold increase in

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morbidity and mortality [4, 5], with insulin resistance being a main contributor to myocardial damage [4, 5, 15–17].

Multi-morbidity, or the presence of two or more chronic diseases in an individual, is highly prevalent in HFpEF patients [3–7]. Obesity is present in most patients with type 2 DM [4–6]. The presence of obesity in DM may exacerbate cardiovascular risk factors, as the added presence of obesity raises the mortality risk from five to eightfold compared to DM alone [4–6, 18], likely due to deteriorated insulin resistance [12, 19–22]. Insulin resistance is shared among both diseases and represents a critical initial step in myocardial alteration [12, 19–22]. Currently, the association between obesity and cardiovascular morbidity and mortality in diabetic patients is inconclusive [12, 19–23]. Therefore, studies investigating the link between myocardial structure/function and weight in DM patients may provide further insight into underlying pathophysiological processes.

Cardiovascular magnetic resonance imaging (CMR) offers a promising lens for assessing HFpEF-specific cardiac remodelling. Cardiac morphology and function are crucial steps in the diagnosis and management of HFpEF patients and can be accurately analyzed by CMR [24–27]. Moreover, native  $T_1$  mapping allows quantification of interstitial myocardial fibrosis [28, 29] and CMR features tracking (CMR-FT) techniques based on cine sequences allow assessment of myocardial longitudinal contractility indices such as global longitudinal strain (GLS) which has prognostic value in HFpEF patients [30]. In multimorbid HFpEF patients, significant deterioration of the myocardial structure and function can occur, beyond the independent effects of diabetes and obesity.

In this study, we hypothesized that the presence of both obesity and DM in HFpEF patients is associated with increased subclinical myocardial damage, potentially due to increased insulin resistance. We therefore sought to investigate the impact of obesity, DM, and their combination in HFpEF patients by myocardial fibrosis and longitudinal contractility assessment using CMR.

## Methods

### Study population

One hundred and sixty-two patients with HFpEF ( $55 \pm 12$  years, 95 men) and 45 healthy controls ( $53 \pm 12$  years, 27 men) were retrospectively enrolled in an observational study. Patients were categorized into three groups according to their DM and obesity status [(36 in the obese group defined as obese patients without DM], [53 in the DM group defined as diabetic patients without obesity], and [73 in the Diabesity group defined as patients with both obesity and DM)]. The DM diagnosis was based on medical history and/or documented HbA<sub>1c</sub> values  $> 6.5\%$ . Obesity was defined

using a body mass index (BMI) threshold of  $30 \text{ kg/m}^2$ . Coronary artery disease (CAD) was defined based on a history of coronary angiography with reported obstructive coronary lesions. Exclusion criteria included severe valvular disease, renal impairment ( $\text{eGFR} < 30 \text{ ml/min/m}^2$ ), specific causes of HF (i.e. pericardial disease, hypertrophic, dilated and amyloid cardiomyopathies, and congenital diseases), isolated right sided HF, and severe pulmonary disease. Control subjects were selected among those with normal cardiac dimensions/volumes, normal cardiac function on CMR and echocardiography exams (if applicable), no clinical symptoms/cardiac history, BMI values  $< 30 \text{ kg/m}^2$ , and H<sub>2</sub>FPEF scores  $\leq 1$ . The study protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board, and a written informed consent was obtained from each study participant.

### Demographic and laboratory analyses

Clinical assessments and biochemical tests such as fasting plasma glucose, HbA<sub>1c</sub>, cholesterol panels, C-reactive protein, and creatinine levels were obtained from medical records. All biochemical blood tests were performed within a median of 37 days [interquartile range (IQR) 1–82 days] before or after CMR imaging. Vital signs such as blood pressure measurements, pulse, and BMI and current medication history were collected on the day of the CMR scan.

### Heart failure with preserved ejection fraction diagnosis

In accordance with contemporary guidelines [31] and publications [2, 14, 15, 32, 33], HFpEF diagnosis was based on three main criteria: (1) clinical symptoms consistent with HF (New York Heart Association (NYHA) status  $\geq \text{II}$ ), (2) preserved systolic function ( $\text{LVEF} \geq 50\%$ ), and (3) evidence of cardiac dysfunction. Cardiac dysfunction was defined as diastolic dysfunction assessed by tissue Doppler echocardiography in accordance with guidelines and publications [31–34], and a H<sub>2</sub>FPEF score  $\geq 6$  points [range 0 to 9] [32]. According to Reddy et al. [32], a score of 6 or above indicates  $> 90\%$  probability of HFpEF prevalence in patients with unexplained dyspnea. For this purpose, New York Heart Association (NYHA) classification was applied and this data were acquired through patient medical records accordingly.

### Diastolic dysfunction assessment

Transthoracic echocardiography (TTE) was conducted using conventional two-dimensional guided tissue and pulse-wave Doppler imaging in accordance to the American Society of Echocardiography guidelines [31, 34]. Images were interpreted by a level 2 or 3 trained reader certified by the National Board of Echocardiography Special Competence

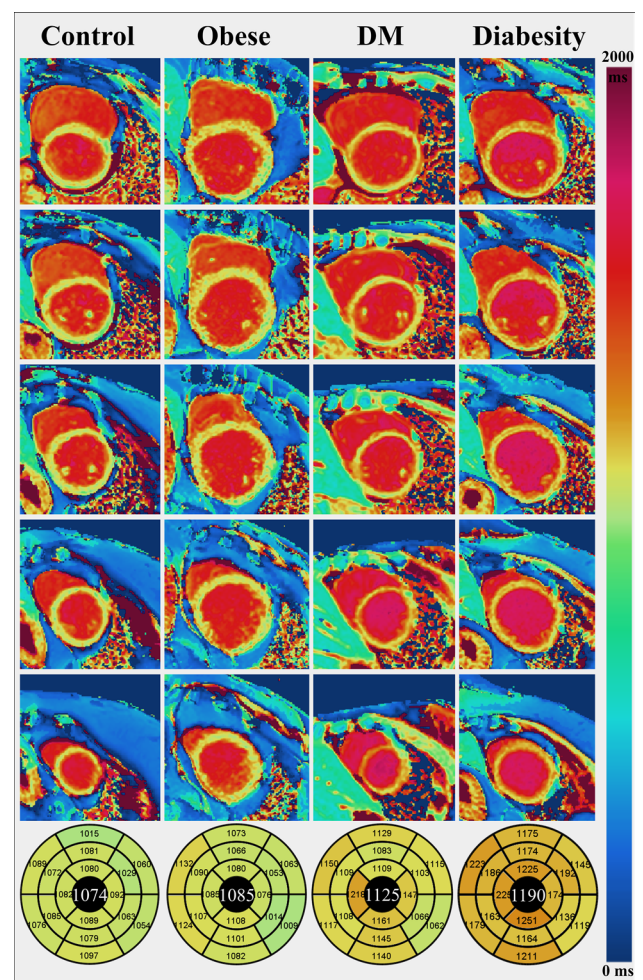
in Echocardiography examination. The rationale for inclusion of Doppler echocardiography data was improved diagnostic accuracy for HFpEF by the H<sub>2</sub>FPEF score system. Peak early (E) and atrial (A) velocities of mitral inflow, early mitral inflow deceleration time (DT), septal and lateral mitral annular E' velocities were measured and averaged. The E/A ratio and trans-mitral early diastolic velocity ratios (E/E') were calculated. Furthermore, pulmonary systolic pressure (PASP) was obtained for use in the H<sub>2</sub>FPEF score calculation, and PASP was computed as the sum of the tricuspid gradient and the estimated right atrial pressure. All diastolic function measurements by TTE were performed either prior to CMR scanning or after 3 months at the latest.

### Cardiovascular MR protocol

CMR was performed on a 1.5-T scanner (Phillips Achieva, Best, Netherlands), using a 5-element or 32-element cardiac coil. Images were analyzed using commercial workstations (Extend MR Workspace, version 2.3.6.3, Philips Healthcare). To determine LV myocardial function, volumes, and mass, 10 to 12 short-axis stack cine images and 4 and 2-chamber long axis images were acquired using a breath-hold balanced steady-state free precession cine sequence with ECG gating (slice thickness, 8-mm; in-plane spatial resolution 2×2 mm, 30 ms temporal resolution). At end-diastole and end-systole, endocardial and epicardial contours were manually delineated on contiguous short-axis cine images covering the LV apex to the mitral valve plane for calculation of end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume, and LVEF. Papillary muscles were excluded from the myocardial mass, and included when measuring LV volumes. LV mass (LVM) was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/mL) of the myocardial tissue, and LV mass index (LVMI) was calculated according to indexed body surface area (BSA). To quantify myocardial remodeling, the LV remodeling index (LVRI) was calculated as the ratio between LVM and LVEDV [35], and the relative wall thickness (RWT) was defined as (2×diastolic posterior wall thickness)/LV diastolic diameter [36]. All volume measurements were indexed to BSA. LVRI, LVMI, and RWT were used as myocardial remodeling parameters [37].

Native T<sub>1</sub> mapping was performed using an ECG-triggered free-breathing slice-interleaved T<sub>1</sub> (STONE) sequence with the following parameters: 5 slices, in-plane resolution = 2.1 × 2.1 mm<sup>2</sup>, slice thickness = 8 mm, slice gap = 4 mm, field-of-view = 360 × 351 mm<sup>2</sup>, TR/TE/flip angle = 2.8 ms/1.4 ms/70°, TFE factor = 86, a sensitivity encoding (SENSE) rate = 2, linear ordering, 10 linear ramp-up pulses and bandwidth = 1894 Hz, acquisition duration = 1 min 38 s. Eleven inversion images were acquired with inversion times of ∞, 130, 1030, 1930, 2830, 3730, 350, 1250, 2150, 3050, and 3950 ms [38, 39]. The inversion

preparation pulse was an adiabatic hyperbolic secant pulse with an 11 ms pulse duration. The radiofrequency (RF) excitation pulse was a slice-selective Sinc-Gauss pulse with a duration of 0.43 ms. Images were acquired without prospective slice tracking, and the slice order was 1-4-2-5-3. STONE T<sub>1</sub> maps were generated by performing voxel-wise curve fitting of the signal with a 2P model to the image intensities of all four T<sub>1</sub>-weighted imaging volumes [38–40]. The crosses on the inversion recovery curve correspond to different images acquired along the recovery curve with pre-defined inversion times. Short-axis slices of native T<sub>1</sub> mapping images were analyzed using custom software (MedI-ACare, Boston, Massachusetts) on MATLAB (MathWorks Inc., Natick, Massachusetts, USA). To calculate the global native T<sub>1</sub> of the LV, 5 short-axis LV slices were divided



**Fig. 1** Native T<sub>1</sub> maps from base to apex slices for each group. Native T<sub>1</sub> maps were performed using STONE sequence from basal (top) to apex (bottom). Four different individuals represent each study subgroup (left to right): healthy subjects (global native T<sub>1</sub> time, 1074 ms), obese group (global native T<sub>1</sub> time, 1085 ms), DM group (global native T<sub>1</sub> time, 1125 ms), and Diabesity group (global native T<sub>1</sub>, 1190 ms). Bulls-eye representations in the bottom row show per segment native T<sub>1</sub> values and corresponding average values in the center. DM diabetes mellitus

into 6 segments for basal and mid-ventricular slices, and into 4 segments for the apical slice using the anterior right ventricular-LV insertion point as the reference (Fig. 1).

CMR-FT analysis was performed using CVi42 (Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). Corresponding two- and four-chamber LV images were uploaded into the software. Endo- and epicardial borders on the end-diastolic frame of each slice were manually traced (excluding papillary muscles and trabeculae). Tracking was visually reviewed and manually corrected by border adjustment with consecutive reapplication of the algorithm as necessary. GLS, 2-chamber strain, and 4-chamber strain were automatically calculated and displayed for further analysis (Fig. 2).

### Triglyceride-glucose (TyG)-BMI index as an insulin resistance biomarker

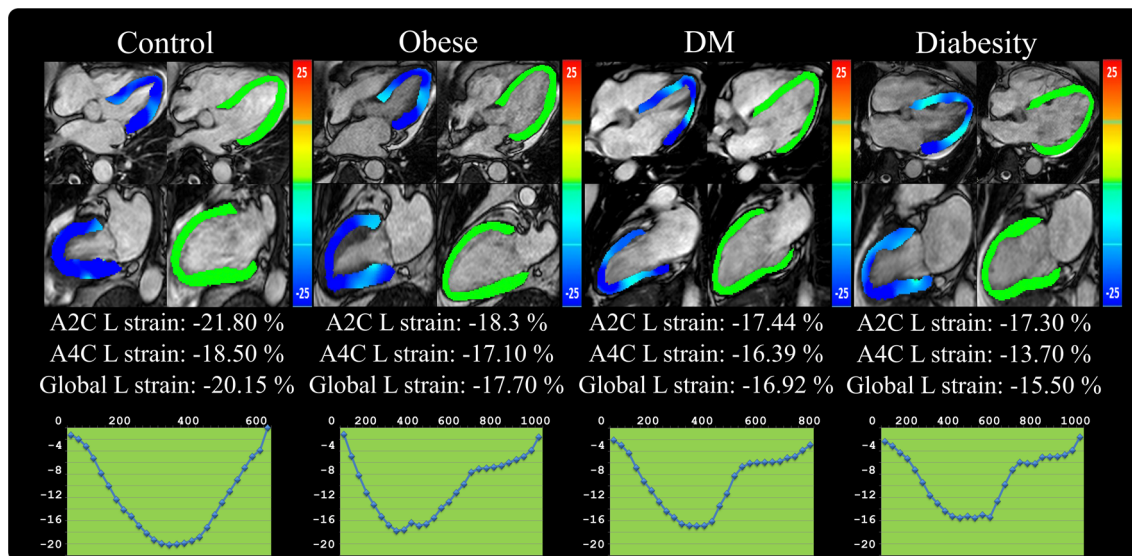
The metabolic biomarker TyG-index was calculated as  $\text{Ln} [\text{triglyceride level (mg/dL)} \times \text{fasting plasma glucose level (mg/dL)/2}]$  to estimate insulin resistance in individuals with DM [41, 42]. The product of TyG-index and BMI (TyG-BMI index) has previously proven to be a clinically useful surrogate marker for early identification of insulin resistance and cardiovascular events, particularly in obese individuals [43–45].

### Data analysis and statistics

Statistical analyses were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean  $\pm$  standard deviations (SD), while categorical variables are expressed as a frequency (%). Differences in baseline characteristics according to diabetes status were evaluated by one-way analysis of variance. Scheffe and Games–Howell post hoc analyses were performed for equal and unequal variances, respectively. Chi square tests were used to compare categorical data. The Bonferroni correction adjusted for multiple comparisons. Univariate linear regression analyses were used to test confounding variables for GLS and native  $T_1$ . Parameters significantly associated with GLS and native  $T_1$  were included in the analysis of covariance models. To test for synergism between two entities, the interaction value, such as partial eta squared ( $\eta^2$ ), and its significance were calculated via linear regression analysis.

### Results

Clinical and demographic characteristics of 162 patients were separated into 3 groups and 45 healthy controls (Table 1). Hypertension and ACEI/ARB usage were more prevalent in the DM and Diabetesity groups ( $P < 0.01$ , for both), while hyperlipidemia and statin usage were more frequent in obese patients ( $P < 0.01$ , for obese and



**Fig. 2** Global longitudinal strain measurements in two and four chamber for each group. Peak (blue) and rest (green) global longitudinal strain (GLS) measurements superimposed on cine images (top row) are depicted for the four study groups: healthy subjects (GLS,  $-20.15\%$ ), obese group (GLS,  $-16.92\%$ ), DM group

(GLS,  $-17.70\%$ ), Diabetesity group (GLS,  $-15.50\%$ ). The bottom row covers GLS over one heart cycle for each subject. *DM* indicates diabetes mellitus, *A2C* apical two chambers, *A4C* apical four chambers, *L* longitudinal

**Table 1** Clinical and demographic features of patients and control cohorts

Characteristics	Control N = 45	Obese N = 36	DM N = 53	Diabetesity N = 73
Age, years	52.9 ± 12	52.3 ± 11	58.5 ± 12 <sup>†‡</sup>	56.7 ± 10*
Men, n (%)	27 (60%)	24 (63%)	34 (61%)	42 (55%)*
Systolic blood pressure, mmHg	125 ± 12	127 ± 15	132 ± 19 <sup>‡</sup>	128 ± 16
Diastolic blood pressure, mmHg	73 ± 11	76 ± 12	75 ± 13	77 ± 11
BMI, kg/m <sup>2</sup>	24.0 ± 2	31.1 ± 4 <sup>†</sup>	28.0 ± 2 <sup>‡</sup>	33.9 ± 2*
CAD, n (%)	0 (0%)	4 (11%)	7 (13%)	7 (9%)
Hypertension, n (%)	1 (2%)	13 (36%) <sup>†</sup>	25 (47%) <sup>†‡</sup>	33 (45%)*
Hyperlipidemia, n (%)	15 (33%)	19 (52%) <sup>†</sup>	13 (24%) <sup>†‡</sup>	35 (47%)*
Smoking, n (%)	8 (17%)	5 (14%) <sup>†</sup>	19 (35%) <sup>‡†</sup>	20 (27%)*
NYHA class				
II–III	Nan	8 (22%)	11 (21%)	27 (37%)*
IV		5 (13%)	3 (5%) <sup>‡</sup>	17 (23%)*
Oral anti-diabetic, n (%)	0 (0%)	0 (0%)	41 (77%) <sup>†‡</sup>	48 (65%)*
Insulin, n (%)	0 (0%)	0 (0%)	18 (34%) <sup>†‡</sup>	31 (42%)*
Diuretic, n (%)	0 (0%)	7 (19%)	11 (20%)	24 (32%)*
ACE inhibitor/ARB, n(%)	4 (9%)	10 (27%) <sup>†</sup>	16 (30%) <sup>†</sup>	24 (32%)*
Statin, n (%)	13 (29%)	13 (36%) <sup>†</sup>	9 (16%) <sup>†‡</sup>	30 (41%)*
Beta blocker, n (%)	4 (9%)	7 (19%) <sup>†</sup>	22 (41%) <sup>†‡</sup>	18 (24%)*
Blood glucose, mg/dl	90 ± 13	101 ± 10	123 ± 21 <sup>†‡</sup>	131 ± 21*
HbA1c (%)	5.5 ± 0.5	5.3 ± 0.3	7.1 ± 0.7 <sup>†‡</sup>	7.4 ± 0.8*
LDL, mg/dl	109 ± 25	118 ± 27 <sup>†</sup>	107 ± 17 <sup>‡</sup>	114 ± 23*
Triglyceride, mg/dl	133 ± 29	154 ± 43 <sup>†</sup>	145 ± 37 <sup>†‡</sup>	157 ± 46*
C-reactive protein, mg/l	2.1 ± 0.8	2.5 ± 1.1 <sup>†</sup>	2.2 ± 0.7 <sup>†‡</sup>	2.5 ± 1.1*
Creatinine, mg/dl	0.89 ± 0.21	0.94 ± 0.19 <sup>†</sup>	0.98 ± 0.19 <sup>†</sup>	0.95 ± 0.20
TyG index	8.4 ± 0.2	8.7 ± 0.3 <sup>†</sup>	9.1 ± 0.5 <sup>†</sup>	9.3 ± 0.3*
TyG-BMI index	208 ± 19	258 ± 32 <sup>†</sup>	266 ± 18 <sup>†‡</sup>	302 ± 23*

*BMI* body mass index, *CAD* coronary artery disease, *HFpEF* heart failure with preserved ejection fraction, *NYHA* New York Heart Association, *ACEI/ARB* angiotensin-converting enzyme/angiotensin receptor blockers, *LDL* low density lipoprotein, *CRP* C-reactive protein, *TyG index* Triglyceride–glucose index

Scheffe Post-Hoc and Games–Howell Post-Hoc analyses were performed for equal and unequal variance, respectively, and categorical variables were compared by the Pearson Chi Square test. Bonferroni correction was used for multiple comparisons ( $p < 0.01$ ). Continuous variables are expressed as mean ± standard deviations (SD), while categorical variables are expressed as a frequency (%). There were no significant differences between the groups, except \*for comparison with DM group, <sup>‡</sup>for comparison with obese group and <sup>†</sup>for comparison with control group

Diabetesity groups). Consistent with HFpEF disease, diuretic usage and heart failure symptoms were most prevalent in the Diabetesity group ( $P < 0.0001$ , for all). Additionally, both the TyG index ( $8.7 \pm 0.3$  for obese,  $9.1 \pm 0.5$  for DM and  $9.3 \pm 0.3$  in patients\ group compared to  $8.4 \pm 0.2$  for control group) and the TyG-BMI index ( $258 \pm 32$  for obese,  $266 \pm 18$  for DM and  $302 \pm 23$  for Diabetesity groups compared to  $208 \pm 19$  for control group) were greater in patients than in control subjects ( $P < 0.01$ ).

TTE and CMR findings for patients and control subjects are summarized in Table 2. Myocardial remodeling parameters including RWT ( $0.52 \pm 0.04$ ,  $p < 0.0001$ ), LVMI ( $66 \pm 13$ ,  $p = 0.002$ ) and LVRI ( $0.84 \pm 0.19$ ,  $p = 0.004$ ) were significantly elevated in the Diabetesity group relative to the

other three groups. Native  $T_1$  was significantly altered in DM ( $1129 \pm 25$  ms) and Diabetesity groups ( $1162 \pm 37$  ms) compared to the obese ( $1069 \pm 29$  ms) and control groups ( $1071 \pm 27$  ms) ( $P < 0.01$  for all). Comparisons among the DM and Diabetesity groups showed a significant increase in native  $T_1$  in the Diabetesity group ( $1162 \pm 37$  ms) ( $P < 0.0001$ ; Fig. 1). GLS was significantly impaired in the Diabetesity group ( $-15 \pm 2\%$ ,  $P < 0.01$ , Fig. 2), while no statistically significant difference was detected among the remaining groups ( $P > 0.01$ , Fig. 3). Imaging markers of remodeling, myocardial fibrosis, and longitudinal contractility were similar between the control and obese groups (RWT:  $0.39 \pm 0.04$  vs  $0.42 \pm 0.06$ ; LVMI:  $46 \pm 11$  g/m<sup>2</sup> vs  $47 \pm 9$  g/m<sup>2</sup>; LVRI:  $0.52 \pm 0.12$  vs  $0.55 \pm 0.32$ ; native

**Table 2** Transthoracic echocardiography and Cardiac MRI parameters

Parameters	Control	Obese	DM	Diabetesity
TTE features	N=40	N=28	N=45	N=59
Peak E, cm/s	100±36	115±54 <sup>†</sup>	97±30 <sup>‡†</sup>	109±35*
Peak A, cm/s	111±30	78±25 <sup>†</sup>	74±21 <sup>†</sup>	75±26
E/A ratio	1.17±0.3	1.61±0.4 <sup>†</sup>	1.54±0.3 <sup>†</sup>	1.85±0.2*
Mean E', cm/s	14.1±2.8	8.2±2.3 <sup>†</sup>	7.8±2.2 <sup>†</sup>	7.5±2.9*
Mean E/E' ratio	7.6±1.8	14.8±3.2 <sup>†</sup>	14.2±3.4 <sup>†</sup>	16.8±4.1*
Deceleration time, ms	191±39	185±24	193±31 <sup>‡</sup>	199±42*
Estimated PASP, mmHg	13±3.7	20±4.5 <sup>†</sup>	26±8.6 <sup>‡†</sup>	25±7.4
CMR features	N=45	N=36	N=53	N=73
LVEDVI, ml/m <sup>2</sup>	81±12	79±14	79±16	80±13
LVESVI, ml/m <sup>2</sup>	30±6	28±7	29±10	31±8
LV ejection fraction, %	61±5	63±5	62±7.3	61±8
Cardiac index, ml/min/m <sup>2</sup>	3197±457	3112±458	3130±546	3225±569
Relative wall thickness	0.39±0.04	0.42±0.06	0.43±0.03 <sup>†</sup>	0.52±0.04*
LV mass index, g/m <sup>2</sup>	46±11	47±9	53±9 <sup>†‡</sup>	66±13*
LV remodeling index	0.52±0.12	0.55±0.32	0.69±0.17 <sup>†‡</sup>	0.84±0.19*
GLS, %	−17.2±1.8	−16.7±2.2	−16.5±2.4	−15.0±2.1*
native T <sub>1</sub> , ms	1071±27	1069±29	1129±25 <sup>†‡</sup>	1162±37*

TTE transthoracic echocardiography, CMR cardiovascular magnetic resonance, Peak E Peak A, Mean E' mean septal mitral relaxation velocity, PASP pulmonary artery systolic pressure, LVEDVI left ventricular end-diastolic volume index, LVESVI left ventricular end-systolic volume index; ch chamber, GLS global longitudinal strain. (There were 17% missing data for TTE)

Scheffe Post-Hoc and Games–Howell Post-Hoc analyses were performed for equal and unequal variance, respectively, and categorical variables were compared by the Pearson Chi Square test. Bonferroni correction was used for multiple comparisons ( $p < 0.01$ ). Continuous variables are expressed as mean ± standard deviations (SD). There were no significant differences between the groups, except \*for comparison with DM group, <sup>‡</sup>for comparison with Obese group and <sup>†</sup>for comparison with control group

T<sub>1</sub>: 1071 ± 27 ms vs 1069 ± 29 ms; GLS: −17.2 ± 1% vs −16.6 ± 2%, respectively) ( $P > 0.01$  for all) (Table 2). To illustrate potential correlation between insulin resistance and myocardial structure and function, the relationship between TyG-BMI index vs. GLS ( $R = 0.590$ ,  $P < 0.0001$ ) and TyG-BMI index vs. native T<sub>1</sub> ( $R = 0.349$ ,  $P < 0.001$ ) was depicted (Fig. 4). TyG-BMI index was significantly correlated with mean E' ( $R = -0.552$ ,  $P < 0.0001$ ), and the mean E/E' ratio ( $R = 0.576$ ,  $P < 0.0001$ ) emphasized the association between insulin resistance and LV diastolic function (Fig. 5).

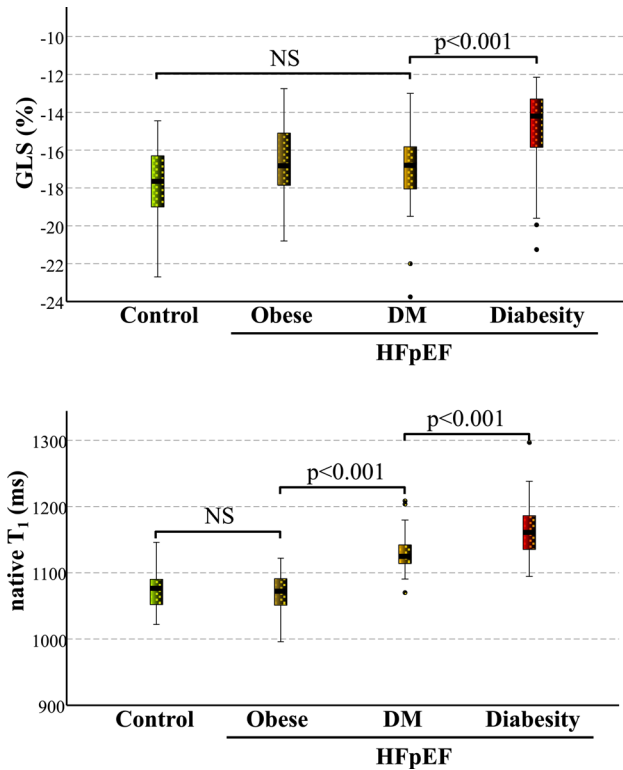
In univariate linear regression analyses, GLS was associated with gender ( $\beta = 0.81$ ,  $R^2 = 0.03$ ,  $p = 0.03$ ), ACEI/ARB usage ( $\beta = 0.86$ ,  $R^2 = 0.03$ ,  $p = 0.012$ ), and TyG-BMI index ( $\beta = 0.02$ ,  $R^2 = 0.35$ ,  $p < 0.0001$ ) (Table 3). Native T<sub>1</sub> was associated with age ( $\beta = 0.79$ ,  $R^2 = 0.03$ ,  $p = 0.01$ ), hypertension ( $\beta = 17.74$ ,  $R^2 = 0.1$ ,  $p = 0.01$ ), and TyG-BMI index ( $\beta = 0.6$ ,  $R^2 = 0.16$ ,  $p < 0.001$ ) (Table 3). Consequently, analysis of covariance controlled for age, gender, ACEI/ARB usage, hypertension, and TyG-BMI index. Table 4 lists the fibrosis and longitudinal contractility markers and the corresponding predicted means for each subgroup after adjustment for confounding variables.

A statistically significant difference was observed between the Diabetesity group and all other groups regardless of adjusting for confounders ( $P < 0.01$ ), with the notable exception of GLS. There was no difference in GLS between the Diabetesity group vs. obese and DM groups after adjustment for TyG-BMI and Bonferroni correction ( $P = 0.03$ ; Table 4).

Significant synergistic effects between obesity and DM ( $f = 49.89$ ,  $p < 0.0001$ ,  $\eta_p^2 = 0.288$  on GLS, and  $f = 118.92$ ,  $p = 0.002$ ,  $\eta_p^2 = 0.273$  on native T<sub>1</sub>) were more powerful than the effect of each individual comorbidity [ $(f = 19.29$ ,  $p = 0.003$ ,  $\eta_p^2 = 0.095$  for DM and  $f = 9.5$ ,  $p = 0.058$ ,  $\eta_p^2 = 0.048$  for obesity on GLS) vs. ( $f = 87.11$ ,  $p = 0.015$ ,  $\eta_p^2 = 0.182$  for DM and  $f = 14.6$ ,  $p = 0.14$ ,  $\eta_p^2 = 0.068$  for obesity on native T<sub>1</sub>)] (Table 5).

## Discussion

This retrospective study investigates the interaction between obesity and DM on the myocardium in HFpEF patients by assessment of LV remodeling, fibrosis, and longitudinal contractility. The findings make several contributions to current

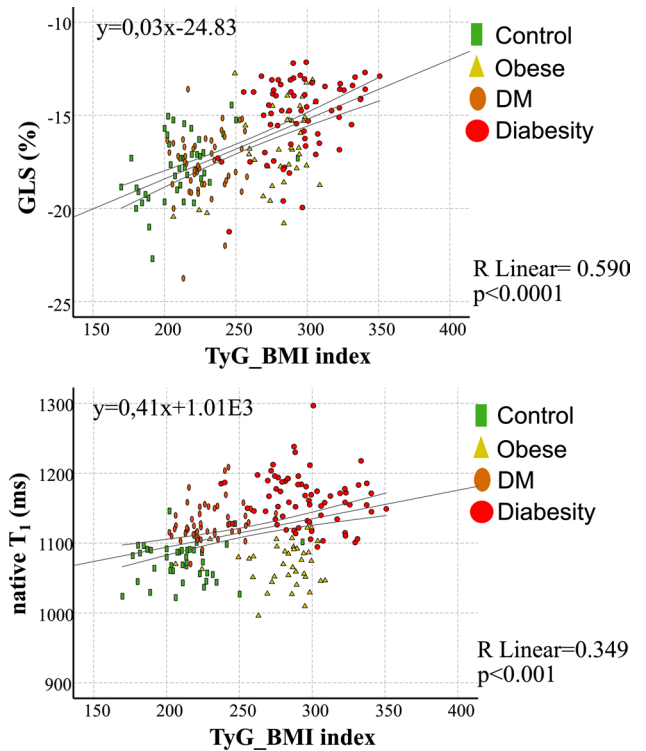


**Fig. 3** Boxplots illustrating mean  $\pm$ SD value of GLS and native T<sub>1</sub> for each group. Association between the groups in terms of GLS and native T<sub>1</sub>. Box plots are consistent to the visual assessment. DM diabetes mellitus, GLS global longitudinal strain, TyG\_BMI index triglyceride–glucose–Body mass index, NS statistically non-significant

literature on HFpEF related processes: (1) Obesity and DM have a negative synergistic relationship. Co-occurring DM and obesity show high native T<sub>1</sub>, deterioration in global longitudinal strain, and increased LV remodeling; (2) DM is associated with structural myocardial changes, whereas obesity alone is not; and (3) there is a well-recognized association between insulin resistance and GLS, native T<sub>1</sub>, and LV diastolic function parameters.

**CMR parameters and the synergism of comorbidities**

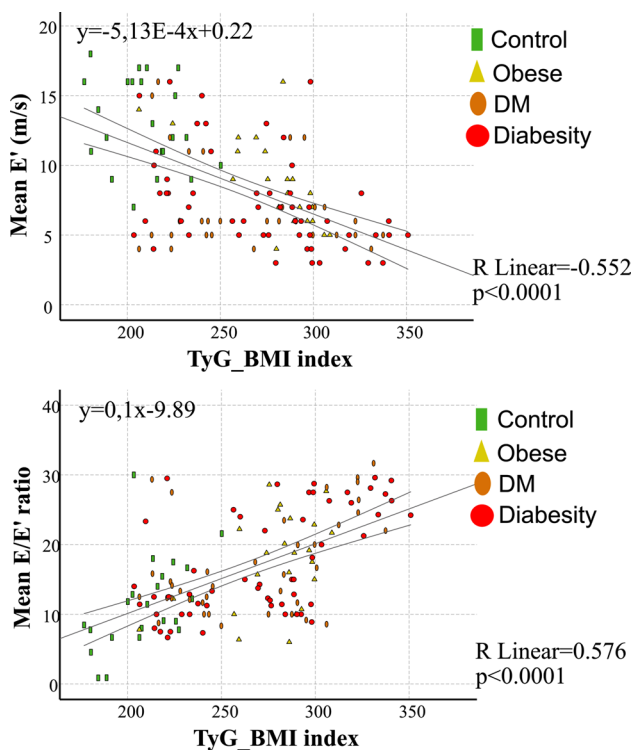
Structural myocardial changes in HFpEF patients, such as diffuse fibrosis, LV remodeling, and impairment in longitudinal contractility, are well documented [5, 27, 46] and the influence of isolated obesity or DM on these changes has been reported [12, 14, 15, 21]. Lindman et al. observed an elevation in LV filling pressures in obese and diabetic HFpEF patients compared to those without DM in their randomized multicenter RELAX study [4]. In a report from the I-Preserve study [16], presence of diabetes in obese HFpEF patients is not only associated with cardiac changes in structure and function, but also correspond to symptom severity. HFpEF patients with obesity and DM are generally more



**Fig. 4** Association between GLS, native T<sub>1</sub>, and TyG-BMI index. Scatterplots show the relationship between GLS, native T<sub>1</sub>, and the TyG-BMI index. Linear regression correlation coefficients (R) corresponding p values, and linear regression equations are listed. Each study subgroup is color and shape coded (controls=green squares; non-diabetic obese=yellow triangles; lean diabetics=orange ovals; obese diabetics=red circles). DM diabetes mellitus, GLS global longitudinal strain, TyG\_BMI index triglyceride–glucose–Body mass index

susceptible to clinical signs of cardiac congestion, worse quality of life, and poorer prognosis with an increased risk for cardiovascular mortality and HF hospitalization. Our study results extend these findings to non-obese diabetic patients. Moreover, our study shows that myocardial fibrosis calculated by native T<sub>1</sub>, myocardial longitudinal contractility measured by GLS, and LV remodeling markers such as LVMI, LVRI, and RWT can differentiate between obese and diabesity patients.

Preclinical studies in HFpEF rats have shown synergism between obesity and hypertension in the development of diastolic dysfunction [47]. Similar to Brandt et al., animals in our study were divided into four groups. The group characterized by obesity and hypertension showed a high remodeling ratio, increased inflammation, expansion of the extracellular spaces, and accumulation of collagen tissue—all biomarkers of myocardium injury and interstitial fibrosis. In our clinical study, tissue characterization by CMR replicates some of these histological findings. In particular, we found that combinations of comorbidities had different effects on



**Fig. 5** Association between mean mitral annular E' velocity, mean trans-mitral early diastolic velocity ratio (E/E'), and the TyG-BMI index. Scatterplots show the relationship between mean E', mean E/E', and the TyG-BMI index. Linear regression correlation coefficients (R) corresponding p values, and linear regression equations are listed. Each study subgroup is color and shape coded (controls = green squares; non-diabetic obese = yellow triangles; lean diabetics = orange ovals; obese diabetics = red circles). DM diabetes mellitus, TyG\_BMI index triglyceride–glucose–Body mass index

native T<sub>1</sub> time, a surrogate marker of myocardial fibrosis. Our detailed CMR phenotyping was therefore able to non-invasively confirm the synergistic effect between obesity and DM on the myocardium.

**Table 3** Association between traditional risk predictors for myocardial disease and GLS vs. native T<sub>1</sub>

Predictors	GLS			Native T <sub>1</sub>		
	β	95% CI	R <sup>2</sup>	β	95% CI	R <sup>2</sup>
Age	0.008	− 0.02;0.04	0.002	0.79	0.17;1.41	0.03 <sup>†</sup>
Gender	0.81	0.12;1.51	0.03 <sup>†</sup>	− 13.16	− 27.56;1.23	0.02
HTN	0.15	− 0.23;0.54	0.004	17.74	9.95;25.53	0.10 <sup>†</sup>
ACEI/ARB usage	0.86	0.05;1.67	0.03 <sup>†</sup>	16.72	0.38;33.1	0.02
B-Blocker usage	− 0.41	− 1.21;0.38	0.007	15.09	− 1.28;31.47	0.02
TyG_BMI index	0.02	0.01;0.03	0.35 <sup>†</sup>	0.6	0.47;0.72	0.16 <sup>†</sup>

β indicates standardized regression coefficient. P value is not significant, except (†)

CI indicates confidence interval, GLS, Global longitudinal strain, ACEI/ARB angiotensin-converting enzyme/Angiotensin receptor blockers, HTN hypertension, TyG-BMI triglyceride–glucose index–Body mass index

### Cardiac alterations in patients with obesity or DM

Although the ASIAN-HF [7] registry compared isolated obesity with isolated DM in HFpEF patients, our direct comparisons verify the importance of DM prevalence in myocardial deterioration. In its study of 6,480 enrolled patients with HF and multi comorbidities from various Asian countries, isolated diabetics had the highest incidence of all-cause mortality and HF related hospitalization. In subgroup analyses for HFpEF patients, isolated diabetics had increased LVMI and RWT, LV filling pressures, and left atrial volume indexes by TTE indicating a higher degree of subclinical damage, LV remodeling and diastolic dysfunction than their metabolic or diabetic obese counterparts. In our study, DM patients had increased LVMI and LV remodeling indexes relative to healthy controls; furthermore, CMR imaging demonstrated myocardial fibrosis and impairment in LV longitudinal contractility despite maintained LV function.

### Insulin resistance and heart failure

Insulin resistance not only has a strong association with HF, but also predicts the development of HF in cohorts with various risk factors [17, 20, 22, 48]. In a mice study, cardiomyocyte-specific deletion of insulin receptors led to decreased insulin-stimulated glucose uptake and a decline in cardiac function [48]. Insulin resistance is a characteristic feature of HF pathophysiology that affects symptoms and mortality [17].

Abdominal obesity is closely associated with insulin resistance and diabetes manifestation [12, 23, 49]. In this context, DM and obesity are associated with myocardial disease, even after adjustment for traditional risk factors. In a community-dwelling cohort of 22,681 participants, Savji et al. [11] showed the effects of obesity and cardiometabolic traits on incident of HFpEF and HFrfEF. They observed that greater BMI portends higher HFpEF risk,



**Table 4** Change in GLS and Native T<sub>1</sub> after adjustment for significant confounders

Parameters	Control (95% CI)	Obese (95% CI)	DM (95% CI)	Diabetesity (95% CI)
Age, gender, HTN, and ACEI/ARB adjusted				
GLS, %	− 17.2 (− 17.9;− 16.6)	− 16.8 (− 17.3;− 16.1)	− 16.6 (− 17.0;− 15.9)	− 15.1 (− 15.7;− 14.6)*
Native T <sub>1</sub> , ms	1075.4 (1065;1085)	1070.9 (1061;1080)	1127.6 (1119;1135) <sup>‡</sup>	1160.4 (1153;1167)*
Age, gender, HTN, ACEI/ARB and TyG-BMI adjusted				
GLS, %	− 17.2 (− 18;− 16.5)	− 16.9 (− 17.6;− 16.3)	− 16.7 (− 17.2;− 15.7)	− <b>15.8 (− 16.5;− 14.9)</b>
Native T <sub>1</sub> , ms	1073.2 (1059;1086)	1071.0 (1060;1081)	1126.4 (1115;1136) <sup>‡</sup>	1163.4 (1150;1176)*

GLS Global longitudinal strain, DM diabetes mellitus, ACEI/ARB angiotensin-converting enzyme/angiotensin receptor blockers, HTN hypertension, TyG-BMI Triglyceride–glucose–Body mass index

Predicted means after linear regression. Multiple comparisons of estimated averages have been adjusted using Bonferroni correction ( $p < 0.01$  in sig.). There were no significant differences between the groups, except \*for comparison with DM group, <sup>‡</sup>for comparison with obese group and <sup>†</sup>for comparison with control group

**Table 5** Interaction between DM and obesity on GLS and native T<sub>1</sub>

	F value	d.f.	P value	$\eta_p^2$
GLS				
DM	19.29	1	0.003	0.095
Obesity	9.5	1	0.058	0.048
DM & obesity synergism	49.89	1	< 0.0001	0.288
Native T <sub>1</sub>				
DM	87.11	1	0.015	0.182
Obesity	14.6	1	0.14	0.068
DM & obesity synergism	118.92	1	0.002	0.273

d.f. degrees of freedom,  $\eta_p^2$  partial eta squared from linear regression, DM indicates diabetes mellitus, GLS global longitudinal strain

and insulin resistance is associated with HFpEF with a hazard ratio of 1.20. Their findings are consistent with the results of our study, in which we observed that a high BMI and high insulin resistance tend to deteriorate myocardial structure in HFpEF patients. In another study, increased insulin resistance was independently associated with LVMI, LV filling pressures, and GLS [20]. Similarly, we show the association of insulin resistance with LVMI and GLS and observed moderate correlation between insulin resistance and LV filling pressures parameters. Furthermore, elevation of Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), a common marker for insulin resistance, was associated with the onset of HFpEF [17]. TyG-BMI index, our approach to insulin resistance quantification based on several contemporary research studies [41–44], showed a strong correlation with HOMA-IR and basal insulin level, as well as high sensitivity and specificity for recognition of insulin resistance [41–44]. The observed association between insulin resistance and myocardial alterations warrant further investigation on reversibility.

Our study has some limitations. With late gadolinium enhancement and extracellular volume (ECV) quantification,

CMR provides further myocardial characterization techniques that are not consistently available in our study cohort. Contrary to native T<sub>1</sub> time, an established marker of myocardial fibrosis [29, 50, 51], both LGE and ECV require gadolinium administration and are therefore not routinely performed at our institution. Given the context of our retrospective observational study, HOMA-IR, which currently uses insulin resistance quantification in clinical practice, was also unavailable. However, its surrogate, the TyG-BMI index, provided results consistent with the contemporary literature [41–44]. Lastly, echocardiography data was lacking in 17% of our cohort. Considering its contribution to the H2FPEF score system, the HFpEF diagnosis may be under-represented in a small number of patients.

## Conclusions

We demonstrate that DM is associated with myocardial fibrosis and impairment in longitudinal contraction independent of confounding factors, whereas no such relationship is observed in obese patients without DM. However, presence of obesity and DM in the same HFpEF patients is associated with a negative synergistic effect. Furthermore, the close correlation of CMR biomarkers with TyG-BMI index indicates that insulin resistance contributes to cardiac function and structure deterioration in HFpEF.

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## Compliance with ethical standards

**Conflict of interest** All authors declare that they have no conflict of interests.

**Ethical approval** The study protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

**Informed Consent** A written informed consent was obtained from each study participant.

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