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Association of body fat mass with left ventricular longitudinal myocardial systolic function in type 2 diabetes mellitus

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ABSTRACT

Background: Left ventricular (LV) longitudinal myocardial systolic dysfunction (LVSD) has been identified in type 2 diabetes mellitus (T2DM) patients, and it should be considered the first marker of a preclinical form of DM-related cardiac dysfunction. Overweight has been postulated to contribute to the development of LVSD in T2DM patients, but the impact of amount of body fat mass on LVSD in T2DM patients remains uncertain.

Methods: We studied 71 asymptomatic T2DM patients with preserved LV ejection fraction (LVEF) (all≥55%) without coronary artery disease. LVSD for T2DM patients with preserved LVEF was identified as global longitudinal strain (GLS)<18%. Body fat mass was measured with a commercially available body composition analyzer (In Body S-10), and corrected by body surface area (BFI: body fat index).

Results: Univariate logistic regression analysis revealed that body weight, body mass index (BMI), and BFI were all associated with LVSD, whereas multivariate logistic regression analysis showed BFI was the only variable independently associated with LVSD (OR 1.147; 95% CI 1.001–1.314; p=0.027). For sequential logistic regression models to predict LVSD, clinical variables including age, DM duration, and HbA1c tended to be improved by addition of BMI, but without statistical significance (p=0.09), while it was significantly improved by addition of BFI (p=0.047).

Conclusions: Using BFI for the control of body compression by means of a bioelectrical impedance assay is simple and easy-to-use, and this may have clinical implications for better management of T2DM patients with preserved LVEF to prevent future development of DM-related cardiac dysfunction.

Introduction

Diabetes mellitus (DM)-related cardiac dysfunction is currently defined as a form of left ventricular (LV) diastolic dysfunction, which is the earliest functional alteration in the course of DM-related diabetic injury[1-4], leading to the development of heart failure (HF) with preserved ejection fraction (HFpEF). Furthermore, the presence of LV longitudinal myocardial systolic dysfunction (LVSD) has been identified in DM patients with preserved LV ejection fraction (LVEF) without overt coronary artery disease or HF [5-17], and should be considered the first marker of a preclinical form of DM-related cardiac dysfunction in such patients[9, 16, 17]. Thus, the coexistence of LVSD with LV diastolic dysfunction in patients with DM leads to HFpEF. Several investigators have shown the association of overweight with LV functional variables including LV diastolic function and LV longitudinal myocardial systolic function in DM patients with preserved LVEF[18-24]. In addition, our group previously reported that LV longitudinal myocardial function in type 2 DM (T2DM) patients with preserved LVEF may be more susceptible to the effect of overweight compared to that in healthy subjects[19]. Overweight has been postulated to contribute to the development of LVSD in T2DM patients, but the impact of the amount of body fat mass on LVSD in T2DM patients remains uncertain. Furthermore, body mass index (BMI) or body weight is often used as a parameter of overweight, but does not accurately reflect the amount of body fat mass because the former is a simple parameter of body weight.

The aim of this study was thus to investigate by means of a bioelectrical impedance assay the effect of body fat mass on LV function, especially LV longitudinal myocardial systolic function in asymptomatic T2DM patients with preserved LVEF without coronary artery disease.

Materials and Methods

Study population

We retrospectively enrolled 80 asymptomatic T2DM hospitalized patients at Kobe University Hospital who underwent both echocardiography and body composition analysis between

September 2013 and December 2017. Patients were excluded from enrolment study if they met any of the following criteria: (1) history or suspicion of coronary artery disease; (2) LVEF <55%; (3) previous history of open-heart surgery; (4) serious renal dysfunction defined as glomerular filtration rate <30 mL/min/1.73m^2; (5) uncontrolled hypertension >180/100mmHg; (6) more than moderate valvular heart disease; (7) atrial fibrillation. All patients underwent exercise stress or pharmacological testing such as treadmill exercise or stress myocardial perfusion scintigraphy less than 2 weeks after admission, and none of them showed an ischemic response. The diagnosis of T2DM was based on the World Health Organization criteria[25]. Dyslipidemia was defined as fasting low-density lipoprotein ≥140 mg/dL, or current use of anti-dyslipidemia drugs[26]. Blood pressure was obtained simultaneously with transthoracic echocardiography. Hypertension was then defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or current treatment with anti-hypertensive agents[27]. This study was approved by the local ethics committee of our institution (No. 180086).

Echocardiographic examination

Within two weeks after admission, all patients underwent a resting standard echocardiographic examination by means of a 3.5 MHz transducer on a single commercially available echocardiographic system (Vivid E9; General Electric Medical Systems, Milwaukee, WI). Digital routine grayscale two-dimensional cine loops from three consecutive heart beats were obtained at end-expiratory apnea from standard parasternal and apical views and used for speckle-tracking strain analysis. Sector width was optimized to allow complete myocardial visualization while maximizing the frame rate. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[28].

LV speckle-tracking strain analysis

Two-dimensional speckle-tracking strain analysis was performed with dedicated software (EchoPAC version 113; General Electric Medical Systems) to evaluate LV longitudinal myocardial

function, which was assessed as global longitudinal strain (GLS). GLS was determined as the averaged peak longitudinal strain of 18 segments from the three standard apical views, and was expressed as an absolute value in accordance with current guidelines (Figure 1)[28]. As previously detailed, LVSD in T2DM patients with preserved LVEF was set at GLS<18%[8-10, 17, 29, 30].

Body compression analysis

All patients underwent body compression analysis by means of a commercially available bioelectrical impedance assay within 7 days of echocardiography (InBody S10 body composition analyzer; Biospace, Tokyo, Japan). The body compression analysis using this system was described elsewhere[31-33]. Briefly, electricity is applied at frequencies of 1, 5, 50, 250, 500 kHz, and 1 MHz throughout the body. Whole-body impedance was then measured using an ipsilateral foot-hand electrical pathway. Measurements at multiple frequencies allow accurate and separate estimation of both intracellular and extra cellular water content inside and outside cells. Body weight, body fat mass, and skeletal muscle mass were obtained in this study according to the manufacturer's guidelines. Body fat mass was then corrected by body surface area to obtain the body fat index (BFI). The reliability and accuracy of the measurements using bioelectrical impedance assay has been already reported by various authors[34-36].

Statistical analysis

Continuous variables were expressed as mean values ± SD, while categorical data were summarized as frequencies and percentages. The parameters of the two subgroups were compared by using the unpaired t test. Proportional differences were evaluated with Fisher's exact test. Independent association of GLS with clinical and echocardiographic parameters in DM patients was evaluated with multiple regression analysis. Sequential logistic regression models were used to determine the utility of GLS over that of clinical variables including age, DM duration, HbA1c and BMI. An improvement in associated value was interpreted as a statistically significant increase in the global log-likelihood χ^2 of the model. Statistical significance for each step was basically defined as p value <0.05. MedCalc version 15.11.4 (MedCalc Software, Mariakerke, Belgium) was used for all

analyses.

Results

Baseline characteristics of patients

Of the 80 T2DM patients enrolled in this study, 9 patients (8.9%) were excluded from all subsequent analyses because of suboptimal quality of echocardiographic images. As a result, the final study population consisted of 71 T2DM patients. LVSD, defined as GLS <18% was observed in 39 patients (55%), and the remaining 32 patients (45%) were classified as T2DM patients without LVSD (Table 1). Clinical characteristics and echocardiographic parameters of the two groups were similar except that LV mass index for was significantly larger (76 ± 20 g/m^2 vs. 71 ± 19 g/m^2, $p<0.05$), and GLS was significantly lower (16.3 ± 1.5% vs. 19.9 ± 1.1%, $p<0.001$) for T2DM patients with LVSD than for those without LVSD. Body compression analysis showed that body weight (72.1±15.1 kg vs. 61.4±15.9 kg, $p<0.01$), body mass index (BMI) (28.3±5.2 kg/m^2 vs. 24.4±6.7 kg/m^2, $p<0.01$), body fat mass (24.9±11.3 kg vs. 16.5±10.7 kg, $p<0.01$), and BFI (9.4±4.4 kg/m^2 vs. 6.5±4.9 kg/m^2, $p<0.01$) were all significantly larger for T2DM patients with LVSD than for those without LVSD. The inter- and intra-observer reproducibility of GLS in our group for asymptomatic DM patients with preserved LVEF were acceptable[15, 17, 29].

Association of LV longitudinal myocardial function with T2DM

Table 2 shows the result of the univariate and multiple logistic regression analysis for the associations of LVSD with clinical characteristics and echocardiographic parameters. Univariate analysis showed that body weight, BMI and BFI were associated with LVSD. An important finding of the multiple regression analysis was that BFI was the only independent determinant parameters for LVSD (OR 1.147; 95% CI 1.001–1.314; p=0.027) and that GLS was significantly and inversely correlated with BFI (Figure 2).

The incremental advantage of the association of BFI with LVSD using sequential logistic regression models over that of other variables is shown in Figure 3. A model based on clinical

variables including age, DM duration, and HbA1c (χ^2 = 6.26) tended to be improved by addition of BMI, although the difference was not statistically significant (χ^2 = 8.35, p =0.09), while it was significantly improved by addition of BFI (χ^2 = 11.45, p = 0.047).

Figure 4 shows representative cases of LV longitudinal strain curves from patients with and without LVSD.

Discussion

This study offers the first evidence that the amount of body fat mass determined by means of a bioelectrical impedance assay is more closely associated than BMI or body weight with LV longitudinal myocardial function in asymptomatic T2DM patients with preserved LVEF without coronary artery disease.

Importance of LV longitudinal myocardial dysfunction as a DM-related cardiac injury

The presence of LV longitudinal myocardial dysfunction has been identified in DM patients with preserved LVEF without overt coronary artery disease or HF [5-10, 12-17]. Nakai et al. reported that GLS for T2DM patients was significantly lower than that for age-matched normal subjects in spite of a similar LVEF, and that 43% of DM patients showed LV longitudinal myocardial dysfunction [5], while Ernande et al. showed that 23% of DM patients with preserved LVEF had LV longitudinal myocardial dysfunction defined as GLS<18% [8]. In addition, Holland et al. found that patients with GLS<18.9% had significantly worse outcome than those without during a 10-year follow-up, and that GLS was independently associated with outcomes for 230 asymptomatic T2DM patients with preserved LVEF [37].

DM is a major cause of HFpEF, with HFpEF usually presenting as LV diastolic dysfunction. Some investigators have maintained that LV longitudinal myocardial dysfunction, rather than LV diastolic dysfunction, should be considered the first marker of a preclinical form of DM-related cardiac dysfunction in DM patients with preserved LVEF without overt HF [9, 16, 17]. Ernande et al. showed that LV longitudinal myocardial dysfunction detected as GLS<18% was present even in

T2DM patients with preserved LVEF and normal LV diastolic function [9]. Furthermore, our group showed that GLS was a strong determinative factor for e' and E/e' independently of age in asymptomatic DM patients with preserved LVEF [17]. For normal subjects, however, only age was associated with all LV diastolic parameters. It has thus been suggested that progression of uncontrolled DM leads to LV myocardial dysfunction as well as LV diastolic dysfunction, that GLS is associated with LV diastolic function, and that the coexistence of reduced GLS with LV diastolic dysfunction in DM patients with preserved LVEF leads to HFpEF. Furthermore, because multiple factors other than DM and obesity including hypertension, ischemia, dyslipidemia, chronic kidney disease, and so on can be associated with low GLS, a comprehensive approach addressing these factors may well be required to minimize the development of HFpEF.

Association of the amount of body fat mass with LV function in T2DM

Several investigators have reported on the associations of BMI with GLS in T2DM patients. Ho et al. observed that higher BMI was associated with low GLS in 6,231 participants [38]. They showed that higher circulating leptin concentrations were associated with lower GLS, suggesting potential involvement of circulating adipokines in obesity-related LV damage. Our group also showed that GLS of overweight patients with BMI≥25kg/m^2 was significantly lower than that of patients with BMI<25 kg/m^2, while multiple regression analysis revealed that BMI as well as LV mass index was an independent determinant parameter for GLS of 145 asymptomatic T2DM patients with preserved LVEF without coronary artery disease [19]. Furthermore, Leung et al. showed that in eight obese patients with T2DM with BMI of 44±9 kg/m^2 who underwent sleeve gastrectomy, GLS improved from 13.2 ± 3.7% to 19.7± 2.2% after surgery[21].

BMI is often used as a parameter of overweight/obesity in various cardiovascular disease[39, 40], but it does not accurately reflect the amount of body fat mass because the former is a simple parameter of body weight. In this study, BFI, which is a parameter of the amount of body fat mass rather than BMI or body weight, was found to be associated with GLS in asymptomatic T2DM patients with preserved LVEF. Obesity-related inflammatory responses, such as metabolic and

insulin resistance and hormonal changes, have been shown to be associated with adverse effect of cardiac function[22-24]. An increase in inflammatory cytokines, such as interleukin-6, interleukin-8 and monocyte chemoattractant protein-1, has been shown to be a significant indicator of the severity of HFpEF[23]. In addition, high plasma levels of tumor necrosis factor-α and interleukin-6 may cause LV diastolic dysfunction by reducing diastolic calcium reuptake in myocytes[24]. The assessment of the amount of body fat mass rather than BMI may therefore be more useful for the prediction of obesity-related cardiac injury. In fact, Ichikawa et al. used multivariate liner regression analysis to show that abdominal visceral adipose tissue as quantified by computed tomography was an independent determinant of LV diastolic parameters, including left atrial volume, E/A, e', and E/e', in T2DM patients with preserved LVEF and that BMI was not[20]. In addition, Laing et al. showed that the assessment of cardiometabolic risk including hypertension, hypertriglyceride, low high-density lipoprotein cholesterol, DM and insulin resistance was more effective for detection of early atherosclerosis development than assessment of BMI alone, and that non-obese but metabolically unhealthy participants presented similar development of subclinical atherosclerosis to that of their obese counterparts[41]. Finally, Markus et al. showed that an increase in fat mass was associated with LV concentric remodeling as well as impairment of LV diastolic functional parameters such as E/A ratio and isovolumetric relaxation time[22]. In this study, BFI had a trend for a correlation between BFI and LV diastolic function such as E/e' ($p=0.18$), but not statistically significant.

Clinical implications

Some previous investigations have shown that visceral adiposity or epicardial fat was associated with LV dysfunction[20, 22, 42, 43]. Though significant correlation was observed between BFI and BMI in this study ($p<0.0001$, $r=0.86$), the amount of body fat mass by BFI may be more reliable parameter of obesity-related cardiac injury rather than BMI due to aforementioned reasons. Thus, the assessment of the amount of body fat can be a therapeutic target for preventing LV function. The amount of body fat mass can usually be assessed by means of computed tomography

or magnetic resonance imaging. Although these modalities are useful, they are rather costly and time-consuming. On the other hand, BFI, which was evaluated by means of a bioelectrical impedance assay in the current study, is a simple and easy-to-use parameter for the assessment of the amount of body fat mass. Thus, using BFI for the control of body compression as targeted therapy for reducing body fat, not simply weight loss alone, may have clinical implications for better management of asymptomatic T2DM patients with preserved LVEF to prevent the future development of DM-related cardiac dysfunction.

Study limitations

This study covered a relatively small number of patients in a single center study, so that future studies of larger patient populations are needed to verify our findings. Moreover, obese patients have often insufficient echocardiographic image quality, so that speckle-tracking analysis may be difficult for such patients. Finally, waist circumference is a predictor of visceral fat mass[44], but the assessment of the association of central adiposity such as waist circumference with BFI, BMI or GLS was not part of this study. However, the assessment of body fat by means of computed tomography rather than waist circumference would be a currently established when feasible [45].

Conclusions

Using BFI rather than BMI or body weight for the control of body compression by means of a bioelectrical impedance assay may have clinical implications for better management of asymptomatic T2DM patients with preserved LVEF to prevent the future development of DM-related cardiac dysfunction.

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Figure Legends

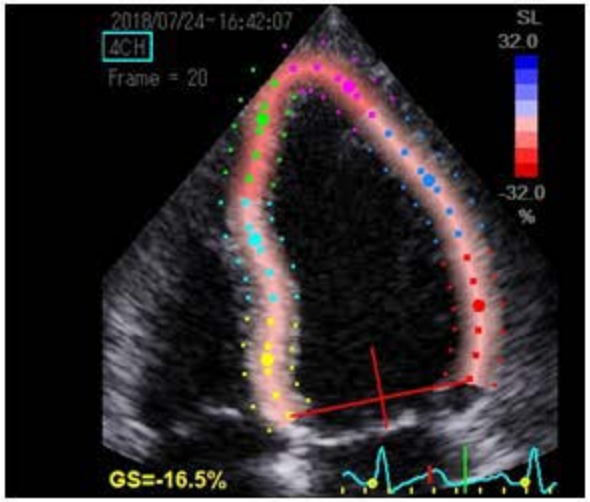
Figure 1: An example of a color-coded two-dimensional display of the left ventricle and corresponding time-strain curves obtained from 18 left ventricular (LV) sites using the three standard apical views for measurement of global longitudinal strain (GLS). GLS was the determined as the average peak strain of the 18 LV segments and expressed as an absolute value.

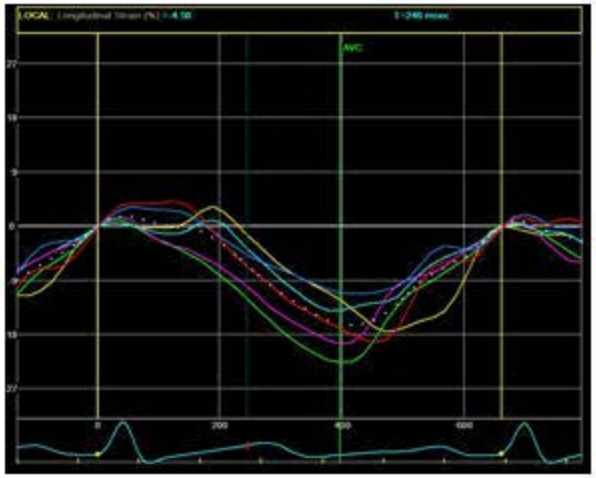
Figure 2: Dot plots of the association of global longitudinal strain (GLS) and body fat index (BFI), indicating that GLS was significantly and inversely correlated with BFI.

Figure 3: Bar graphs of sequential logistic regression models showing that a model based on clinical variables including age, diabetes mellitus (DM) duration, and HbA1c tended to be improved by addition of body mass index (BMI), although the difference was not statistically significant, while it was significantly improved by addition of the body fat index (BFI).

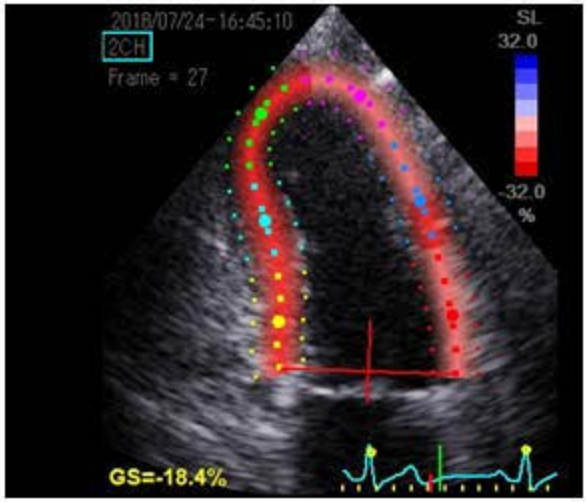
Figure 4: Representative cases of left ventricular (LV) longitudinal strain rate curves from patients with (A) and without (B) LV longitudinal myocardial systolic dysfunction (LVSD).

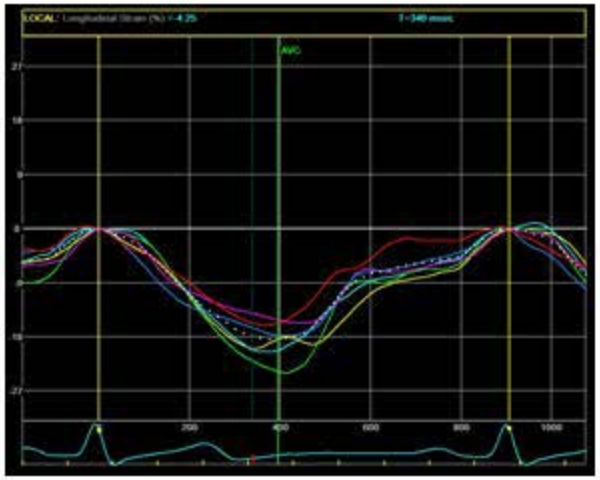
Apical 4-chamber view



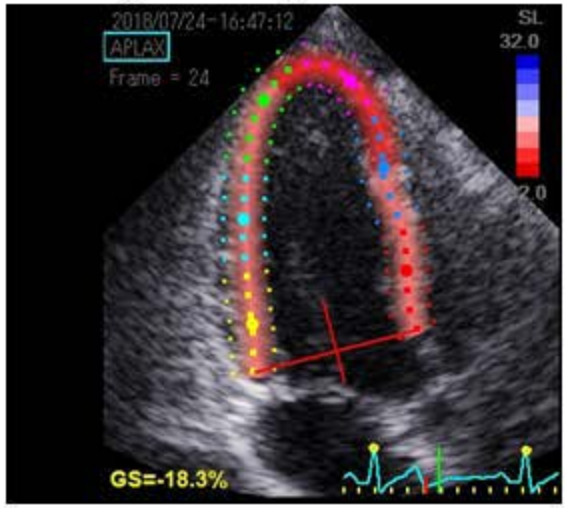


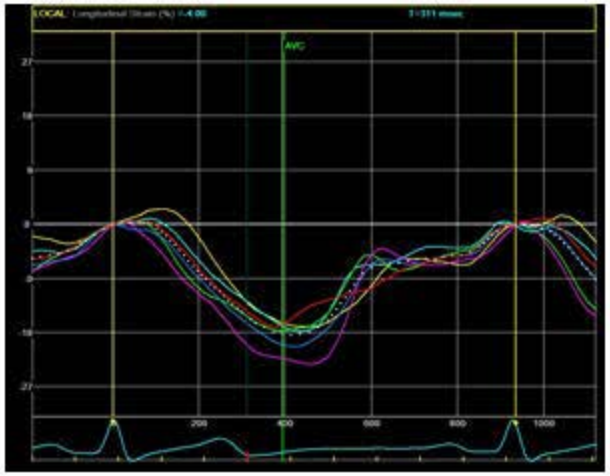
Apical 2-chamber view

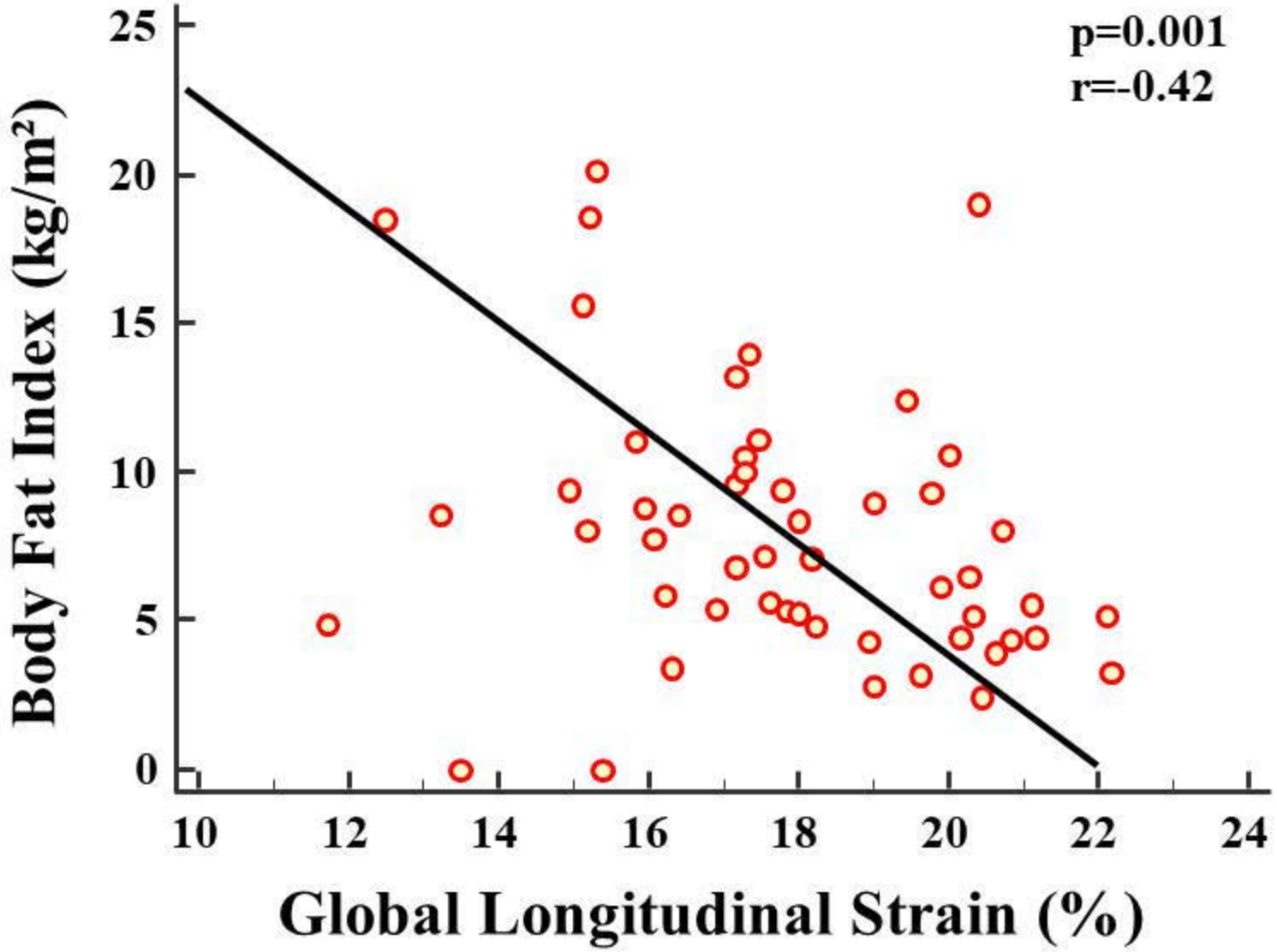


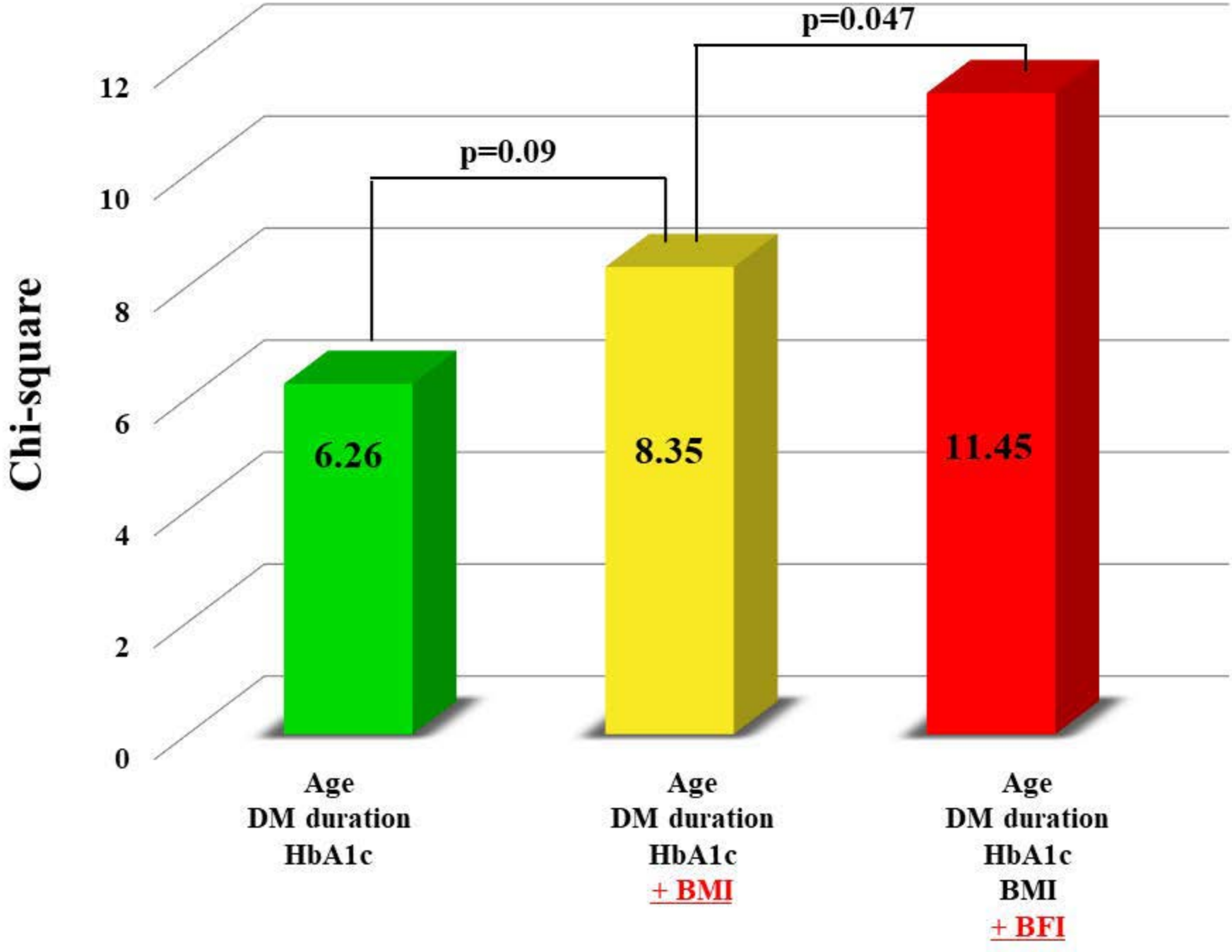


Apical long-axis view



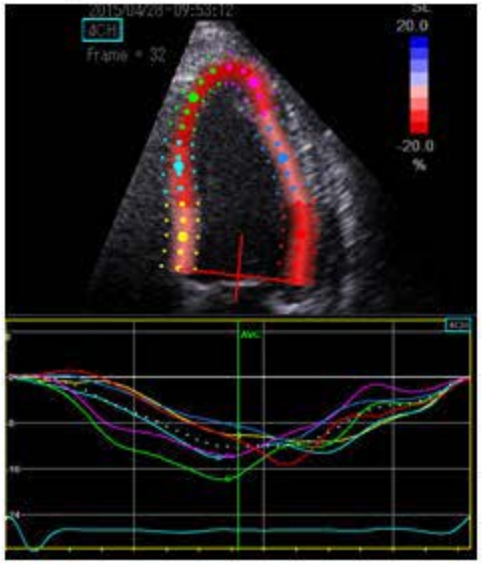



p=0.001
r=-0.42
Body Fat Index (kg/m²)
25
20
15
10
5
0
10
12
14
16
18
20
22
24
Global Longitudinal Strain (%)

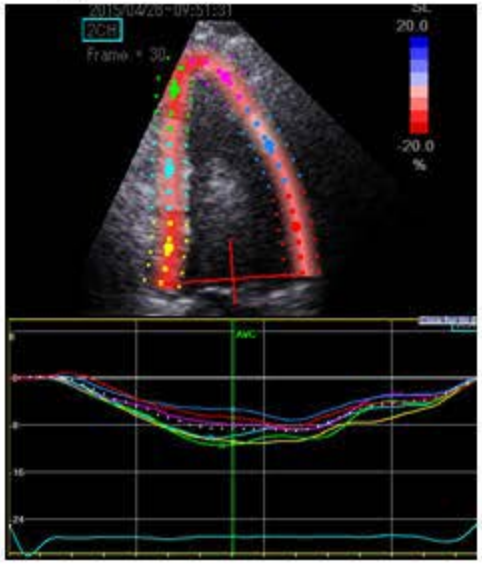

p=0.047
p=0.09
12
10
8
6
4
2
0
Chi-square
6.26
8.35
11.45
Age
DM duration
HbA1c
Age
DM duration
HbA1c
+ BMI
Age
DM duration
HbA1c
BMI
+ BFI

(A) Patients <u>with</u> LVSD (GLS=12.5%)

Apical 4-chamber view

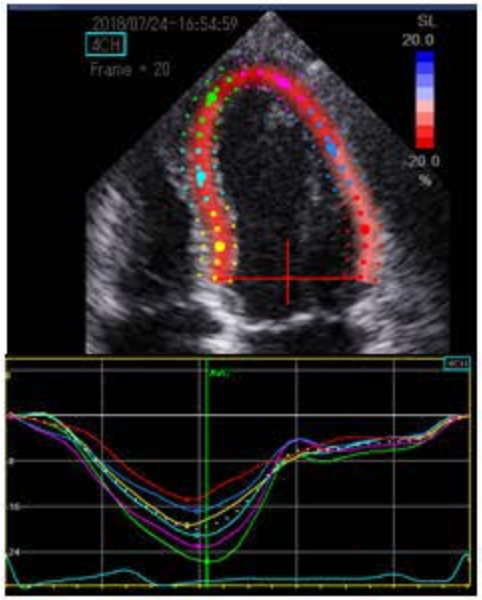


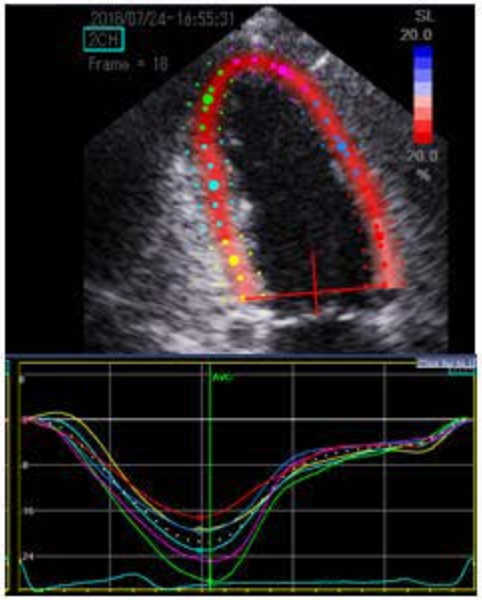
Apical 2-chamber view



Apical long-axis view

(B) Patients <u>without</u> LVSD (GLS=22.2%)





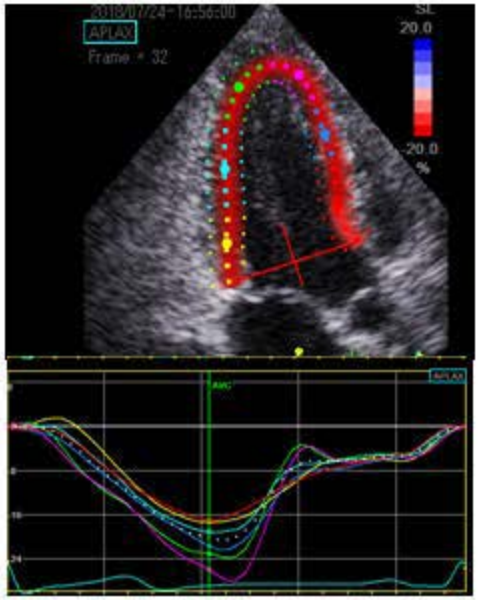


Table 1
Compassion between Patients with and without LVSD

	T2DM patients with LVSD (n=39)	T2DM patients without LVSD (n=32)	P value
Clinical characteristics			
Age, years	57.7 ± 12.0	61.7 ± 12.6	0.19
Female, n (%)	16 (41)	14 (44)	0.65
Duration of T2DM, months	84 (32-138)	163 (45-240)	0.08
HbA1c, %	8.1 ± 1.5	8.8 ± 2.3	0.13
Dyslipidemia, n (%)	27 (69)	15 (47)	0.11
Hypertension, n (%)	23 (59)	15 (47)	0.46
eGFR, mL/min/1.73m^2	65.8 ± 25.9	74.0 ± 24.9	0.19
Body composition analysis			
Body weight, kg	72.1 ± 15.1	61.4 ± 15.9	<0.01
Body mass index, kg/m^2	28.3 ± 5.2	24.4 ± 6.7	<0.01
Body fat mass, kg	24.9 ± 11.3	16.5 ± 10.7	<0.01
Skeletal muscle mass, kg	25.7 ± 5.2	24.2 ± 5.6	0.26
Body fat index, kg/m^2	9.4 ± 4.4	6.5 ± 4.9	<0.01
Medical treatment			
CCB, n (%)	14 (35.9)	9 (28.1)	0.35
ACEI/ARB, n (%)	22 (56.4)	11 (34.4)	0.05
β-Blocker, n (%)	4 (10.3)	3 (9.3)	0.81
Statin, n (%)	20 (51.3)	14 (43.8)	0.46

Insulin, n (%)	15 (38.5)	15 (46.9)	0.68
DPP-4I, n (%)	20 (51.3)	20 (62.5)	0.44
GLP-1RA, n (%)	3 (7.7)	8 (25)	0.07
Sulfonylurea, n (%)	10 (25.6)	10 (31.3)	0.77
α-GI, n (%)	6 (15.4)	10 (31.3)	0.41
Thiazolidine, n (%)	6 (15.4)	3 (9.4)	0.38
Metformin, n (%)	20 (51.3)	19 (59.3)	0.77
Echocardiography			
LV end-systolic volume, mL	26.9 ± 13.2	23.8 ± 13.0	0.30
LV end-diastolic volume, mL	71.6 ± 21.8	66.3 ± 19.7	0.30
LV ejection fraction, %	65.3 ± 6.2	67.4 ± 5.7	0.14
Stroke volume, mL	66.4 ± 14.3	65.8 ± 14.5	0.85
Left atrial volume index, mL/m^2	31.5 ± 6.8	29.7 ± 9.3	0.34
LV mass index, g/m^2	76 ± 20	71 ± 19	<0.05
Relative wall thickness	0.46 ± 0.1	0.44 ± 0.1	0.50
E/A	0.84 ± 0.3	0.84 ± 0.3	0.96
e', cm	5.9 ± 1.8	6.5 ± 1.8	0.14
E/e'	11.2 ± 4.7	10.0 ± 3.4	0.25
Global longitudinal strain, %	16.3 ± 1.5	19.9 ± 1.1	<0.001

Values are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).
DM=diabetes mellitus; CCB=calcium channel blocker; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; DPP-4I=dipeptidyl peptidase-4 inhibitor; GLP-1RA=glucagon like peptide-1receptor agonist; α-GI=α-glucosidase inhibitor; LV=left ventricular; E=peak early diastolic mitral flow velocity; e'= Spectral pulsed-wave Doppler–derived early diastolic velocity from the septal mitral annulus.

Table 2

Univariate and multivariate logistic regression analysis for association with increased LVSD

	Univariate analysis			Multivariate analysis		
Covariate	OR	95% CI	P value	OR	95% CI	P value
Age	0.971	0.932-1.012	0.15			
Female	0.928	0.347-2.480	0.88			
HbA1c	0.825	0.631-1.080	0.15			
T2DM duration	0.995	0.991-1.000	0.04			
Triglyceride	1.010	1.001-1.019	0.01			
Hypertension	1.246	0.468-3.317	0.66			
LV ejection fraction	0.941	0.865-1.023	0.14			
E/e’	1.075	0.948-1.219	0.24			
Relative wall thickening	3.155	0.024-419.6	0.64			
LV mass index, g/m^2	1.011	0.984 -1.031	0.41			
Body weight	1.049	1.012-1.088	<0.01			
Body mass index	1.222	1.014-1.242	<0.01			
Body fat index	1.159	1.011-1.328	<0.01	1.147	1.001-1.314	0.027

CI=confidence interval; OR=Odds ratio; Other abbreviations as in Table1.