Multimodality imaging in metabolic heart disease

Ng, A.

3

Impact of Diabetes and Increasing Body Mass Index Category on Left Ventricular Systolic and Diastolic Function

Arnold C.T. Ng, Francesca Prevedello, Giulia Dolci, Cornelis J. Roos, Roxana Djaberi, Matteo Bertini, See Hooi Ewe, Christine Allman, Dominic Y. Leung, Nina Ajmone Marsan, Victoria Delgado, Jeroen J. Bax

J Am Soc Echocardiogr. 2018;31(8):916-925

ABSTRACT

Background: Diabetes and obesity are both a world-wide growing epidemic, and both are independently associated with an increased risk for heart failure and death. We aimed at examining the additive detrimental effect of both diabetes and increasing body mass index (BMI) category on left ventricular (LV) myocardial systolic and diastolic functions.

Methods: The present retrospective multicenter study included 653 patients (337 type 2 diabetic and 316 non-diabetic) of increasing BMI category. All patients had normal LV ejection fraction. LV myocardial systolic (peak systolic global longitudinal strain, peak systolic global longitudinal strain rate) and diastolic (average mitral annular e' velocity and early diastolic global longitudinal strain rate) functions were quantified by echocardiography.

Results: Increasing BMI category was associated with progressively more impaired LV myocardial function in diabetic patients ($p < 0.001$). Diabetic patients had significantly more impaired LV myocardial function at all BMI categories compared to non-diabetic patients ($p < 0.001$). On multivariate analysis, both diabetes and obesity were independently associated with an additive detrimental effect on LV myocardial systolic and diastolic functions. However, obesity was associated with greater LV myocardial dysfunction than diabetes.

Conclusion: Both diabetes and increasing BMI category had an additive detrimental effect on LV myocardial systolic and diastolic functions. Furthermore, increasing BMI category was associated with greater LV myocardial dysfunction than diabetes. As they frequently coexist together, future studies on diabetic patients should also focus on obesity.

INTRODUCTION

There is currently a worldwide epidemic of obesity and type 2 diabetes. The latest projection by the World Health Organization estimated that globally in 2005, approximately 1.6 billion adults over the age of 15 years were overweight, and at least 400 million adults were obese (www.WHO.int). Due to the obesity epidemic, there is a concomitant increase in the prevalence of type 2 diabetes. In the year 2000, the World Health Organization estimated more than 170 million people worldwide had diabetes and the prevalence was projected to double in the next 20 years.[1] Both obesity and diabetes are independently associated with an increased risk of heart failure.[2] Although the pathophysiological mechanisms underlying obesity and diabetic cardiomyopathy are not identical, the combination of insulin resistance, hyperinsulinemia and hyperglycemia leads to inflammation, neurohormonal activation of the renin-angiotensin-aldosterone system, and eventual myocardial structural and functional changes.[3-8] Despite previous studies showing obesity to be an independent risk factor for subsequent development of diabetes and heart failure,[2, 9, 10] few have examined the simultaneous impact of increasing body mass index (BMI) category and concomitant diabetes on changes in left ventricular (LV) myocardial function. We hypothesized that both increasing BMI category and diabetes are independently associated with progressive impairment of LV myocardial systolic and diastolic functions, and that the association is additive and not synergistic. Thus, we conducted a multicenter retrospective study (Leiden University Medical Center, The Netherlands, and Liverpool Hospital, Australia) whereby both diabetic and non-diabetic patients without coronary artery disease were evaluated with the aim to:

1. examine the impact of increasing BMI category on LV myocardial systolic (peak systolic global longitudinal strain, peak systolic global longitudinal strain rate) and diastolic functions average mitral annular e' velocity and early diastolic global longitudinal strain rate) as quantified by echocardiography in type 2 diabetic patients;
2. compare LV myocardial systolic and diastolic functions with increasing BMI category between diabetic and non-diabetic patients; and
3. determine the independent and additive detrimental effect of increasing BMI category and diabetes on LV myocardial systolic and diastolic functions.

METHODS

Patient population

The overall patient population consisted of a mix of 653 patients recruited from 2 institutions (104 from Liverpool Hospital [Australia] and 549 from Leiden University Medical Center [The Netherlands]). All patients were identified over a 10 year period

from each Australian and Dutch departmental combined echocardiographic and clinical databases. Of these, 337 had type 2 diabetes, which was diagnosed according to World Health Organization criteria.[11] Although BMI does not take into account the wide variation in body fat distribution, it is the most useful population-level measure of obesity and is recommended by the World Health Organization to define overweight and obesity within a population and the risks associated with it.[12] Furthermore, several multicenter and epidemiology studies have demonstrated the independent prognostic value of BMI as a measure of general obesity for predicting all-cause mortality.[13-15] As there were only 2 diabetic patients with BMI < 20 kg/m^2 measured at the time of echocardiography, all 337 diabetic patients were divided into 3 categorical groups: 80 lean diabetics (BMI < 25 kg/m^2); 139 overweight diabetics (BMI 25 – 29.9 kg/m^2); and 118 obese diabetics (BMI ≥ 30kg/m^2).

Type 2 diabetic patients were compared against 316 non-diabetic patients of similar age, gender and BMI. All non-diabetic patients were clinically referred for assessment of LV and/or valvular function, and had structurally normal heart on echocardiography. Similarly, as there were only 5 non-diabetic patients with BMI < 20kg/m^2, all 316 non-diabetic patients were divided into 3 categorical groups: 89 lean non-diabetics (BMI < 25 kg/m^2); 134 overweight non-diabetics (BMI 25 – 29.9 kg/m^2); and 93 obese non-diabetics (BMI ≥ 30kg/m^2).

The exclusion criteria for all diabetic and non-diabetic patients included age < 18 years, rhythm other than sinus rhythm, LV ejection fraction (EF) < 50%, moderate or severe valvular stenosis or regurgitation, and congenital heart disease. To avoid coronary artery disease as a potential confounding factor for any changes observed in myocardial function, all patients with known significant underlying coronary artery disease, previous myocardial infarction, previous coronary artery bypass surgery or percutaneous coronary intervention, presence of segmental wall motion abnormalities on echocardiography, or positive stress testing were excluded.

All patients underwent a history, physical, biochemical, and transthoracic echocardiographic examination. Baseline biochemical analyses included hemoglobin level, glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease formula as recommended by the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative Guidelines[16], and glycated hemoglobin (HbA1c) level. The definition of hypertension was different between diabetic and non-diabetic patients. In diabetic patients, the cut-off was > 130/80 mmHg on 2 separate occasions after > 5min of rest. In non-diabetic patients, the cut-off was > 140/90 mmHg on 2 separate occasions after

> 5min of rest. All clinical and biochemical variables were collected by an independent observer blinded to the echocardiographic results.

The impact of increasing BMI categories on LV structure (LV volumes, mass) and function were initially assessed in the type 2 diabetic patients. LV myocardial function within each BMI category (lean, overweight, obese) in the diabetic population were then compared against non-diabetic patients. Finally, to determine the independent and additive detrimental effect of increasing obesity and diabetes on LV myocardial function, multivariate analysis was performed with BMI categories and the presence/absence of diabetes entered as covariates, adjusted for baseline age, gender, systolic blood pressure, heart rate, LV mass and LV volume. Echocardiographic analyses for all diabetic and non-diabetic patients, including 2D speckle tracking, were performed offline. Therefore, the present evaluation does not tabulate the results summarized in clinical reports.

The institutional review boards approved the study. The institutional review board of the Leiden University Medical Center waived the need for patient written informed consent for retrospective analysis of clinically acquired data anonymously handled.

Echocardiography

Transthoracic echocardiography was performed in all subjects at rest using commercially available ultrasound systems (Vivid 7 and E9, GE-Vingmed, Horten, Norway). All images were digitally stored on hard disks for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway). A complete 2D, color, pulsed and continuous-wave Doppler echocardiogram was performed according to standard techniques.[17, 18] LV end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated using the Simpson's biplane method of discs. LVEF was calculated and expressed as a percentage. LV mass was calculated from the formula as recommended by the American Society of Echocardiography.[19]

Transmitral inflow velocities were recorded using conventional pulsed-wave Doppler echocardiography in the apical 4-chamber view using a 2 mm sample volume. Transmitral early (E wave) and late (A wave) diastolic velocities as well as deceleration time were recorded at the mitral leaflet tips. Average mitral annular e' velocity and average E/e' ratio were obtained from the septal and lateral annulus as recommended by current guidelines.[20] Maximal left atrial volume was calculated using the Simpson's biplane method of discs in the 4- and 2-chamber views.

Myocardial functional assessment by 2D speckle tracking

Quantification of longitudinal myocardial function was performed using 2D speckle tracking echocardiography in the 3 apical (2-, 3- and 4 chamber) views. During image analysis, the LV endocardial border was manually traced at end-systole and the region of interest width adjusted to include the entire myocardium. The 2D speckle tracking software then automatically tracks the motion of LV myocardial segments throughout the entire cardiac cycle. LV myocardial segments of good tracking quality were automatically accepted for further analyses whereas poorly tracked segments were rejected, while simultaneously allowing the user to manually override the software's decisions based on visual assessments of tracking quality. From the 3 individual apical views, peak systolic global longitudinal strain, peak systolic global longitudinal strain rate and early diastolic global longitudinal strain rate were calculated.

Variability analysis

Intraobserver and interobserver measurement variabilities were performed in 20 randomly selected patients and expressed as mean absolute difference ± 1 standard deviation (SD). The respective intraobserver and interobserver measurement variabilities for peak systolic global longitudinal strain were 1.2 ± 0.6% and 1.2 ± 1.0%, peak systolic global longitudinal strain rate were 0.10 ± 0.06s^{-1} and 0.11 ± 0.08s^{-1}, and early diastolic global longitudinal strain rate were 0.09 ± 0.05s^{-1} and 0.16 ± 0.09s^{-1}.

Statistical analysis

All continuous variables were tested for Gaussian distribution as determined by Kolmogorov-Smirnov test. Continuous variables were presented as mean ± 1 SD and categorical variables were presented as frequencies and percentages. Unpaired Student's t-test was used to compare 2 independent groups of continuous variables and the Chi-square test with Yates' correction was used to compare categorical variables. To assess the univariable linear relationship between 2 variables: Pearson correlation was performed between 2 continuous variables, Spearman correlation was performed between 1 continuous variable and 1 ordinal variable (e.g. BMI categories), and point-biserial correlation was performed between 1 continuous and 1 dichotomous variable (e.g. gender and presence of diabetes categories).

One-way analysis of variance (ANOVA) was initially used to examine the influence of increasing BMI subgroup categories on LV myocardial function (peak systolic global longitudinal strain, peak systolic global longitudinal strain rate, average mitral annular e' velocities, average E/e' ratio and early diastolic global longitudinal strain rate) in type 2 diabetic patients. Next, factorial ANOVA was used to compare peak systolic global longitudinal strain, peak systolic global longitudinal strain rate, average mitral annular

e' velocities, average E/e' ratio and early diastolic global longitudinal strain rate changes with increasing BMI category between diabetic and non-diabetic patients. Finally, multiple linear regression analyses were used to determine the independent and additive detrimental effect of increasing BMI category and diabetes on peak systolic global longitudinal strain, peak systolic global longitudinal strain rate, average mitral annular e' velocities and early diastolic global longitudinal strain rate, with correction for baseline age, gender, systolic blood pressure, heart rate, LV mass and LVESV. Standardized coefficients were presented to demonstrate the relative contribution of each variable to the multivariable linear regression model. To avoid multicolinearity, a tolerance of > 0.5 was set. All post-hoc multiple pairwise comparisons were performed with Bonferroni corrections. A 2-tailed p value of < 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago), version 17.

RESULTS

Increasing BMI category in diabetic patients

Table 1 outlines the clinical, biochemical and echocardiographic characteristics of the entire cohort of type 2 diabetic patients, and the 3 diabetic groups categorized according to BMI category. The mean age was 57 ± 12 years, 63.2% men. With increasing BMI category, there were progressive increases in systolic (p by one-way ANOVA = 0.002) and diastolic (p by one-way ANOVA < 0.001) blood pressures, and higher HbA1c level (p by one-way ANOVA = 0.046).

On echocardiography, increasing BMI category was associated with LV structural changes with progressive increases in LVEDV, LVESV and LV mass. Assessment of LV systolic function showed that LVEF did not differ significantly across the diabetic BMI subgroups. However, increasing BMI category was significantly associated with progressively more impaired peak systolic global longitudinal strain (p by one-way ANOVA < 0.001). Multiple pairwise comparisons with Bonferroni corrections showed that peak systolic global longitudinal strain became increasingly more impaired with each increase in BMI category (both p < 0.001). Similarly, increasing BMI category was also significantly associated with progressively more impaired peak systolic global longitudinal strain rate (p by one-way ANOVA < 0.001), and multiple pairwise comparisons with Bonferroni corrections showed that peak systolic global longitudinal strain rate was significantly more impaired in overweight versus lean diabetic patients (p = 0.008), and in obese versus overweight diabetic patients (p = 0.003).

Assessment of LV diastolic function showed that increasing BMI category in the diabetic patients was significantly associated with progressive prolongation of transmitral deceleration time, and a non-significant trend towards worsening of transmitral E/A ratio. Increasing BMI category was also significantly associated with progressively more impaired average mitral annular e' velocity (p by one-way ANOVA < 0.001) and average E/e' ratio (p by one-way ANOVA = 0.004). Similarly, increasing BMI was significantly associated with progressively more impaired early diastolic global longitudinal strain rate (p by one-way ANOVA < 0.001). On multiple pairwise comparisons with Bonferroni corrections, early diastolic global longitudinal strain rate was significantly more impaired in overweight versus lean diabetic patients (p = 0.001), and in obese versus overweight diabetic patients (p = 0.004).

Table 1. *Clinical, biochemical and echocardiographic characteristics of diabetic patient population*

Variable	Total diabetic population (n = 337)	Lean diabetic BMI < 25 kg/m^2 (n = 80)	Overweight diabetic BMI 25–29.9 kg/m^2 (n = 139)	Obese diabetic BMI≥30 kg/m^2 (n = 118)	p value*
Clinical					
Age (years)	57 ± 12	56 ± 12	57 ± 12	56 ± 11	0.63
Male gender (%)	63.2	67.5	74.1	47.5	< 0.001
Height (cm)	173 ± 10	173 ± 10	172 ± 11	173 ± 10	0.83
Weight (kg)	84 ± 17	69 ± 10	81 ± 11	101 ± 15	< 0.001
BMI (kg/m^2)	28.9 ± 5.6	22.8 ± 1.5	27.2 ± 1.4	35.0 ± 4.4	< 0.001
Hypertension (%)	56.4	42.5	56.1	66.1	0.005
Hyperlipidemia (%)	51.0	40.0	54.0	55.1	0.076
Family history of ischemic heart disease (%)	15.7	20.0	16.5	11.9	0.29
Current smoker (%)	29.4	28.8	25.9	33.9	0.37
Systolic blood pressure (mmHg)	139 ± 20	134 ± 20	139 ± 19	144 ± 20	0.002
Diastolic blood pressure (mmHg)	81 ± 11	78 ± 11	81 ± 10	85 ± 11	< 0.001
Biochemical					
Hemoglobin (g/dL)	13.9 ± 1.6	13.6 ± 1.8	14.1 ± 1.5	13.9 ± 1.6	0.076
Glomerular filtration rate (mL/min/1.73m^2)	87.7 ± 26.9	85.2 ± 22.8	87.1 ± 27.7	90.2 ± 28.6	0.42
HbA1c (%)	7.3 ± 1.5	7.1 ± 1.4	7.2 ± 1.5	7.6 ± 1.4	0.046
Echocardiography					
Heart rate (beats/min)	74 ± 13	72 ± 13	74 ± 12	75 ± 14	0.20
Left ventricular end-diastolic volume (mL)	93 ± 24	88 ± 23	93 ± 25	98 ± 24	0.020
Left ventricular end-systolic volume (mL)	38 ± 12	36 ± 12	37 ± 12	40 ± 12	0.048
Left ventricular ejection fraction (%)	59 ± 5	59 ± 5	60 ± 5	59 ± 5	0.53
Left ventricular mass (g)	183 ± 49	161 ± 42	182 ± 47	200 ± 48	< 0.001

Table 1. *Clinical, biochemical and echocardiographic characteristics of diabetic patient population (continued)*

Variable	Total diabetic population (n = 337)	Lean diabetic BMI < 25 kg/m² (n = 80)	Overweight diabetic BMI 25–29.9 kg/m² (n = 139)	Obese diabetic BMI≥30 kg/m² (n = 118)	p value*
Transmitral E/A ratio	0.97 ± 0.32	1.04 ± 0.40	0.96 ± 0.28	0.94 ± 0.30	0.084
Deceleration time (msec)	198 ± 54	190 ± 58	192 ± 45	209 ± 58	0.016
Average mitral annular e' velocity (cm/s)	6.7 ± 2.0	7.5 ± 2.2	6.5 ± 1.9	6.3 ± 1.8	< 0.001
Average E/e' ratio	10.9 ± 5.3	9.5 ± 4.6	10.7 ± 4.1	12.1 ± 6.6	0.004
Maximal left atrial volume (mL)	58.5 ± 17.9	54.6 ± 14.7	57.3 ± 16.7	62.5 ± 20.3	0.006
Peak systolic global longitudinal strain (%)	-17.6 ± 2.3	-18.9 ± 2.2	-17.7 ± 1.9	-16.6 ± 2.3	< 0.001
Peak systolic global longitudinal strain rate (s^{-1})	-0.93 ± 0.16	-1.01 ± 0.17	-0.94 ± 0.14	-0.88 ± 0.16	< 0.001
Early diastolic global longitudinal strain rate (s^{-1})	0.99 ± 0.27	1.13 ± 0.28	1.00 ± 0.25	0.89 ± 0.25	< 0.001

* p value by one-way analysis of variance. BMI: body mass index; HbA1c: glycated hemoglobin.

Comparisons between diabetic and non-diabetic patients

Table 2 compares the clinical and echocardiographic characteristics of the diabetic patients versus non-diabetic patients. There were no significant differences in age, gender and BMI. Diabetic patients were more likely to have a positive history of hypertension and hyperlipidemia. However, there were no significant differences in systolic and diastolic blood pressure at the time of echocardiographic examination.

On echocardiography, there were no significant differences in LVEDV, LVESV and LV mass. Assessment of LV systolic function demonstrated that there was no significant difference in LVEF between diabetic and non-diabetic patients (59 ± 5 vs. 60 ± 5%, p = 0.40). However, diabetic patients had significantly more impaired peak systolic global longitudinal strain compared to non-diabetic patients (-17.6 ± 2.3 vs. -18.9 ± 2.4%, p < 0.001). Furthermore, diabetic patients had more impaired peak systolic global longitudinal strain than non-diabetic patients across all BMI subgroups (p by factorial ANOVA < 0.001), and there was no significant interaction between the presence of diabetes and BMI categories (p by factorial ANOVA = 0.31, Figure 1). Thus, lean diabetic patients had similar peak systolic global longitudinal strain as overweight non-diabetic patients (-18.9 ± 2.2 vs. -19.0 ± 2.2%, p > 0.99 with Bonferroni correction); overweight diabetic patients had similar peak systolic global longitudinal strain as obese non-diabetic patients (-17.7 ± 1.9 vs. -17.4 ± 2.3%, p = 0.70 with Bonferroni correction); and obese diabetic patients had the most impaired peak systolic global longitudinal strain (-16.6 ± 2.3%).

Table 2. *Comparison of clinical and echocardiographic characteristics between non-diabetic and diabetic patients*

Variable	Non-diabetic (n = 316)	Diabetic (n = 337)	p value
Clinical			
Age (years)	57 ± 14	57 ± 12	0.83
Male gender (%)	62.7	63.2	0.89
BMI (kg/m^2)	28.0 ± 4.9	28.9 ± 5.6	0.074
Lean (%) (BMI < 25kg/m^2)	28.2	23.8	0.24
Overweight (%) (BMI 25–29.9 kg/m^2)	42.4	41.2	-
Obese (%) (BMI≥30 kg/m^2)	29.4	35.0	-
Hypertension (%)	27.5	56.4	< 0.001
Hyperlipidemia (%)	14.2	51.0	< 0.001
Current smoker (%)	11.4	15.7	0.11
Systolic BP (mmHg)	136 ± 24	139 ± 20	0.08
Diastolic BP (mmHg)	82 ± 12	81 ± 11	0.29
Echocardiography			
Heart rate (beats/min)	71 ± 13	74 ± 13	0.010
Left ventricular end-diastolic volume (mL)	95 ± 25	93 ± 24	0.30
Left ventricular end-systolic volume (mL)	39 ± 12	38 ± 12	0.57
Left ventricular ejection fraction (%)	60 ± 5	59 ± 5	0.40
Left ventricular mass (g)	183 ± 51	183 ± 49	0.94
Transmitral E/A ratio	1.10 ± 0.47	0.97 ± 0.32	< 0.001
Deceleration time (msec)	212 ± 60	198 ± 54	0.001
Average mitral annular e' velocity (cm/s)	7.5 ± 2.5	6.7 ± 2.0	< 0.001
Average E/e' ratio	10.2 ± 4.1	10.9 ± 5.3	0.06
Maximal left atrial volume (mL)	59.4 ± 21.3	58.5 ± 17.9	0.56
Peak systolic global longitudinal strain (%)	-18.9 ± 2.4	-17.6 ± 2.3	< 0.001
Peak systolic global longitudinal strain rate (s^{-1})	-0.99 ± 0.16	-0.93 ± 0.16	< 0.001
Early diastolic global longitudinal strain rate (s^{-1})	1.15 ± 0.32	0.99 ± 0.27	< 0.001

BMI: body mass index

Similarly, diabetic patients had more impaired peak systolic global longitudinal strain rate than non-diabetic patients across all BMI subgroups (p by factorial ANOVA < 0.001), and there was no significant interaction between the presence of diabetes and BMI categories (p by factorial ANOVA = 0.67, Figure 2). Thus, lean diabetic patients had similar peak systolic global longitudinal strain rate as overweight non-diabetic patients (-1.01 ± 0.17 vs. -0.98 ± 0.16s^{-1}, p = 0.68 with Bonferroni correction); overweight diabetic patients had similar peak systolic global longitudinal strain rate as obese non-diabetic patients (-0.94 ± 0.14 vs. -0.92 ± 0.15s^{-1}, p = 0.80 with Bonferroni correction); and obese diabetic patients had the most impaired peak systolic global longitudinal strain rate (-0.88 ± 0.16s^{-1}).

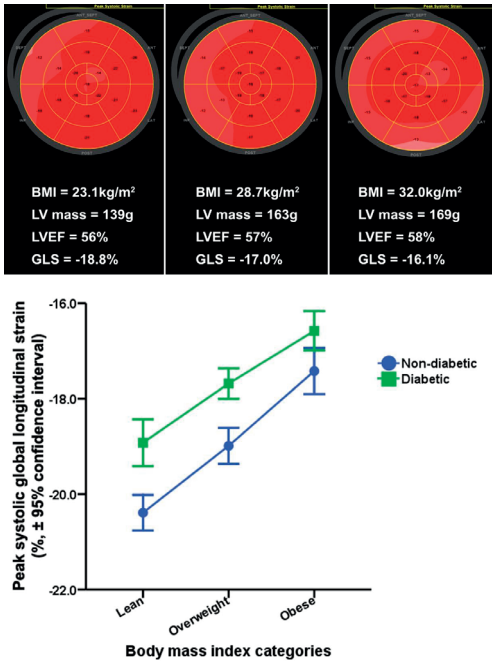

Figure 1. *Comparisons of peak systolic global longitudinal strain in diabetic versus non-diabetic patients across body mass index (BMI) categories. Increasing BMI was associated with progressive impairment of peak systolic global longitudinal strain. Furthermore, diabetic patients had more impaired peak systolic global longitudinal strain across all BMI categories.*

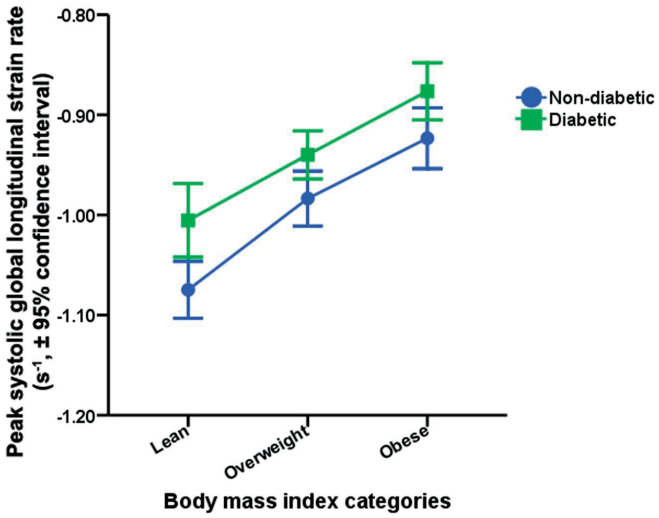

Figure 2. *Comparisons of peak systolic global longitudinal strain rate in diabetic versus non-diabetic patients across body mass index (BMI) categories. Increasing BMI was associated with progressive impairment of peak systolic global longitudinal strain rate. Diabetic patients had more impaired peak systolic global longitudinal strain across all BMI categories.*

On assessment of LV diastolic function, diabetic patients had more impaired LV diastolic function as measured by average mitral annular e' velocity (6.7 ± 2.0 vs. 7.5 ± 2.5cm/s, p < 0.001), and across all BMI categories (p by factorial ANOVA < 0.001, Figure 3). There was no significant interaction between the presence of diabetes and BMI categories in average mitral annular e' velocity (p by factorial ANOVA = 0.63). As shown in Figure 3, lean diabetic patients had similar average mitral annular e' velocity as overweight non-diabetic patients (7.5 ± 2.2 vs. 7.3 ± 2.8cm/s, p > 0.99 with Bonferroni correction); overweight diabetic patients had similar peak systolic global longitudinal strain rate as obese non-diabetic patients (6.5 ± 1.9 vs. 6.8 ± 2.0cm/s, p = 0.56 with Bonferroni correction); and obese diabetic patients had the most impaired peak systolic global longitudinal strain rate (6.3 ± 1.8cm/s).

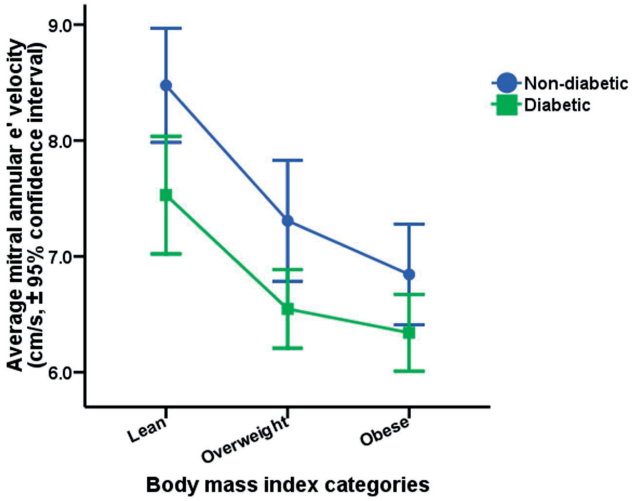

Figure 3. *Comparisons of average mitral annular e' velocity in diabetic versus non-diabetic patients across body mass index (BMI) categories. Increasing BMI was associated with progressive impairment of average mitral annular e' velocity. Diabetic patients had more impaired average mitral annular e' velocity across all BMI categories.*

In contrast, there was no significant difference in the assessment of LV filling pressure between diabetic and non-diabetic patients as quantified by average E/e' ratio in diabetic patients (10.9 ± 5.3 vs. 10.2 ± 4.1, p = 0.06).

Finally, diabetic patients also had more impaired early diastolic global longitudinal strain rate than non-diabetic patients across all BMI categories (p by factorial ANOVA < 0.001). Interestingly, there was a significant interaction between presence of diabetes and increasing BMI categories (p by factorial ANOVA = 0.005). Evaluation of Figure 4 demonstrated that non-diabetic patients had a greater initial decline in early diastolic

global longitudinal strain rate from normal weight to overweight compared to diabetic patients. Similarly, lean diabetic patients had similar early diastolic global longitudinal strain rate as overweight non-diabetic patients (1.13 ± 0.28 vs. 1.11 ± 0.29s^{-1}, p > 0.99 with Bonferroni correction); overweight diabetic patients had similar early diastolic global longitudinal strain rate as obese non-diabetic patients (1.00 ± 0.25 vs. 0.99 ± 0.26s^{-1}, p > 0.99 with Bonferroni correction); and obese diabetic patients had the most impaired early diastolic global longitudinal strain rate (0.89 ± 0.25s^{-1}).

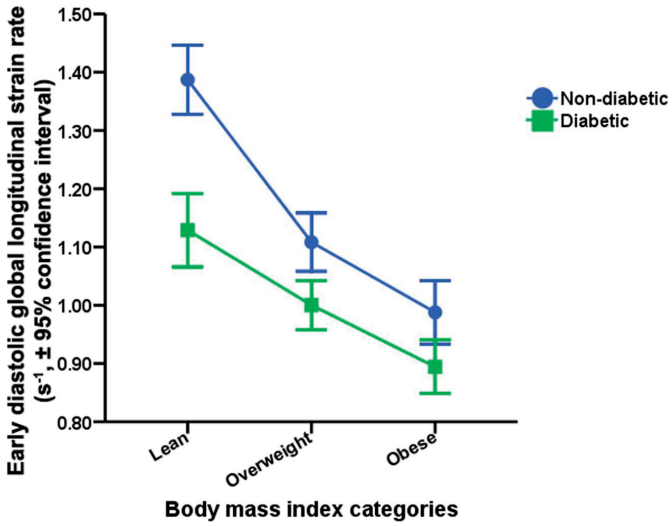

Figure 4. *Comparisons of early diastolic global longitudinal strain rate in diabetic versus non-diabetic patients across body mass index (BMI) categories. Increasing BMI was associated with progressive impairment of early diastolic global longitudinal strain rate. Diabetic patients had more impaired early diastolic global longitudinal strain across all BMI categories. However, non-diabetic patients with a normal BMI had a greater decline in early diastolic global longitudinal strain rate with increasing BMI.*

Diabetes, obesity and myocardial dysfunction

To examine the independent and additive detrimental effect of both increasing obesity and diabetes on peak systolic global longitudinal strain, peak systolic global longitudinal strain rate, average mitral annular e' velocity and early diastolic global longitudinal strain rate, multiple linear regression analyses were performed with the presence of diabetes and BMI categories entered as covariates, corrected for baseline age, gender, systolic blood pressure, heart rate, LV mass and LVESV.

Table 3 shows that both increasing BMI category and the presence of diabetes were independently associated with peak systolic global longitudinal strain (model R = 0.56, p < 0.001). Furthermore, increasing BMI (standardized beta = 0.379, p < 0.001) was associated with greater LV myocardial dysfunction than diabetes (standardized beta = 0.231, p

< 0.001). There was no significant interaction between the presence of diabetes and increasing obesity, suggesting an additive (not synergistic) detrimental effect of diabetes and obesity on LV myocardial function. Similar results were also obtained when BMI was modeled as a continuous variable (standardized beta = 0.355, p < 0.001), when systolic blood pressure was substituted by diastolic blood pressure or history of hypertension, or when all hypertensive patients were excluded from the multivariate analysis.

Table 3. *Independent determinants of left ventricular peak systolic global longitudinal strain*

Variable	Peak systolic global longitudinal strain			
	*Univariable r	p value	Standardized β	p value
Age	-0.027	0.49	0.027	0.49
Male gender	0.063	0.11	0.063	0.087
Systolic blood pressure	0.124	0.002	-0.022	0.55
Heart rate	0.196	< 0.001	0.190	< 0.001
Left ventricular mass	0.200	< 0.001	-0.035	0.41
Left ventricular end-systolic volume	0.265	< 0.001	0.246	< 0.001
Presence of diabetes	0.274	< 0.001	0.231	< 0.001
BMI categories	0.434	< 0.001	0.379	< 0.001

BMI: body mass index. *Pearson correlation performed for 2 continuous variables, Spearman correlation performed for 1 continuous variable and 1 ordinal variable (i.e. BMI categories), and point-biserial correlation performed for 1 continuous variable and 1 dichotomous variable (i.e. gender, presence of diabetes).

Table 4 shows the multivariable regression analysis for peak systolic global longitudinal strain rate (model R = 0.53, p < 0.001). Similarly, increasing BMI category (standardized beta = 0.285, p < 0.001) was associated with greater LV myocardial dysfunction by peak systolic global longitudinal strain rate compared to the presence of diabetes (standard-

Table 4. *Independent determinants of left ventricular peak systolic global longitudinal strain rate*

Variable	Peak systolic global longitudinal strain rate			
	*Univariable r	p value	Standardized β	p value
Age	-0.019	0.63	0.060	0.13
Male gender	-0.118	0.003	-0.177	< 0.001
Systolic blood pressure	0.088	0.027	0.014	0.72
Heart rate	-0.199	< 0.001	-0.202	< 0.001
Left ventricular mass	0.145	< 0.001	-0.069	0.12
Left ventricular end-systolic volume	0.324	< 0.001	0.332	< 0.001
Presence of diabetes	0.179	< 0.001	0.180	< 0.001
BMI categories	0.352	< 0.001	0.285	< 0.001

BMI: body mass index. *Pearson correlation performed for 2 continuous variables, Spearman correlation performed for 1 continuous variable and 1 ordinal variable (i.e. BMI categories), and point-biserial correlation performed for 1 continuous variable and 1 dichotomous variable (i.e. gender, presence of diabetes).

ized beta = 0.180, p < 0.001). Similar results were also obtained when BMI was modeled as a continuous variable (standardized beta = 0.247, p < 0.001).

Table 5 shows the multivariable regression analysis for average mitral annular e' velocity (model R = 0.68, p < 0.001). Increasing BMI (standardized beta = -0.157, p < 0.001) was associated with greater LV diastolic dysfunction by average mitral annular e' velocity compared to the presence of diabetes (standardized beta = -0.146, p < 0.001).

Table 5. *Independent determinants of average mitral annular e' velocity*

Variable	Average mitral annular e' velocity			
	*Univariable r	p value	Standardized β	p value
Age	-0.591	< 0.001	-0.520	< 0.001
Male gender	0.069	0.09	0.043	0.21
Systolic blood pressure	-0.367	< 0.001	-0.078	0.027
Heart rate	-0.165	< 0.001	-0.105	0.001
Left ventricular mass	-0.240	< 0.001	-0.103	0.010
Left ventricular end-systolic volume	0.167	< 0.001	0.080	0.034
Presence of diabetes	-0.175	< 0.001	-0.146	< 0.001
BMI categories	-0.238	< 0.001	-0.157	< 0.001

BMI: body mass index. *Pearson correlation performed for 2 continuous variables, Spearman correlation performed for 1 continuous variable and 1 ordinal variable (i.e. BMI categories), and point-biserial correlation performed for 1 continuous variable and 1 dichotomous variable (i.e. gender, presence of diabetes).

Finally, Table 6 shows the multivariable regression analysis for early diastolic global longitudinal strain rate (model R = 0.64, p < 0.001). Increasing BMI category (standardized beta = -0.337, p < 0.001) was associated with greater LV myocardial dysfunction by early diastolic global longitudinal strain rate compared to the presence of diabetes (standard-

Table 6. *Independent determinants of left ventricular early diastolic global longitudinal strain rate*

Variable	Early diastolic global longitudinal strain rate			
	*Univariable r	p value	Standardized β	p value
Age	-0.400	< 0.001	-0.399	< 0.001
Male gender	-0.068	0.08	-0.071	0.039
Systolic blood pressure	-0.298	< 0.001	-0.020	0.56
Heart rate	-0.128	0.001	-0.098	0.002
Left ventricular mass	-0.313	< 0.001	-0.043	0.28
Left ventricular end-systolic volume	-0.095	0.015	-0.119	0.002
Presence of diabetes	-0.257	< 0.001	-0.230	< 0.001
BMI categories	-0.392	< 0.001	-0.337	< 0.001

BMI: body mass index. *Pearson correlation performed for 2 continuous variables, Spearman correlation performed for 1 continuous variable and 1 ordinal variable (i.e. BMI categories), and point-biserial correlation performed for 1 continuous variable and 1 dichotomous variable (i.e. gender, presence of diabetes).

ized beta = -0.230, $p < 0.001$). Finally, similar results were also obtained when BMI was modeled as a continuous variable (standardized beta = -0.297, $p < 0.001$).

DISCUSSION

The present multicenter observational study demonstrated that increasing BMI category was associated with progressive and detrimental changes in LV structure, systolic and diastolic functions in diabetic patients. Compared to non-diabetic patients of similar age, gender and BMI, diabetic patients had more impaired LV function at all categories of BMI. Multivariate analysis showed that both increasing BMI category and diabetes were independent predictors of impaired LV myocardial systolic and diastolic functions despite preserved LVEF. Furthermore, both diabetes and increasing BMI category had an additive detrimental effect on LV myocardial function, and increasing BMI was a stronger determinant of impaired LV myocardial function than diabetes.

Pathogenesis of diabetic and obesity cardiomyopathy

Various mechanisms underlie the etiology of diabetic cardiomyopathy, including processes such as altered myocardial metabolism with subsequent steatosis and lipotoxicity, endothelial dysfunction with microvascular disease, autonomic neuropathy, altered myocardial structure with fibrosis and atherosclerosis.[21-26] Often, these processes act together and result in myocardial hypertrophy, increased interstitial fibrosis with increased LV stiffness, and manifesting as diastolic dysfunction in early diabetic heart disease.[5] Over time, there is progressive loss of myocardial contractile function resulting in global LV systolic dysfunction.

Recent large epidemiological studies had unequivocally demonstrated increased all-cause mortality in patients with higher levels of BMI.[15, 27] Furthermore, increasingly obese patients had progressively higher cardiovascular mortality.[15] Compared to diabetic cardiomyopathy, obesity cardiomyopathy is a clinically less well-recognized phenomenon. Obesity cardiomyopathy is characterized by a variety of cardiac structural and hemodynamic changes.[6] Previous studies have shown that obese patients have larger LV chamber sizes and increased hypertrophy compared to their lean counterparts.[28-31] These cardiac structural changes are associated with changes in cardiovascular hemodynamics, including an increased total blood volume, cardiac output and reduced systemic vascular resistance.[6, 32] Although it has been suggested that the association between obesity and incident heart failure may be secondary to these hemodynamic and cardiac structural changes[6], recent evidence suggests that the relationship may be mediated by obesity-related metabolic, inflammatory and neurohormonal changes.[2, 7, 8]

The presence of obesity-related insulin resistance, systemic vascular and adipose tissue inflammation, increased free fatty acid delivery, and activation of the renin-angiotensin-aldosterone system all contribute to atherosclerosis, myocardial hypertrophy, increased interstitial fibrosis and subsequent myocardial dysfunction.[2, 7, 8, 29]

Although the underlying pathogenesis of diabetic and obesity cardiomyopathy may not be identical, the final common pathway appears to be an increased interstitial fibrosis followed by initial myocardial diastolic dysfunction and eventually systolic dysfunction. However, few studies to date have evaluated the combined detrimental effects of both diabetes and obesity on LV function. In the present study, both diabetes and increasing BMI category were associated with LV myocardial systolic and diastolic dysfunction. Figure 4 demonstrated that non-diabetic patients had a greater initial decline in early diastolic global longitudinal strain rate from normal weight to overweight compared to diabetic patients. This suggests that early diastolic global longitudinal strain rate is most sensitive to the detrimental LV myocardial functional changes secondary to diabetes or increasing BMI, and is in agreement with the pathophysiological process of diastolic dysfunction occurring before systolic dysfunction.

Diabetes, obesity and myocardial dysfunction

Numerous echocardiographic studies examining diabetes have demonstrated the presence of both LV diastolic and systolic dysfunction compared to normal controls.[33-35] Similarly, studies on non-diabetic obese subjects have also demonstrated LV diastolic and systolic dysfunction compared to lean controls.[29, 30, 36] Although diabetes and obesity frequently co-exist together,[37] few studies to date have evaluated the combined impact of both diabetes and obesity on LV function.[38, 39] Kuperstein and co-workers recruited a large number of predominately obese subjects and demonstrated a synergistic effect of obesity and diabetes on LV mass.[38] However, the study was confounded by the small number of diabetic patients (6% of the total study population) and that all of the obese diabetic patients were women.[38] Furthermore, the combined impact of diabetes and obesity on LV function in their study was unknown. Di Stante and co-workers demonstrated LV diastolic dysfunction in 40 obese diabetic patients compared to 93 obese non-diabetic patients.[39] However, the impact of increasing obesity on LV dysfunction was not evaluated, and multivariate analysis identifying independent determinants of LV dysfunction was not performed.

In contrast, the present study is the largest to date evaluating the combined impact of diabetes and increasing BMI category on LV myocardial function. Both diabetes and increasing BMI were independent determinants of LV myocardial dysfunction. Furthermore, both increasing BMI and obesity had an additive detrimental effect on LV

myocardial function, and increasing BMI was associated with a greater impairment of LV myocardial function than diabetes. This was demonstrated in the standardized beta coefficients that demonstrated increasing BMI had a greater relative contribution to the multiple linear regression models than the presence of diabetes, despite similar p values. Importantly, the present study excluded all patients with known or suspected significant underlying coronary artery disease. Therefore, it was unlikely that the presence of undiagnosed significant coronary artery disease could have significantly influenced the results. Similarly, although increasing BMI and diabetes were associated with a higher incidence of hypertension, the independent associations between diabetes, obesity and myocardial dysfunction were still significant despite adjusting for differences in systolic blood pressure on multivariate analysis. Similar results were also obtained when systolic blood pressure was substituted by diastolic blood pressure or history of hypertension, or when all hypertensive patients were excluded from analysis.

Study Limitations

As the present study was a cross-sectional analysis on the effects of diabetes and BMI on myocardial function, there were no longitudinal follow-up clinical outcome data. Similarly, there was no information on the influences of weight loss and intensity of diabetic control on myocardial function. Finally, there was a potential enrolment/selection bias as clinical patients were referred for a clinical echocardiogram, thereby possibly increasing the incidence of subclinical myocardial dysfunction despite a normal LVEF.

Clinical implications

Both obesity and diabetes are world-wide growing epidemics. Previous epidemiological studies demonstrated that both diabetes and obesity were independent risk factors for the development of heart failure.[9, 13, 40, 41] These studies have shown that diabetes and obesity were each associated with an approximately 2-fold increased risk of heart failure.[9, 13, 41] However, these studies generally examined the prognostic impact of diabetes and obesity separately. The present study demonstrated that diabetes and obesity was independently associated with an additive detrimental effect on LV myocardial function, and increasing obesity was associated with greater LV myocardial dysfunction than diabetes. Thus, future clinical studies on diabetic patients should also focus on the frequently associated obesity problem in this patient population.

CONCLUSION

Both diabetes and obesity were independently associated with an additive detrimental effect on LV myocardial function. Furthermore, increasing BMI category was associated with greater LV myocardial dysfunction than diabetes. Therapies aiming at reducing cardiac morbidity and mortality in diabetic patients should also focus on weight reduction.

REFERENCE LIST

(1) Boudina S, Abel ED. Diabetic Cardiomyopathy Revisited. *Circulation* 2007;115:3213-3223.

(2) Rijzewijk LJ, van der Meer RW, Smit JWA, Diamant M, Bax JJ, Hammer S, Romijn JA, De Roos A, Lamb HJ. Myocardial Steatosis Is an Independent Predictor of Diastolic Dysfunction in Type 2 Diabetes Mellitus. *J Am Coll Cardiol* 2008;52:1793-1799.

(3) Fang ZY, Leano R, Marwick TH. Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. *Clin Sci* 2004;106:53-60.

(4) Vinereanu D, Nicolaides E, Tweddel AC, Mädler CF, Holst B, Boden LE, Cinteza M, Rees AE, Fraser AG. Subclinical left ventricular dysfunction in asymptomatic patients with Type II diabetes mellitus, related to serum lipids and glycated haemoglobin. *Clin Sci* 2003;105:591-599.

(5) Moir S, Hanekom L, Fang ZY, Haluska B, Wong C, Burgess M, Marwick TH. Relationship between myocardial perfusion and dysfunction in diabetic cardiomyopathy: a study of quantitative contrast echocardiography and strain rate imaging. *Heart* 2006;92:1414-1419.

(6) Fang ZY, Schull-Meade R, Downey M, Prins J, Marwick TH. Determinants of subclinical diabetic heart disease. *Diabetologia* 2005;48:394-402.

(7) Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH. Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 2003;41:611-617.

(8) Galderisi M, de Simone G, Innelli P, Turco A, Turco S, Capaldo B, Riccardi G, de Divitiis O. Impaired Inotropic Response in Type 2 Diabetes Mellitus: A Strain Rate Imaging Study. *Am J Hypertens* 2007;20:548-555.

(9) Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.

(10) Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8:491-498.

(11) Nishimura R, Miller FJ, Callahan M, Benassi R, Seward J, Tajik A. Doppler echocardiography: theory, instrumentation technique and application. *Mayo Clin Proc* 1985;60:321-343.

(12) Tajik A, Seward J, Hagler D, Mair D, Lie J. Two dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification and validation. *Mayo Clin Proc* 1978;53:271-303.

(13) Reichek N, Helak J, Plappert T, Sutton MS, Weber KT. Anatomic validation of left ventricular mass estimates from clinical two-dimensional echocardiography: initial results. *Circulation* 1983;67:348-352.

(14) Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987;317:1098.

(15) Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310.

(16) Unger RH. Lipotoxic Diseases. *Annu Rev Med* 2002;53:319.

(17) Watts GF, Marwick TH. Ventricular dysfunction in early diabetic heart disease: detection, mechanisms and significance. *Clin Sci* 2003;105:537-540.

(18) McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac Steatosis in Diabetes Mellitus: A 1H-Magnetic Resonance Spectroscopy Study. *Circulation* 2007;116:1170-1175.

(19) Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic. *JAMA* 2003;289:194-202.

(20) Greenbaum RA, Ho SY, Gibson DG, Becker AE, Anderson RH. Left ventricular fibre architecture in man. *Br Heart J* 1981;45:248-263.