BMJ Open Diabetes Research & Care

Hyperinsulinemia and sulfonylurea use are independently associated with left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus with suboptimal blood glucose control

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To cite: Inoue T, Maeda Y, Sonoda N, *et al*. Hyperinsulinemia and sulfonylurea use are independently associated with left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus with suboptimal blood glucose control. *BMJ Open Diabetes Research and Care* 2016;**4**: e000223. doi:10.1136/bmjdrc-2016-000223

► Additional material is available. To view please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2016-000223).

Received 13 March 2016
Revised 26 July 2016
Accepted 29 July 2016

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ABSTRACT

Objective: Although diabetes mellitus is associated with an increased risk of heart failure with preserved ejection fraction, the underlying mechanisms leading to left ventricular diastolic dysfunction (LVDD) remain poorly understood. The study was designed to assess the risk factors for LVDD in patients with type 2 diabetes mellitus.

Research design and methods: The study cohort included 101 asymptomatic patients with type 2 diabetes mellitus without overt heart disease. Left ventricular diastolic function was estimated as the ratio of early diastolic velocity (E) from transmitral inflow to early diastolic velocity (e') of tissue Doppler at mitral annulus (E/e'). Parameters of glycemic control, plasma insulin concentration, treatment with antidiabetic drugs, lipid profile, and other clinical characteristics were evaluated, and their association with E/e' determined. Patients with New York Heart Association class >1, ejection fraction <50%, history of coronary artery disease, severe valvulopathy, chronic atrial fibrillation, or creatinine clearance <30 mL/min, as well as those receiving insulin treatment, were excluded.

Results: Univariate analysis showed that E/e' was significantly correlated with age (p<0.001), sex (p<0.001), duration of diabetes (p=0.002), systolic blood pressure (p=0.017), pulse pressure (p=0.010), fasting insulin concentration (p=0.025), and sulfonylurea use (p<0.001). Multivariate linear regression analysis showed that log E/e' was significantly and positively correlated with log age (p=0.034), female sex (p=0.019), log fasting insulin concentration (p=0.010), and sulfonylurea use (p=0.027).

Conclusions: Hyperinsulinemia and sulfonylurea use may be important in the development of LVDD in patients with type 2 diabetes mellitus.

Key messages

- This study was designed to determine the risk factors for left ventricular diastolic dysfunction in patients with type 2 diabetes mellitus.
- E/e', which is regarded as an index of diastolic function, is significantly and independently correlated with fasting insulin concentration, as well as with sulfonylurea use, age, and sex.
- This study showed that hyperinsulinemia and sulfonylurea use may be independently associated with the development of diastolic dysfunction.

INTRODUCTION

Diabetes mellitus is a major chronic disease affecting a large population worldwide. It has been estimated that 300 million people will have diabetes by 2050.[1] The risk of developing heart failure is fourfold to fivefold higher in patients with diabetes mellitus than in the general population.[2] Thus, it is important to understand the mechanisms underlying the development of diabetes-related heart diseases.

Heart failure with preserved ejection fraction (HFpEF) is common, of increasing prevalence, and causes a substantial reduction in prognosis. Diabetes is associated with a 70–80% increase in mortality and hospitalisations in patients with HFpEF.[3–5] HFpEF is related to left ventricular diastolic dysfunction (LVDD), which is detected in up to 75% of asymptomatic patients with diabetes.[6] However, the risk factors for LVDD in patients with type 2 diabetes mellitus have not been extensively explored. This study was designed to determine the risk factors for preclinical LVDD, using echocardiographic tissue Doppler imaging (TDI), in patients with type 2 diabetes mellitus without overt cardiovascular disease.

RESEARCH DESIGN AND METHODS

Participants

The study enrolled 101 Japanese patients (53 men, 48 women) with type 2 diabetes

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mellitus who had been admitted to the metabolic ward of Fukuoka City Medical Association Hospital for glycemic control from October 2013 to March 2015. All patients were recruited for having suboptimal blood glucose control at admission. The diagnosis of type 2 diabetes mellitus was confirmed according to the criteria of the American Diabetes Association/WHO or by a medical history of diabetes. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital. Written informed consent was obtained from each patient. Patients with overt heart failure, New York Heart Association (NYHA) class >1, ejection fraction (EF) <50%, history of coronary artery disease, severe valvulopathy, chronic atrial fibrillation, or creatinine clearance <30 mL/min, as well as those receiving insulin treatment, were excluded.

All patients underwent clinical evaluation, laboratory assessment, and echocardiographic examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Concentrations of fasting plasma glucose, glycated hemoglobin (HbA1c) (National Glycohemoglobin Standardization Program, NGSP), immunoreactive insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, free fatty acids, creatinine, and urinary albumin, as well as creatinine clearance, were measured. Initially, HbA1c levels were determined using the criteria of the Japanese Diabetes Society (JDS). These concentrations were converted to NGSP concentrations by adding 0.4 (%) to JDS concentrations[7] and converted to International Federation of Clinical Chemistry and Laboratory Medicine mmol/mol units using the NGSP converter for HbA1c (http://www.ngsp.org/convert1.asp).

Echocardiography

All echocardiographic examinations were performed with Vivid E9 (GE, Andover, Massachusetts, USA). Peak velocities of E and A waves in mitral flow, the ratio of their peak velocities (E/A ratio), and deceleration time of the E wave were measured from the mitral flow velocity pattern. TDI of the mitral annulus was obtained from the apical four-chamber view as described.[8] Spectral pulsed-wave Doppler tissue interrogation of longitudinal mitral annular velocity was recorded throughout the cardiac cycle at the septal annulus in the apical four-chamber view. The peak early diastolic myocardial velocity (e' velocity) was measured, and the ratio of E velocity to e' velocity (E/e') was calculated. Since E/e' is regarded as a surrogate marker of left ventricular (LV) filling pressure,[9] particularly in patients with HFpEF, E/e' was used as an index of diastolic function in this study. Additional exploratory analyses, including changes in chamber dimensions and LV EF, were measured according to the recommendations of the American Society of Echocardiography.[10] LV mass was calculated according to the Devereux formula and expressed as a ratio to body surface area (left ventricular mass index (LVMI)). Relative wall thickness was calculated as (2×PWTd)/LVDd, where PWTd is the end-diastolic posterior wall thickness and LVDd is the end-diastolic LV dimension. All measurements were made by experienced physicians who were blinded to patients' clinical data and outcomes.

Statistical analysis

All statistical analyses were performed using JMP statistical software, V.9 (SAS Institute, Cary, North Carolina, USA). For univariate analysis of the relationship of each parameter with E/e', continuous variables were analyzed using Spearman's rank correlation and categorical variables using the Mann-Whitney U test. Variables significant in the univariate model were entered into a multivariate linear regression analysis. Continuous variables that were not normally distributed according to the Kolmogorov-Smirnov test were logarithmically transformed. Groups that did and did not receive sulfonylureas were compared using Mann-Whitney U tests. Continuous variables are presented as a median (IQR) and categorical variables as an absolute number (%). A p value <0.05 was considered statistically significant.

RESULTS

The clinical, anthropometric, and metabolic characteristics of the study groups are shown in table 1. The study cohort consisted of 53 men and 48 women of median age 64 years (IQR 54.5–71.5 years), median BMI 25.4 kg/m^2 (IQR 22.5–28.4 kg/m^2), and median duration of diabetes 8 years (IQR 2–14.5 years). Median HbA1c was 9.3% (IQR 8.1–10.7%) or 78 mmol/mol (IQR 65–93 mmol/mol) and median fasting insulin concentration was 4.7 µU/mL (IQR 2.2–8.3 µU/mL).

Echocardiographic data of the study groups are shown in online supplemental table S1. The median E/e' was 11.0 (IQR 8.5–14.0). Univariate analyses showed that E/e' was significantly correlated with age (p<0.001), sex (p<0.001), duration of diabetes (p=0.002), systolic blood pressure (p=0.017), pulse pressure (p=0.010), fasting insulin concentration (p=0.025), and sulfonylurea use (p<0.001) (table 2). A multivariate linear regression analysis that included the factors significant on univariate analysis was performed to identify parameters independently associated with E/e'. This analysis showed that log E/e' was significantly correlated with log age (p=0.034), female sex (p=0.019), log fasting insulin concentration (p=0.010), and sulfonylurea use (p=0.027) (table 3). Figure 1 showed the significant correlation between E/e' and age, sex, fasting insulin, or sulfonylurea use. Fasting insulin concentrations did not differ significantly in the groups of patients who were and were not treated with a sulfonylurea (see online supplemental table S2). In the group of patients who were treated with a sulfonylurea, e' (p=0.024) and A wave (p=0.005) were significantly lower, while E/e' (p<0.001) was significantly higher than in groups of patients who were not treated with a sulfonylurea (see online supplemental table S2). The most frequent

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Table 1 Demographic and clinical characteristics of the patient cohort (N=101)

Patient characteristics	
Age, years	64 (54.5–71.5)
Sex, male/female, %	53 (52.5)/48 (47.5)
Body mass index, kg/m^2	25.4 (22.5–28.4)
Duration of diabetes, years	8 (2–14.5)
SBP, mm Hg	132 (121–144)
DBP, mm Hg	77 (68–86)
PP, mm Hg	55 (47–65)
Fasting plasma glucose, mg/dL	157 (123.5–203.5)
HbA1c, % (mmol/mol)	9.3 (8.1–10.7) (78 (65–93))
Fasting insulin, μU/mL	4.7 (2.2–8.3)
Total cholesterol, mg/dL	194 (168.5–223.5)
HDL-C, mg/dL	46.6 (39.9–57.8)
TG, mg/dL	142 (114–197)
FFA, μEq/L	704 (558–910)
Cre, mg/dL	0.67 (0.58–0.83)
Ccr, mL/min	106.6 (84.2–131.7)
Urinary albumin, mg/day	9.3 (5.2–33.6)
Diabetes treatment	
Sulfonylurea, %	50 (49.5)
Glinide, %	0 (0)
Biguanide, %	35 (34.7)
Thiazolidinedione, %	13 (12.9)
α-Glucosidase inhibitor, %	18 (17.8)
DPP-4 inhibitor, %	54 (53.5)
SGLT2 inhibitor, %	1 (1.0)

Categorical variables are presented as a number (%) or median (lower quartile–upper quartile).
Ccr, creatinine clearance; Cre, creatinine; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; FFA, free fatty acids; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; SGLT2, sodium glucose cotransporter 2; TG, triglycerides.

sulfonylurea administered to these patients was glimepiride (37.6% of patients), at a median dose of 2 mg/day (IQR 1–3 mg/day). Median doses of gliclazide and glibenclamide, administered to 6.9% and 4.0% of patients, respectively, were 40 mg/day (IQR 40–80 mg/day) and 2.5 mg/day (IQR 2.5–6.2 mg/day), respectively.

CONCLUSIONS

In the present study, we showed that E/e' significantly correlated with fasting insulin concentration, as well as with sulfonylurea use, age, and sex. Our findings confirm previous results, showing that the prevalence of LVDD was higher in women[11] and was associated with age.[11 12] Although hypertension is also a well-known risk factor for LVDD,[3] it was not associated with E/e' in multivariate linear regression analysis. The reason may be that the patients enrolled in this study were currently controlled with antihypertensive medications. The key finding of this study was that fasting insulin and sulfonylurea use were independently associated with E/e' in patients with type 2 diabetes mellitus without overt cardiovascular disease. This finding suggested that

Table 2 Univariate analysis of factors associated with E/e'

Variables	ρ	p Value
Age	0.404	<0.001
Sex, female		<0.001
Body mass index	0.100	0.320
Duration of diabetes	0.302	0.002
SBP	0.243	0.017
DBP	−0.022	0.825
PP	0.259	0.010
Fasting plasma glucose	0.016	0.869
HbA1c	−0.010	0.919
Fasting insulin	0.223	0.025
Total cholesterol	−0.063	0.532
HDL-C	0.154	0.124
TG	0.038	0.704
FFA	−0.010	0.931
Cre	−0.050	0.615
Ccr	−0.175	0.088
Urinary albumin	−0.068	0.497
Diabetes treatment		
Sulfonylurea		<0.001
Biguanide		0.438
Thiazolidinedione		0.959
α-Glucosidase inhibitor		0.592
DPP-4 inhibitor		0.901

p Values were calculated using Spearman's rank correlation test or the Mann-Whitney U test, as appropriate.
Ccr, creatinine clearance; Cre, creatinine; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; FFA, free fatty acids; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; PP, pulse pressure; SBP, systolic blood pressure; TG, triglycerides.

hyperinsulinemia and sulfonylurea use may be involved in the early stage development of diastolic dysfunction. In contrast, this study found no association between LVDD and HbA1c concentration. However, HbA1c levels were measured only at a single time point, whereas cumulative exposure to hyperglycemia over several years is likely to be more important.[13]

In the heart, insulin stimulates glucose uptake and oxidation. Although insulin also increases fatty acid uptake by the heart, it inhibits fatty acid usage for energy. Therefore, hyperinsulinemia accompanied by insulin resistance can result in a reduction of myocardial energy supply due to changes in substrate usage from glucose to free fatty acids.[14 15] In addition, excess expression or activation of protein kinase C (PKC) has been

Table 3 Multivariate linear regression analysis of factors associated with log E/e'

Variables	β	p Value
Log age	0.20	0.034
Sex, female	0.23	0.019
Log duration of diabetes	0.15	0.118
PP	0.10	0.277
Log fasting insulin concentration	0.23	0.010
Sulfonylurea use	0.21	0.027

PP, pulse pressure.

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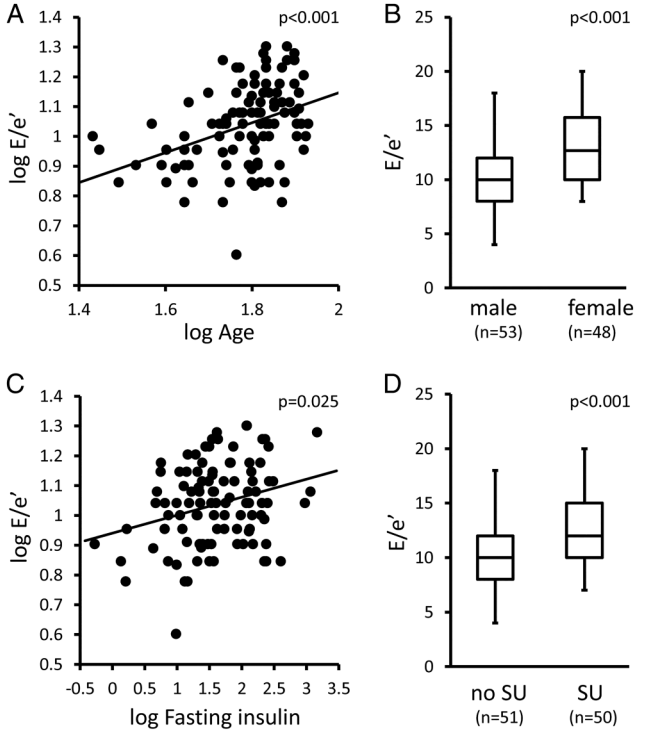

Figure 1 Correlation of E/e' with age (A), gender (B), fasting insulin (C), and sulfonylurea use (SU) (D) among patients with type 2 diabetes mellitus. E/e' was significantly correlated with patient age (p<0.001), gender (p<0.001), fasting plasma insulin concentration (p=0.025), and SU (p<0.001). Box plots show medians (black), 25th and 75th centiles (lower and upper limits of the box), and adjacent values (lower and upper whiskers).

reported to be involved in the development and progression of diabetic cardiomyopathy,[16–18] which manifests as diastolic HFpEF at an early stage. We previously reported that downregulation of adipose triglyceride lipase by hyperinsulinemia activates PKC, which may be involved in the development of diabetic cardiovascular complications in vivo and in vitro.[19 20] Taken together, these findings suggest that hyperinsulinemia may be associated with the development of diastolic dysfunction via these mechanisms. Moreover, this study also showed that sulfonylurea use was independently associated with the development of diastolic dysfunction. Sulfonylureas trigger insulin release by inhibiting ATP-sensitive potassium (KATP) channels on the pancreas; however, additional inhibition of cardiac KATP channels may be harmful.[21–23] KATP channels are thought to play a key role in the cardioprotection seen with KATP channel openers and ischemic preconditioning, a powerful protective mechanism endogenous to cardiac muscle.[24 25] Therefore, sulfonylureas may be involved in the development of diastolic dysfunction via these mechanisms. However, the sulfonylurea used most frequently among these patients was glimepiride, which has not been associated with reduced ischemic preconditioning, because glimepiride has no effect on cardiac mitochondrial KATP.[26] In contrast, glimepiride and other sulfonylureas have been reported to block cardiac and smooth muscle sarcolemmal KATP channels,[27 28] suggesting that sulfonylureas directly affect myocardial and smooth muscle cell functions, such as Ca++ metabolism and contractility, through this mechanism. Additional studies are required to evaluate these molecular mechanisms in detail. Additionally, it is important to analyze the association of diastolic dysfunction and the duration of sulfonylurea use. However, we could not analyze it because our study was a cross-sectional design and because most of the patients enrolled could not remember their correct duration of sulfonylurea use. Thus, further study is necessary for showing the correlation.

One limitation of our study was its cross-sectional design. Therefore, a cause-and-effect relationship could not be determined. Another limitation was the uncertainty of the diagnosis of ischemic heart disease. Ischemic heart disease was excluded based only on the absence of symptoms and the lack of previous cardiovascular disease and ECG results, indications that may not completely rule out ischemic heart disease. In addition, enrolled patients had been admitted for glycemic control in this study population, so they were relatively young and there were not a control group of patients without type 2 diabetes mellitus. Therefore, the results presented here may not be representative of the general population. Additionally, the number of participants was relatively small. Further, a large study cohort is necessary for showing stronger correlation. Also, we recorded longitudinal mitral annular velocity only by septal annulus, although it was better to measure it by four positions (septal, lateral, inferior, and anterior annulus).

Despite these limitations, however, our results suggest that excessive plasma insulin concentration may play a significant role in the development of diastolic dysfunction. In addition, specific antidiabetic drugs may be optimal in the management of patients with diabetes with suboptimal blood glucose control.

In conclusion, this study showed for the first time that fasting insulin concentration and sulfonylurea use were significantly and positively correlated with E/e'.

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Contributors TI wrote the manuscript and researched the data. TI and YM wrote the manuscript, researched the data, contributed to discussions, and reviewed/edited the manuscript. NS, SS, TK and KK contributed to the discussions and reviewed/edited the manuscript. TI is the guarantor of this work and, as such, had full access to all the data in the study. TI also takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This study has been approved by the Ethical Committee of Fukuoka City Medical Association Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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