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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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 tissue Doppler imaging (TDI) to 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...
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 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. 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, 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. 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/m² (IQR 22.5–28.4 kg/m²), 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
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 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 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/m² | 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 | 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, sodium glucose cotransporter 2, % | 1 (1.0) |

Categorical variables are presented as a number (%) or median (lower quartile-upper quartile).

| Table 2 | Univariate analysis of factors associated with E/e’ |
|----------|--------------------------------------------------|
| Variables | 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.

| 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. | | |
Cardiovascular and metabolic risk

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 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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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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