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Association between cortisol and left ventricular diastolic dysfunction in patients with diabetes mellitus

Rikako Sagara, Tomoaki Inoue*, Noriyuki Sonoda, Chieko Yano, Misato Motoya, Hironobu Umakoshi, Ryuichi Sakamoto, Yoshihiro Ogawa

Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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***Correspondence**
Tomoaki Inoue
Tel.: +81-92-642-5284
Fax: +81-92-642-5287
E-mail address:
tomo-i@intmed3.med.kyushu-u.ac.jp

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ABSTRACT

Aims/Introduction: Diabetes mellitus is a major risk factor for the development of cardiovascular diseases. Heart failure with preserved ejection fraction is characterized by left ventricular diastolic dysfunction (LVDD). It has been reported that excess cortisol found in patients with Cushing's syndrome was associated with the development of LVDD. However, the relationship between cortisol concentration and LVDD in patients with diabetes mellitus has not been addressed.

Materials and Methods: We enrolled 109 patients with diabetes mellitus and 104 patients without diabetes mellitus who had undergone echocardiographic examination at Kyushu University Hospital, Fukuoka, Japan, between November 2016 and March 2019. Left ventricular function was evaluated and the ratio of early diastolic velocity from transmitral inflow to early diastolic velocity (E/e′) was used as an index of diastolic function. Plasma cortisol concentrations, glycemic control, lipid profiles, treatment with antidiabetic drugs and other clinical characteristics were evaluated, and their associations with E/e′ were determined using univariate and multivariate analyses.

Results: Multivariate linear regression analysis showed that log E/e′ was positively correlated with age ($P = 0.017$), log systolic blood pressure ($P = 0.004$) and cortisol ($P = 0.037$), and negatively correlated with estimated glomerular filtration rate ($P = 0.016$) and the use of sodium–glucose cotransporter 2 inhibitors ($P = 0.042$) in patients with diabetes mellitus. Multivariate analysis showed that cortisol was positively correlated with age ($P = 0.016$) and glycated hemoglobin ($P = 0.011$). There was no association between E/e′ and cortisol in patients without diabetes mellitus.

Conclusions: Increased cortisol levels might increase the risk of developing LVDD in diabetes mellitus patients.

INTRODUCTION

Diabetes mellitus is a major risk factor for the development of cardiovascular diseases. Heart failure with preserved ejection fraction, which is characterized by left ventricular diastolic dysfunction (LVDD), is clinically important in patients with diabetes. Indeed, the prevalence of diabetes is approximately 45% in patients with heart failure with preserved ejection fraction[1].

Patients with normal left ventricular wall contraction might have symptoms of heart failure. Therefore, it is important to evaluate left ventricular diastolic function separately from left ventricular systolic function[2]. Doppler echocardiography is widely used for the non-invasive assessment of diastolic filling of the left ventricle[3] Tissue Doppler imaging of mitral annular motion has been proposed to correct for the influence of myocardial relaxation on transmitral flows and shown to be an excellent predictor of LVDD[3].

Cushing's syndrome, including Cushing's disease and adrenal Cushing's syndrome, is characterized by excess blood levels of cortisol, and confers an approximately fourfold increase in mortality compared with the general population[4]. The increased mortality is due mainly to cardiovascular complications[5]. It has been recognized that patients with Cushing's syndrome have a

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high incidence of left ventricular hypertrophy and dysfunction[6]. Additionally, the incidence of cardiovascular outcomes in patients with subclinical Cushing's syndrome was more than threefold greater than in patients with non-functioning adrenal adenoma[7,8]. It is likely that cortisol affects cardiac structure and function, although its relationship with LVDD in patients with diabetes mellitus has not been addressed. Therefore, we designed a cross-sectional study to determine the relationship between cortisol and LVDD in patients with diabetes mellitus who did not have overt cardiovascular diseases.

MATERIALS AND METHODS

Participants

Between November 2016 and March 2019, we consecutively recruited 109 patients with diabetes mellitus and 104 patients without diabetes mellitus who had undergone echocardiographic examination at the metabolic ward of Kyushu University Hospital, Fukuoka, Japan. Patients were excluded if they: (i) were taking steroids; (ii) were undergoing hemodialysis treatment; (iii) had overt heart failure; (iv) had acute diseases, such as acute coronary syndromes and cerebrovascular diseases; (v) had complications of infection; or (vi) had acute metabolic disorders, including diabetic ketoacidosis. The diabetes mellitus group recruited patients who were admitted for glycemic control. Patients without diabetes mellitus consisted of those who were hospitalized for hypertension, gastrointestinal polyps and/or adrenal mass whose diagnosis finally became non-functional. All of the patients underwent clinical evaluation, laboratory assessment and echocardiographic examination. In the diabetes mellitus group, the type of diabetes, presence of microvascular disease and hypertension, history of ischemic heart disease, and type of antihypertensive agent were investigated. Blood concentrations of fasting plasma glucose, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, estimated glomerular filtration rate (eGFR), adrenocorticotropic hormone and cortisol (at 08.00 hours, fasting) were measured. Serum cortisol concentrations were determined by electrochemiluminescence immunoassay (ECLusys Cortisol Ⅱ Kits, Roche in Vitro Diagnostics, Tokyo, Japan). HbA1c levels were determined using the criteria of the National Glycohemoglobin Standardization Program. Homeostasis model assessment insulin resistance (HOMA-IR; fasting blood glucose × fasting insulin level / 405) in diabetes patients not using insulin was calculated. Clinical data and information regarding treatment of the patients with antidiabetic drugs and antihypertensive agents were obtained from medical records. The study protocol was approved by the Clinical Ethics Committee of Kyushu University Hospital (protocol #29-645). This study was carried out in accordance with the Declaration of Helsinki of 1964, as revised in 2013.

Echocardiography

All echocardiographic examinations were carried out with an Aplio i900 TUS-AI900 imager (Canon Medical Systems, Inc., Tokyo, Japan). Chamber dimensions and left ventricular ejection fractions were measured in accordance with the recommendations of the American Society of Echocardiography[9]. The left ventricular mass index was calculated according to the Devereux formula and expressed as a ratio of the left ventricular mass to body surface area[9]. The relative wall thickness was based on the end-diastolic posterior wall thickness and the end-diastolic left ventricular dimension. Relative wall thickness was calculated as (2 × end-diastolic posterior wall thickness) / end-diastolic left ventricular dimension. The following mitral pulse wave Doppler and tissue Doppler parameters were measured to assess diastolic function. Peak velocities of E and A waves of mitral inflow, the E/A ratio, and deceleration time of the E wave were measured from the mitral flow velocity pattern using pulse wave Doppler imaging. The peak early diastolic myocardial velocity (e′ velocity) was measured using tissue Doppler imaging, and the ratio of E velocity to e′ velocity (E/e′) was calculated. The left atrial volume index (LAVI) has also been pointed out as one of the indicators of end-diastolic left ventricular dimension[10]. The biplane method of disks was used to calculate left atrial volume. LAVI was calculated by dividing left atrial volume by the body surface area of participants.

Statistical analysis

All statistical analyses were carried out using JMP® statistical software, version 14 (SAS Institute Inc., Cary, NC, USA). For univariate analysis of the relationships between each parameter and E/e′, continuous and categorical variables were analyzed using Spearman's rank-order correlation and the Mann–Whitney *U*-test, respectively. Variables that were significant in the univariate model were entered into a multivariate linear regression analysis. Sex and glucose-lowering therapy were coded as dummy variables. Continuous variables were logarithmically transformed if they were not normally distributed according to the Kolmogorov–Smirnov test. Categorical variables are presented as number (%) or median (lower quartile–upper quartile). A P-value <0.05 was considered statistically significant.

RESULTS

The clinical, anthropometric and metabolic characteristics of the study participants are shown in Table 1. The diabetes group was older than the non-diabetes group, and there was no significant difference in the sex ratio between the two groups. Fasting plasma glucose, HbA1c, systolic blood pressure (SBP) and cortisol concentrations were significantly higher, and eGFR and high-density lipoprotein cholesterol concentrations were significantly lower in the diabetes group than in the non-diabetes group. HOMA-IR was calculated in 40 of the 73 insulin-naive patients. In the diabetes group, 79 (72%) had microvascular disease, 72 (66%) had hypertension and 21 (19%) had a history of ischemic heart disease (Table S1).

The echocardiographic data is shown in Table 2. Left ventricular ejection fraction was preserved in both the diabetes and non-diabetes groups (69%, interquartile range [IQR] 64–73% vs

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Table 1 | Demographic and clinical characteristics of the two patient cohorts

Patient characteristics	Control (n = 104)	DM (n = 109)	P-value
Age (years)	54 (43–69)	66 (56–72)	<0.001
Sex, male/female (%)	53 (51.0)/51(49.0)	54 (49.5)/55 (50.5)	0.836
Body mass index (kg/m^2)	23.7 (21.3–26.1)	25.5 (21.3–29.9)	0.147
Duration of diabetes (years)		10 (5–18)	
SBP (mmHg)	119 (112–129)	126 (111–141)	0.038
DBP (mmHg)	70 (65–79)	75 (68–84)	0.107
Fasting plasma glucose (mg/dL)	91 (84–98)	143 (119–183)	<0.001
HbA1c (%)	5.6 (5.4–5.7)	8.9 (7.7–10.2)	<0.001
HOMA-IR (excluding insulin users, n = 40)		2.27 (1.52–4.00)	
Total cholesterol (mg/dL)	187 (161–211)	176 (151–202)	0.099
HDL-C (mg/dL)	51 (43–63)	45 (37–54)	0.003
TG (mg/dL)	109 (80–146)	123 (85–181)	0.062
UA (mg/dL)	5.5 (4.2–6.4)	5.7 (4.6–6.7)	0.222
Cre (mg/dL)	0.64 (0.58–0.77)	0.69 (0.60–0.96)	0.009
eGFR (mL/min/1.73 m^2)	83.5 (70–98.5)	72.5 (57.0–87.0)	0.001
ACTH (pg/mL)	31.1 (20.9–44.9)	36.0 (21.6–52.6)	0.186
Cortisol (μg/dL)	10.35 (7.4–14.0)	12.1 (10.0–15.2)	0.003
Glucose-lowering therapies			
Biguanide		46 (42)	
Sulfonylureas		27 (25)	
Dipeptidyl peptidase-4 inhibitors		49 (45)	
Thiazolidinediones		4 (4)	
α-Glucosidase inhibitor		13 (12)	
Glinide		8 (7)	
Glucagon-like peptide-1 agonists		20 (18)	
Sodium–glucose cotransporter 2 inhibitor		21 (20)	
Insulin		36 (33)	

Total n = 213. Categorical variables are presented as number (%) or median (lower quartile–upper quartile). ACTH, adrenocorticotropic hormone; Cre, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimate glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid.

Table 2 | Echocardiographic data from each patient cohort

Echocardiograph findings	Control (n = 104)	DM (n = 109)	P-value
LAD (mm)	33 (30–37)	35 (30–40)	0.023
LVDd (mm)	46 (43–49)	45 (42–49)	0.636
LVDs (mm)	28 (25–30)	28 (25–31)	0.690
IVSd (mm)	8 (7–10)	9 (8–11)	<0.001
PWd (mm)	9 (8–10)	9 (9–10)	<0.001
LVMI (g/m^2)	79 (64–95)	83 (74–104)	0.003
RWT	0.38 (0.34–0.44)	0.40 (0.37–0.46)	<0.001
LVEF (%)	70 (66–73)	69 (64–73)	0.141
E wave (cm/s)	67 (57–77)	65 (54–79)	0.657
A wave (cm/s)	63 (54–80)	78 (64–92)	<0.001
E/A	1.0 (0.8–1.3)	0.8 (0.6–1.0)	<0.001
DcT (ms)	193 (169–222)	203 (169–245)	0.202
e′	8.0 (6.1–10.6)	6.1(4.9–7.8)	<0.001
E/e′	8.3 (6.3–10.1)	10.4 (8.2–13.3)	<0.001
LAVI (control: n = 54, DM: n = 68)	27.2 (23.3–32.7)	25.95 (21.9–33.5)	0.757

Total n = 213. Categorical variables are presented as number (%) or median (lower quartile–upper quartile). Dct, deceleration time of mitral E wave; DM, diabetes mellitus; IVSd, interventricular septal wall dimension; LAD, left atrial dimension; LAVI, Left atrial volume index; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; PWd, posterior wall thickness dimension; RWT, relative wall thickness.

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70%, IQR 66–73%, $P = 0.141$). However, the diabetes group had a significantly higher E/e′ ratio compared with the non-diabetes group (10.4, IQR 8.2–13.3 vs 8.3, IQR 6.3–10.1, $P < 0.001$), suggesting diastolic dysfunction in the patients with diabetes. The left ventricular mass index and relative wall thickness were significantly higher in the diabetes group than in the non-diabetes group (83g/m^2, IQR 74–104 vs 79 g/m^2, IQR 64–95, $P < 0.003$).

Because the E/e′ ratio and plasma cortisol concentrations were higher in the diabetes group than in non-diabetes group, we evaluated the relationships between the E/e′ ratio and other variables, including cortisol (Table 3). In this analysis, age ($P < 0.001$), duration of diabetes ($P = 0.039$), SBP ($P < 0.001$) and cortisol ($P = 0.009$) were positively associated with the E/e′ ratio, and eGFR ($P = 0.002$) and the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors ($P < 0.001$) were inversely associated with the E/e′ ratio. There was no association between HbA1c and the E/e′ ratio. The factors that were associated with the E/e′ ratio in the univariate analysis were included in a multivariate linear regression model. The parameters that were independently associated with the E/e′ ratio in the diabetes group are shown in Table 4. The log of the E/e′ ratio was positively correlated with age ($P = 0.017$), the log of SBP ($P = 0.004$) and cortisol ($P = 0.037$), and negatively correlated with eGFR and the use of SGLT2 inhibitors ($P = 0.042$).

We examined the factors that were associated with plasma cortisol concentrations in the diabetic state. Univariate analysis showed that age ($P = 0.021$), fasting plasma glucose ($P = 0.003$), HbA1c ($P = 0.008$), HOMA-IR ($P = 0.008$) and high-density lipoprotein cholesterol ($P = 0.010$) were positively associated with cortisol, and uric acid ($P = 0.039$) was negatively associated with cortisol (Table S2). In addition, the presence of comorbidities and the type of antihypertensive medication were examined as factors involved in elevated serum cortisol concentrations in the diabetes group, and no significant correlation was found (Table S3). Multivariate linear regression analysis excluding HOMA-IR with a small number of patients showed that cortisol was positively and independently correlated with the log of HbA1c ($P = 0.011$) and age ($P = 0.016$) (Table S4). These findings suggest that an elevated cortisol concentration in the blood is associated with diastolic dysfunction in patients with diabetes. In contrast, there was no correlation between E/e′ and cortisol in the non-diabetes group (Table S5). LAVI, one of the indicators of LVDD, was measured in 68 patients in the diabetes group and 54 patients in the non-diabetes group. There was no significant association between serum cortisol concentrations and LAVI in either the diabetes group ($P = 0.324$) or the non-diabetes group ($P = 0.240$; Table S6).

Table 3 | Correlations between E/e′ and other variables in the diabetes patients

Variables	ρ	*P*-value
Age (years)	0.358	<0.001
Sex, male/female (%)	0.132	0.171
Body mass index (kg/m^2)	0.074	0.445
Duration of diabetes (years)	0.199	0.039
SBP (mmHg)	0.306	<0.001
DBP (mmHg)	0.059	0.544
Fasting plasma glucose (mg/dL)	0.150	0.120
HbA1c (%)	0.057	0.573
HOMA-IR (excluding insulin users, $n = 40$)	0.221	0.170
Total cholesterol (mg/dL)	0.012	0.900
HDL-C (mg/dL)	0.025	0.796
TG (mg/dL)	0.078	0.420
UA (mg/dL)	0.095	0.325
Cre (mg/dL)	0.115	0.233
eGFR (mL/min/1.73 m^2)	−0.289	0.002
ACTH (pg/mL)	0.058	0.549
Cortisol (μg/dL)	0.248	0.009
Glucose-lowering therapies		
Biguanide	−0.072	0.459
Sulfonylureas	0.060	0.537
Dipeptidyl peptidase-4 inhibitors	0.030	0.755
Thiazolidinediones	0.026	0.792
α-Glucosidase inhibitor	−0.069	0.477
Glinide	−0.058	0.552
Glucagon-like peptide-1 agonists	0.061	0.526
Sodium glucose cotransporter 2 inhibitor	−0.312	<0.001
Insulin	−0.004	0.967

P-values were calculated using Spearman's rank correlation test or the Mann–Whitney *U*-test, as appropriate. ACTH, adrenocorticotropic hormone; Cre, creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; E, early diastolic filling velocity; e′, mitral annular early diastolic velocity; eGFR, estimate glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; SBP, systolic blood pressure; TG, triglycerides; UA, uric acid.

DISCUSSION

The present study showed a significant correlation between the E/e′ ratio and cortisol, age, SBP, eGFR and use of SGLT2 inhibitors in patients with diabetes. It has been reported that the E/e′ ratio is linearly associated with invasively measured LV

Table 4 | Multivariate linear regression analysis of factors associated with log E/e′ in the diabetes patients

Variables	β	*P*-value
Age	0.22	0.017
Duration of diabetes	0.06	0.515
Log SBP	0.25	0.004
eGFR	−0.21	0.016
Cortisol	0.18	0.037
Use of SGLT2 inhibitor	−0.18	0.042

DM, diabetes mellitus; E, early diastolic filling velocity; e′, mitral annular early diastolic velocity; eGFR, estimate glomerular filtration rate; SBP, systolic blood pressure; SGLT2, sodium–glucose cotransporter 2.

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filling pressures[11]. Therefore, the E/e′ ratio might serve as a surrogate measure of diastolic function.

The key findings of this study were that cortisol concentrations were significantly higher in the diabetes group than in the non-diabetes group, and cortisol levels were independently and positively associated with the E/e′ ratio in patients with diabetes. There was no significant correlation between E/e′ and cortisol concentrations in patients without diabetes. A previous study reported that diabetes patients with microangiopathy and macroangiopathy had higher blood cortisol concentrations than diabetes patients without diabetic complications and non-diabetes patients[12]. It is conceivable that pathological excess of cortisol, such as that found in Cushing's syndrome, and mild cortisol excess found in diabetes plays a critical role in the development of cardiomyopathy.

Glucocorticoid receptors are abundantly expressed in the heart[13,14]. Therefore, cortisol might have direct effects on myocardial tissue. Indeed, in an animal study using several rodent models, glucocorticoids played an important role in the development of cardiac hypertrophy and progression to heart failure[15]. Additionally, the mineralocorticoid receptor (MR) is present in cardiac tissue and has high affinity for both mineralocorticoids and glucocorticoids[16]. As glucocorticoids typically circulate at levels 100-fold higher than mineralocorticoids, the MR is likely to be constitutively occupied by glucocorticoids[16]. In mineralocorticoid target tissues, the enzyme 11beta-hydroxysteroid dehydrogenase type 2 inactivates cortisol, which protects the MR from binding to glucocorticoids. Unlike other MR target tissues, there is no appreciable dehydrogenase activity in the heart, and glucocorticoids are free to activate the MR.[16]

Animal studies have shown that activation of the MR induces ventricular remodeling, hypertrophy and fibrotic changes in the heart[17,18]. Furthermore, high concentrations of glucose stimulate protein kinase C beta signaling, which leads to MR stabilization and induction of its transcriptional activities[19]. Taken together, cortisol might be involved in the development of diastolic dysfunction through activation of the MR in patients with diabetes.

In the present study, multivariate linear regression analysis showed that cortisol was positively correlated with HbA1c and age in the diabetes group. Patients with poor glycemic control and older patients with diabetes have higher cortisol concentrations, which might lead to the development of LVDD. Previous studies suggest that LVDD was correlated with insulin resistance[20].

In the present study, HOMA-IR correlated with cortisol, but not with E/e'. As for the relationship between HOMA-IR and serum cortisol concentrations, it has been reported that cortisol suppresses insulin signaling and translocation of glucose transporter to the cell membrane[21], thereby inducing insulin resistance, suggesting that higher cortisol might have increased insulin resistance. The relationship between E/e' and HOMA-IR needs to be validated in a larger number of patients.

The data from the present study are consistent with previous reports that the prevalence of LVDD is associated with age, blood pressure and eGFR[22–24]. Recent studies have shown that the SGLT2 inhibitors, empagliflozin and canagliflozin, significantly reduced cardiovascular-mediated death, overall mortality and hospitalization for heart failure in patients with type 2 diabetes[24–26]. Additionally, another study reported that canagliflozin improved LVDD[27], which is consistent with the association between LVDD and SGLT2 inhibitors found in the present study. Taken together, these observations suggest that SGLT2 inhibitors might protect against the development of heart failure with preserved ejection fraction, which is characterized by LVDD, in patients with type 2 diabetes.

The present study had several limitations. First, our study design was cross-sectional, and, therefore, cause and effect relationships could not be determined. Second, we did not collect 24-h urine samples to measure cortisol, and cortisol measurements in blood might have been affected by diurnal fluctuations. Third, the number of study participants was relatively small. Future studies with larger cohorts will be required to validate the correlations that were observed in the present study.

The present study is the first demonstration of a positive correlation between cortisol and diastolic dysfunction in patients with diabetes. This study facilitates a greater understanding of the pathogenesis of LVDD, and might provide a mechanism for predicting the development of LVDD in patients with diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This article is compliant with all ethical guidelines and permission was obtained to carry out this study from the Clinical Ethics Committee of Kyushu University Hospital.

Informed Consent: Informed consent was obtained from all patients who were included in the study.

Approval date of Registry and the Registration No. of the study/trial: The approval number; No. 29-33, The date on which the approval was granted: 17 April 2017.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Demographic and clinical characteristics of the diabetes group (n = 109).

Table S2 | Correlations between cortisol and other variables in the diabetes patients.

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Table S3 | Correlations between cortisol and those variables in the diabetes patients.

Table S4 | Multivariate linear regression analyses of factors associated with cortisol in the diabetes patients.

Table S5 | Correlations between E/e′ and other variables in the non-diabetes patients.

Table S6 | Involvement of cortisol in left atrial volume index in both groups (n = 122).

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