

# Association Between Cortisol and Left Ventricular Diastolic Dysfunction in Patients With Diabetes Mellitus: A Case Control Study

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## Original investigation

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# Abstract

## Introduction:

Diabetes mellitus (DM) 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 DM has not been addressed.

## Research Design and Methods:

We enrolled 109 patients with DM and 104 patients without DM who had undergone echocardiographic examination at Kyushu University Hospital, 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 anti-diabetic 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 eGFR ( $p = 0.016$ ) and the usage of SGLT2 inhibitors ( $p = 0.042$ ) in patients with DM. Multivariate analysis showed that cortisol was positively correlated with age ( $p = 0.016$ ) and HbA1c ( $p = 0.011$ ). There was no association between  $E/e'$  and cortisol in patients without DM.

## Conclusions

Increased cortisol levels may increase the risk of developing LVDD in DM patients.

## Background

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

Patients with normal left ventricular wall contraction may 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 noninvasive assessment of diastolic filling of the left ventricle(3). Tissue Doppler imaging (TDI) 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 4-fold 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 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 three times greater than in patients with nonfunctioning adrenal adenoma(7)(8). It is likely that cortisol affects cardiac structure and function, although its relationship with LVDD in patients with DM has not been addressed. Therefore, we designed a cross-sectional study to determine the relationship between cortisol and LVDD in patients with DM who did not have overt cardiovascular diseases.

## Methods

Some of the methods used in this study were described previously(9).

### Subjects

Between November 2016 and March 2019, we consecutively recruited 109 patients with DM and 104 patients without DM who had undergone echocardiographic examination at the metabolic ward of Kyushu University Hospital, Fukuoka, Japan. Patients were excluded if they 1) were taking steroids, 2) were undergoing hemodialysis treatment, or 3) had overt heart failure. Patients without DM consisted of those who were hospitalized for hypertension, gastrointestinal polyps, and/or adrenal mass whose diagnosis finally became nonfunctional. All of the patients underwent clinical evaluation, laboratory assessment, and echocardiographic examination. Blood concentrations of fasting plasma glucose, HbA1c, total cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, estimated glomerular filtration rate (eGFR), ACTH, and cortisol (at 8:00 am, fasting) were measured. Serum cortisol concentrations were determined by electrochemiluminescence immunoassay (ECLusys Cortisol  $\times$  Kits, Roche in Vitro Diagnostics, Tokyo, Japan). Clinical data and information regarding treatment of the patients with anti-diabetic drugs were obtained from medical records. HbA1c levels were determined using the criteria of the National Glycohemoglobin Standardization Program. The study protocol was approved by the Clinical Ethics Committee of Kyushu University Hospital (protocol #29-645). This study was performed in accordance with the Declaration of Helsinki.

### Echocardiography

All echocardiographic examinations were performed with an Aplio i900 TUS-AI900 imager (Canon Medical Systems, Inc., Tokyo, Japan). Chamber dimensions and left ventricular ejection fractions (LVEF)

were measured in accordance with the recommendations of the American Society of Echocardiography(10). The left ventricular mass index (LVMI) was calculated according to the Devereux formula and expressed as a ratio of the left ventricular mass to body surface area(10). The relative wall thickness (RWT) was based on the end-diastolic posterior wall thickness (PWTd) and the end-diastolic left ventricular dimension (LVDd). RWT was calculated as  $(2 \times \text{PWTd})/\text{LVDd}$ . 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.

## Data Analysis

All statistical analyses were performed using JMP<sup>®</sup> 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. Gender 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 DM group was older than the non-DM group, and there was no significant difference in the sex ratio between the 2 groups. Fasting plasma glucose, HbA1c, systolic blood pressure (SBP), and cortisol concentrations were significantly higher, and eGFR and high-density lipoprotein (HDL) cholesterol concentrations were significantly lower in the DM group than in the non-DM group.

Table 1  
Demographic and clinical characteristics of the 2 patient cohorts (N = 213)

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 <sup>2</sup>	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
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/1.73m <sup>2</sup>	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)	

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

Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; Cre, creatinine; eGFR, estimate glomerular filtration rate; ACTH, adrenocorticotrophic hormone

Patient characteristics	Control (N = 104)	DM (N = 109)	<i>p</i> value
Glucagon-like peptide-1 agonists		20 (18)	
Sodium glucose cotransporter 2 inhibitor		21 (20)	
Insulin		36 (33)	
Categorical variables are presented as number (%) or median (lower quartile–upper quartile).			
Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; Cre, creatinine; eGFR, estimate glomerular filtration rate; ACTH, adrenocorticotrophic hormone			

The echocardiographic data is shown in Table 2. LVEF was preserved in both the DM and non-DM groups [69% (IQR 64–73%) vs. 70% (IQR 66–73%),  $p = 0.141$ ]. However, the DM group had a significantly higher E/e<sub>max</sub> ratio compared with the non-DM 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 DM. The LVMI and RWT were significantly higher in the DM group than in the non-DM group [83g/m<sup>2</sup> (IQR 74–104) vs 79 g/m<sup>2</sup> (IQR 64–95),  $p < 0.003$ ].

Table 2  
Echocardiographic data from each patient cohort (N = 213)

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 <sup>2</sup>	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/sec	67 (57–77)	65 (54–79)	0.657
A wave, cm/sec	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
Categorical variables are presented as number (%) or median (lower quartile–upper quartile).			
Abbreviations: DM, diabetes mellitus; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; IVSd, interventricular septal wall dimension; PWd, posterior wall thickness dimension; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; DcT, deceleration time of mitral E wave.			

Because the E/e' ratio and plasma cortisol concentrations were higher in the DM group than in non-DM 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 DM 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 ( $p = 0.042$ ).

Table 3  
Correlations between E/e<sub>0</sub> and other variables in the DM patients

Variables	$\rho$	$p$ value
Age, years	0.358	< 0.001
Sex, male/female, %	0.132	0.171
Body mass index, kg/m <sup>2</sup>	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
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/1.73m <sup>2</sup>	-0.289	0.002
ACTH, pg/ml	0.058	0.549
Cortisol, $\mu$ g/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
$\alpha$ -Glucosidase inhibitor	-0.069	0.477

$p$  values were calculated using Spearman's rank correlation test or the Mann-Whitney U test, as appropriate.

Abbreviations: DM, diabetes mellitus; E, early diastolic filling velocity; e<sub>0</sub>, mitral annular early diastolic velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; Cre, creatinine; eGFR, estimate glomerular filtration rate; ACTH, adrenocorticotrophic hormone.

Variables	$\rho$	$p$ value
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.		
Abbreviations: DM, diabetes mellitus; E, early diastolic filling velocity; $e_{\text{a}}$ , mitral annular early diastolic velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; Cre, creatinine; eGFR, estimate glomerular filtration rate; ACTH, adrenocorticotrophic hormone.		

Table 4

Multivariate linear regression analysis of factors associated with log E/ $e_{\text{a}}$  in the DM patients

Variables	$\beta$	$p$ 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
Abbreviation: DM, diabetes mellitus; E, early diastolic filling velocity; $e_{\text{a}}$ , mitral annular early diastolic velocity; SBP, systolic blood pressure; eGFR, estimate glomerular filtration rate; SGLT2, sodium glucose cotransporter 2.		

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 ( $p = 0.008$ ), and HDL cholesterol ( $p = 0.010$ ) were positively associated with cortisol, and uric acid ( $p = 0.039$ ) was negatively associated with cortisol (Table S1). Multivariate linear regression analysis showed that cortisol was positively and independently correlated with the log of HbA1c ( $p = 0.011$ ) and age ( $p = 0.016$ ) (Table S2). These findings suggest that an elevated cortisol concentration in the blood is associated with diastolic dysfunction in patients with DM. In contrast, there was no correlation between E/ $e_{\text{a}}$  and cortisol in the non-DM group (Table S3).

## Discussion

This study demonstrated a significant correlation between the E/e<sub>0</sub> ratio and cortisol, age, SBP, eGFR, and usage of SGLT2 inhibitors in patients with DM. It has been reported that the E/e<sub>0</sub> ratio is linearly associated with invasively measured LV filling pressures(11)(3). Therefore, the E/e<sub>0</sub> ratio may serve as a surrogate measure of diastolic function.

The key findings of this study were that cortisol concentrations were significantly higher in the DM group than in the non-DM group, and cortisol levels were independently and positively associated with the E/e<sub>0</sub> ratio in patients with DM. There was no significant correlation between E/e<sub>0</sub> and cortisol concentrations in patients without DM. A previous study reported that DM patients with microangiopathy and macroangiopathy had higher blood cortisol concentrations than DM patients without diabetic complications and non-DM patients.(12). It is conceivable that pathological excess of cortisol, such as that found in Cushing's syndrome, and mild cortisol excess found in DM plays a critical role in the development of cardiomyopathy.

Glucocorticoid receptors are abundantly expressed in the heart(13)(14). Therefore, cortisol may 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). Since 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 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11  $\beta$ -HSD2) 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 may be involved in the development of diastolic dysfunction via activation of the MR in patients with DM. In this study, multivariate linear regression analysis showed that cortisol was positively correlated with HbA1c and age in the DM group. Patients with poor glycemic control and older patients with diabetes have higher cortisol concentrations, which may lead to the development of LVDD.

The data from this study are consistent with previous reports that the prevalence of LVDD is associated with age, blood pressure, eGFR(20)(21)(22)(23). 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 DM (T2DM)(23)(24)(25). Additionally, another study reported that canagliflozin improved LVDD(26), which is consistent with the association between LVDD and SGLT2 inhibitors found in this study. Taken together, these observations suggest that SGLT2 inhibitors may protect against the development of HFpEF, which is characterized by LVDD, in patients with T2DM.

This 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-hour urine samples to measure cortisol, and cortisol measurements in blood may 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 our study.

## Conclusions

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

## Abbreviations

DM

Diabetes mellitus; LVDD:left ventricular diastolic dysfunction; HFpEF:Heart failure with preserved ejection fraction; eGFR:estimated glomerular filtration rate; LVEF:left ventricular ejection fractions; LVMI:left ventricular mass index; RWT:relative wall thickness; PWTd:end-diastolic posterior wall thickness; LVDd:end-diastolic left ventricular dimension;  $e_{\text{a}}$  velocity:peak early diastolic myocardial velocity;  $E/e_{\text{a}}$ :ratio of E velocity to  $e_{\text{a}}$  velocity; SBP:systolic blood pressure; HDL:high-density lipoprotein; SGLT2:sodium glucose cotransporter 2; MR:mineralocorticoid receptor; 11  $\beta$ -HSD2:11 $\beta$ -hydroxysteroid dehydrogenase type 2; T2DM:type 2 DM.

## Declarations

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### Authors' Contributions

R.S. wrote the manuscript and researched the data. T.I. contributed to the discussion and reviewed/edited the manuscript. C.Y., M.M., N.S., and Y.O. provided advice on the interpretation of the results. R.S. and T.I. are the guarantors of this work and, as such, had full access to all of the data in the study. R.S. and T.I. also take responsibility for the integrity of the data and the accuracy of the data analysis. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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### **Availability of data and materials**

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

### **Ethics approval and consent to participate**

This article is compliant with all ethical guidelines and permission was obtained to conduct this study from the Clinical Ethics Committee of Kyushu University Hospital (No. 29-33). All procedures conducted in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients who were included in the study.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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