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The effects of DPP4 inhibitors on the levels of plasma catecholamines and their metabolites in patients with type 2 diabetes

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ABSTRACT

Aims: Dipeptidyl peptidase 4 inhibitors (DPP4Is) can increase sympathetic activity. We aimed to evaluate the direct association between serum DPP4 activity and sympathetic activity in humans.

Methods: Fasting serum DPP4 activity and plasma levels of catecholamines and their metabolites were measured in 211 patients with type 2 diabetes mellitus (T2DM) treated with DPP4I (n = 146) or non-DPP4I therapy (n = 65) and in healthy control subjects (n = 30).

Results: Although there were no differences in plasma levels of catecholamines and their metabolites between the DPP4I and non-DPP4I groups, the levels in both of these groups were lower than those in the healthy control group. In DPP4I-treated patients, serum DPP4 activity showed an inverse correlation with plasma levels of norepinephrine (NE) ($r = -0.339$, $p < 0.01$), metanephrine (MET) ($r = -0.251$, $p < 0.01$) and normetanephrine ($r = -0.312$, $p < 0.001$). In addition, plasma MET level showed a weak inverse correlation with serum DPP4 activity in the combined T2DM group. In DPP4I-treated patients, the inverse correlation between DPP4 activity and plasma NE remained significant even after multiple adjustments.

Conclusions: Our results suggest that although sympathetic activity is lower in patients with T2DM, the greater the suppression of DPP4 activity by DPP4I therapy, the greater the increase in sympathetic activity is, which may have clinical implications in high risk T2DM patients.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CV, cardiovascular; DPP4, dipeptidyl peptidase 4; DPP4I, DPP4 inhibitor; eGFR, estimated glomerular filtration rate; Epi, epinephrine; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HDL, high density lipoprotein; HF, heart failure; LDL, low density lipoprotein; NE, norepinephrine; MET, metanephrine; NMET, normetanephrine; NPY, neuropeptide Y; T2DM, type 2 diabetes mellitus; TG, triacylglyceride; UACR, urine albumin-to-creatinine ratio

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1. Introduction

Dipeptidyl peptidase 4 (DPP4) is a widely expressed serine protease that regulates the bioactivity of incretin hormones and other hormones, neuropeptides, and chemokines [1,2]. DPP4 inhibitors (DPP4Is) have been widely used as antidiabetic agents to treat patients with type 2 diabetes mellitus (T2DM), as they potentiate the actions of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), to stimulate postprandial insulin secretion [3].

Heart failure (HF) is a prevalent cardiovascular (CV) disease in patients with T2DM, and DPP4Is are associated with a potential risk of HF [4–6]. A previous study showed that vildagliptin treatment in T2DM patients with reduced left ventricular contractility led to adverse effects on cardiac remodeling and a higher risk of CV hospitalization and death [4,7]. Furthermore, some studies have suggested that interactions between DPP4 activity and the sympathetic nervous system occur via various pathways [4,5,8]. In addition to GLP-1 and GIP, there are more than 40 peptide substrates for DPP4 [1,2,5,9,10]. Among these substrates, neuropeptide $Y_{1\text{-}36}$ ($NPY_{1\text{-}36}$) is coreleased with norepinephrine (NE) from sympathetic nerves that innervate blood vessels, and the subsequent activation of the Y1 receptor by $NPY_{1\text{-}36}$ results in vasoconstriction and the postsynaptic potentiation of the effects of catecholamines on blood pressure (BP) [11]. The DPP4 enzyme converts $NPY_{1\text{-}36}$ to $NPY_{3\text{-}36}$ which presynaptically inhibits the release of NPY and NE through the Y2 receptor [11]. $NPY_{1\text{-}36}$ causes slow-acting, potent, and persistent vasoconstriction, especially during periods of high stress, while NE produces rapid vasoconstriction that dissipates more quickly [11]. Thus, DPP4Is can potentiate and prolong the vasoconstrictive effects of $NPY_{1\text{-}36}$ [12]. Substance P, which is released via various visceral afferent pathways, produces a central enhancement in sympathetic outflow to some cardiovascular regions [13]. Both DPP4 and angiotensin-converting enzyme (ACE) are involved in the inactivation of substance P by targeting different cleavage sites [14]. Thus, when an ACE inhibitors and a DPP4I are used together, as is common in T2DM patients, substance P levels can be increased, leading to sympathetic activation [8]. In addition, GLP-1 receptor activation in the brain has previously been shown to increase sympathetic activity in laboratory animals [15].

A previous study showed that short-term vildagliptin treatment in patients with T2DM caused postprandial lipid mobilization through sympathetic activation [16]. The chronic effect of DPP4Is on sympathetic tone in relation with DPP4 activity may have additional clinical implications for the management of T2DM patients at high CV risk. We aimed to investigate whether DPP4I therapy in patients with T2DM has any effect on sympathetic activity by measuring serum DPP4 activity and the levels of plasma catecholamines [epinephrine (Epi) and NE] and their metabolites [metanephrine (MET) and normetanephrine (NMET)].

2. Methods

2.1. Study population and protocol

Patients with T2DM (n = 211) and healthy control subjects (n = 30) were involved in this cross-sectional study. Male or female patients aged 30–75 years with T2DM diagnosed at the age of 30 years or later and healthy controls without T2DM of similar ages were eligible to participate in the study. Patients were required to have hemoglobin A1c value of 11% or less, a urine albumin-to-creatinine ratio (UACR) of less than 3500 mg/g, a hemoglobin level of 11 g/dL or more, and a serum albumin level of 3.6 g/dL or more at screening. If patients were on antihypertensive mediation or had been taking an ACE inhibitor or angiotensin II receptor blocker (ARB) for diabetic kidney disease, they were only included if they had been on a stable dose for at least 2 weeks. Patients with poor BP control or those taking 4 or more antihypertensive drugs were excluded. Patients on renal replacement therapy, those with chronic kidney disease presumed to be a result of nondiabetic causes, or those with a single kidney were excluded. Patients with a history of acute kidney injury, a long-term history of the use of renally toxic drugs for more than 3 months, or end-stage renal disease were also excluded from the study.

Study participants were instructed to visit the laboratory after fasting overnight. After study subjects rested for at least 5 min in the seated position, stable blood pressure was confirmed and blood sampling was performed for laboratory studies including plasma catecholamines and their metabolites by two trained persons. The serum and plasma samples from each subject were aliquoted and stored at −80 °C until further use.

All protocols and procedures were approved by the Gachon University Gil Medical Center Institutional Review Board (#2016-195), and written informed consent was obtained from all participants. This study followed the ethical guidelines of the Declaration of Helsinki and was registered at https://cris.nig.go.kr (registration number KCT0003573) in accordance with the requirements of the WHO International Clinical Trials Registry Platform.

2.2. Measurements

Plasma Epi and NE were measured by high performance liquid chromatography using their respective commercial kits (Chromsystems, Gräfelfing, Germany). Plasma MET and NMET were measured by liquid chromatography-tandem mass spectrometry [17].

DPP4 activity was determined according to the cleavage rate of p-nitroaniline (pNA; Sigma) using the synthetic substrate glycyl-prolyl-p-nitroanilide (Gly-Pro-pNA; Sigma), as previously described [18]. Briefly, 100 μl of assay mixture was prepared containing 50 mM Tris (pH 8.0) and serum (50 μl) from the study subjects. The reaction was initiated by the

addition of a 5 mM Gly-Pro-pNA substrate solution to a final concentration of 2.5 mM. After incubation for 10 ~ 30 min at 37 °C, the absorbance of the sample in each well was measured at 405 nm using a plate reader. Serum DPP4 activity was expressed as the amount of cleaved pNA released per minute per ml of serum (nmol/min/ml). .

3. Statistical analysis

The plasma levels of catecholamines and their metabolites did not conform to a normal distribution. If not otherwise indicated, the continuous variables were presented as the median and the interquartile range (IQR). Differences in the characteristics between groups were tested by one-way analysis of variance with Tukey post hoc analysis, *t* tests, or Mann-Whitney *U* tests for the continuous variables appropriately, while Spearman correlation analysis was used to determine the correlations between the levels of plasma catecholamines or their metabolites and other parameters, including serum DPP4 activity. The categorical variables are expressed as numbers and percentages, and the between-group differences for these variables were tested by Chi-squared tests. Multiple linear regression analyses were used to determine whether there was an independent relationship between the levels of plasma catecholamines or their metabolites and DPP4 activity after multiple adjustments for age, body weight, duration of diabetes, estimated glomerular filtration rate (eGFR), and fasting plasma levels of glucose and total cholesterol. Statistical significance was assumed at $P < 0.05$. Statistical analyses were performed using the R software/environment. R is an open source project that is distributed under the GNU General Public License (Copyright 2007 Free Software Foundation, Inc.; (http://www.gnu.org/licenses/gpl.html). Sources, binaries, documentation, and additional packages for R can be obtained from the Comprehensive R Archive Network mirror sites. At the time of this writing, R-2.9.1 was available. For analysis, we have used the "base" packages.

4. Results

4.1. *Characteristics of study subjects*

We included 211 T2DM patients in our study (125 men, 86 women). Table 1 provides the characteristics of the study participants. The DPP4I group was less likely to be on insulin therapy and to have a higher diastolic BP compared with the non-DPP4I group. Additionally, the DPP4I group showed significantly lower plasma DPP4 activity [0.22 (0.14, 0.33) nmol/min/mL] compared with the non-DPP4I group [0.60 (0.52, 0.68) nmol/min/mL] and the control group [0.62 (0.52, 0.78) nmol/min/mL], demonstrating the presence of DPP4 inhibition in this group ($p < 0.01$ for each comparison) (Fig. 1). In the present study, 7 different DPP4Is and various doses were used in the DPP4I group: 50–100 mg of sitagliptin (n = 42), 2.5–5 mg of linagliptin (n = 27), 10–20 mg of teneligliptin (n = 26), 25–50 mg of gemigliptin (n = 19), 25 mg of alogliptin (n = 15), 50–100 mg of vildagliptin (n = 14), 2.5–5 mg of saxagliptin (n = 3), per day, respectively. When we compared subgroups according to 3 different DPP4I types (i.e., sitagliptin, teneligliptin, and linagliptin), linagliptin-treated patients showed the lowest level of DPP4 activity [0.10 (0.08, 0.12) nmol/min/mL] among the 3 subgroups (Supplemental Table 1).

4.2. *The effect of DPP4I on the levels of plasma catecholamines and their metabolites in patients with T2DM*

Compared to those in the healthy control subjects, plasma levels of catecholamines and their metabolites were all lower in the T2DM patients in both the DPP4I-treated group and the non-DPP4I-treated group. However, there were no significant differences in median plasma levels of Epi, NE, MET, and NMET between the DPP4I and non-DPP4I groups (Fig. 2). The results of the comparison of the levels of plasma catecholamines and their metabolites between the two treatment groups were not affected by therapy with either beta blockers or ARBs. The effect of ACE inhibitor could not be evaluated because of the very small number of patients treated with ACE inhibitors (data not shown).

4.3. *Correlations between serum DPP4 activity and the levels of plasma catecholamines and their metabolites in patients with T2DM*

In the combined T2DM patient group, serum DPP4 activity had an inverse correlation with plasma MET level ($r = -0.139$, $p < 0.05$), but no correlation with the levels of catecholamines or the NMET level (Supplemental Fig. 1). However, in DPP4I-treated T2DM patients, DPP4 activity had inverse correlations with the levels of plasma NE, MET, and NMET (Fig. 3). In line with that linagliptin-treated patients had the lowest level of DPP4 activity among the 3 different DPP4I subgroups, this subgroup showed higher plasma levels of ME and NMET compared to those in sitagliptin- or teneligliptin-treated subgroups (Supplemental Table 1). Such correlations were not observed in the healthy control group or in the non-DPP4I group (data not shown). These results suggest that the decrease in DPP4 activity by DPP4I treatment leads to higher sympathetic activity.

In patients on DPP4I therapy, DPP4 activity remained an independent factor that affected plasma NE levels in a multivariate analysis after adjustments for multiple factors, including age, body weight, duration of T2DM, hemoglobin A1c level, fasting plasma levels of glucose and total cholesterol, and eGFR (Table 2). However, in these analyses, Epi and catecholamine metabolites did not show an independent association with DPP4 activity in any of the study groups (data not shown).

The proportion of patients with a higher concentration than the upper normal limits of catecholamines or their metabolites was higher in the DPP4I-treated T2DM group than in the non-DPP4I-treated T2DM group. However, the difference in the proportion was not statistically significant between the two groups (data not shown). In addition, when the DPP4I-treated patients were divided into tertiles by plasma levels of catecholamines or their metabolites, DPP4 activities in upper tertile groups for NE (data not shown) and NMET (Supplemental Table 2) were significantly lower

Table 1 – The characteristics of the study populations (n = 241).

Parameter	Control (n = 30)	Non-DPP4I (n = 65)	DPP4I (n = 146)	P value
Age (years)	55.5 (52.0, 62.5)	60.0 (54.0, 64.5)	60.0 (54.0, 65.0)	0.173
Male, N (%)	18 (60.0)	36 (55.4)	89 (61.0)	0.746
Body mass index (kg/m^2)	23.0 (22.1, 25.7)[a]	25.6 (23.4, 27.3)[b]	25.5 (23.5, 27.9)[b]	<0.05
Past history, N (%)				
Hypertension	2 (6.7)[a]	45 (69.2)[b]	91 (62.3)[b]	<0.01
CV disease	2 (6.7)	15 (23.1)	44 (30.1)	0.082
Current smoker	6 (20.0)	16 (24.6)	29 (19.9)	0.799
WBC ($\times 10^3$/mm^3)	5.5 (4.3, 6.7)[a]	6.3(5.2, 8.4)[b]	6.3 (5.6, 7.7)[b]	<0.05
Hemoglobin (g/dL)	14.4 (13.6, 15.3)[a]	13.6 (12.1, 15.1)[b]	13.3 (11.8, 14.3)[b]	<0.01
Serum insulin (mU/L)	8.0 (5.6, 10.6)	9.7 (6.6, 14.2)	9.2 (5.7, 13.6)	0.225
Fasting glucose (mg/dL)	94.0 (89.3, 97.3)[a]	124.0 (101.0, 157.5)[b]	135.0 (113.0, 162.5)[b]	<0.01
Hemoglobin A1c (%)	5.5 (5.3, 5.7)[a]	7.4 (6.6, 8.9)[b]	7.6 (6.9, 8.6)[b]	<0.01
Systolic BP (mmHg)	134.0 (117.5, 147.5)	130.0 (120.0, 148.0)	134.0 (125.8, 150.3)	0.159
Diastolic BP (mmHg)	83.5 (76.8, 90.0)[a]	76.0 (67.5, 86.5)[b]	80.0 (74.8, 87.0)[a]	<0.01
Total cholesterol (mg/dL)	187.0 (175.3, 216.5)[a]	170.0 (146.5, 188.0)[b]	159.0 (139.8, 179.0)[b]	<0.01
HDL cholesterol (mg/dL)	55.0 (46.0, 63.8)[a]	45.0 (35.0, 54.0)[b]	43.5 (37.8, 51.0)[b]	<0.01
LDL cholesterol (mg/dL)	110.5 (94.3, 131.5)[a]	99.0 (72.0, 114.0)[b]	84.0 (66.0, 107.5)[b]	<0.01
Triacylglyceride (mg/dL)	113.5 (71.3, 187.3)	140.0 (116.0, 197.0)	125.0 (97.0, 198.3)	0.108
Serum creatinine (mg/dL)	0.77 (0.60, 0.89)[a]	0.97 (0.72, 1.51)[b]	0.90 (0.71, 1.67)[b]	<0.01
eGFR (mL/min/1.73 m^2)	99.3 (93.2, 102.8)[a]	76.8 (40.6, 98.0)[b]	82.4 (39.2, 98.6)[b]	<0.01
UACR (ug/mg Cr)	4.4 (3.3, 10.8)[a]	87.1 (10.9, 1093.7)[b]	38.0 (5.8, 916.3)[b]	<0.01

Data are expressed as the median (interquartile range) or N (%), unless otherwise specified. Different superscript letters (a and b) indicate statistically significant differences among experimental groups (one-way analysis of variance and Tukey tests for continuous variables and Chi-squared tests for categorical variables; P < 0.05 respectively). Abbreviations: CV, cardiovascular; WBC, white blood cell; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

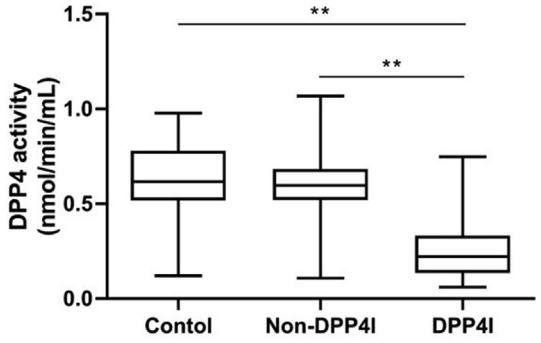

Fig. 1 – Serum DPP4 activity in T2DM patients treated with DPP4 inhibitors (DPP4I), other agents (non-DPP4I) and the healthy control group (Control). Box-whisker-plots are shown, with the bottom and top of the box representing the 25th and 75th percentiles, respectively, and the middle line representing the median. The whiskers represent the smallest and largest values, respectively. In the statistical analyses, the between-group differences in the log-transformed values were tested by one-way analysis of variance with Tukey post hoc analysis. *, P < 0.05; **, P < 0.01.

compared to those in their respective lower tertile groups. In addition, the upper NMET tertile group was more likely to have hypertension compared with the lower NMET tertile group (Supplemental Table 2)

5. Discussion

This is the first study to evaluate the direct relationship between serum DPP4 activity and the levels of plasma catecholamines and their metabolites in T2DM patients on DPP4I therapy and those not on DPP4I therapy to examine the hypothesis that DPP4 inhibition affects sympathetic activity. Our results showed that plasma levels of NE, MET, and NMET showed an inverse correlation with DPP4 activity in T2DM patients on DPP4I therapy. Although such associations were not observed in healthy control subjects and in T2DM patients treated with other glucose-lowering agents, a weak inverse correlation between DPP4 activity and plasma MET level was observed in the combined T2DM patient group. Furthermore, a multivariate analysis showed that DPP4 activity remained an independent factor that affected plasma NE levels in the DPP4I-treated group. Although we observed some difference in plasma levels of catecholamines and their metabolites between 3 different DPP4Is, these differences seemed to be related with the degree of DPP4 inhibition. Thus, our results showed that in patients with T2DM, the higher the suppression of DPP4 activity with DPP4I therapy, the greater the increase in sympathetic activity was.

In line with our results, other clinical studies have shown that DPP4I therapy increased plasma NE levels in some conditions [8,16,19]. Boschmann et al. [16] showed that vildagliptin treatment in patients with T2DM caused postprandial lipolysis, which was associated with increased levels of plasma NE, but not Epi. The mechanism involved in the increase in NE

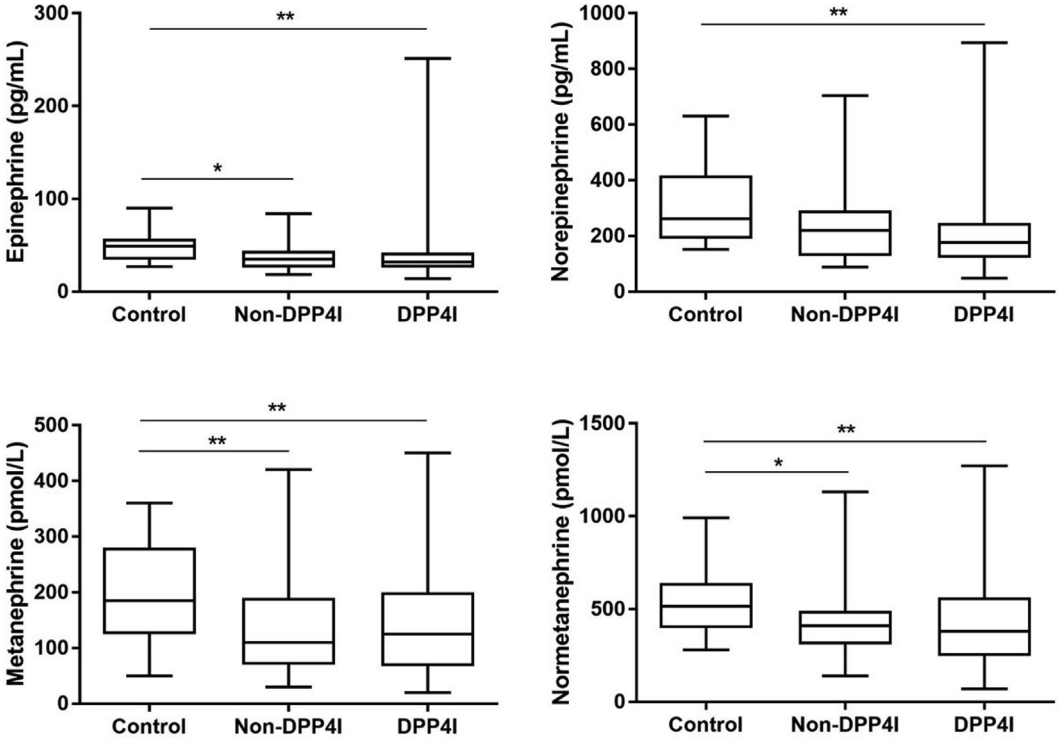

Fig. 2 – The levels of plasma catecholamines and their metabolites in the study subjects. Presented similarly as in Fig. 1.

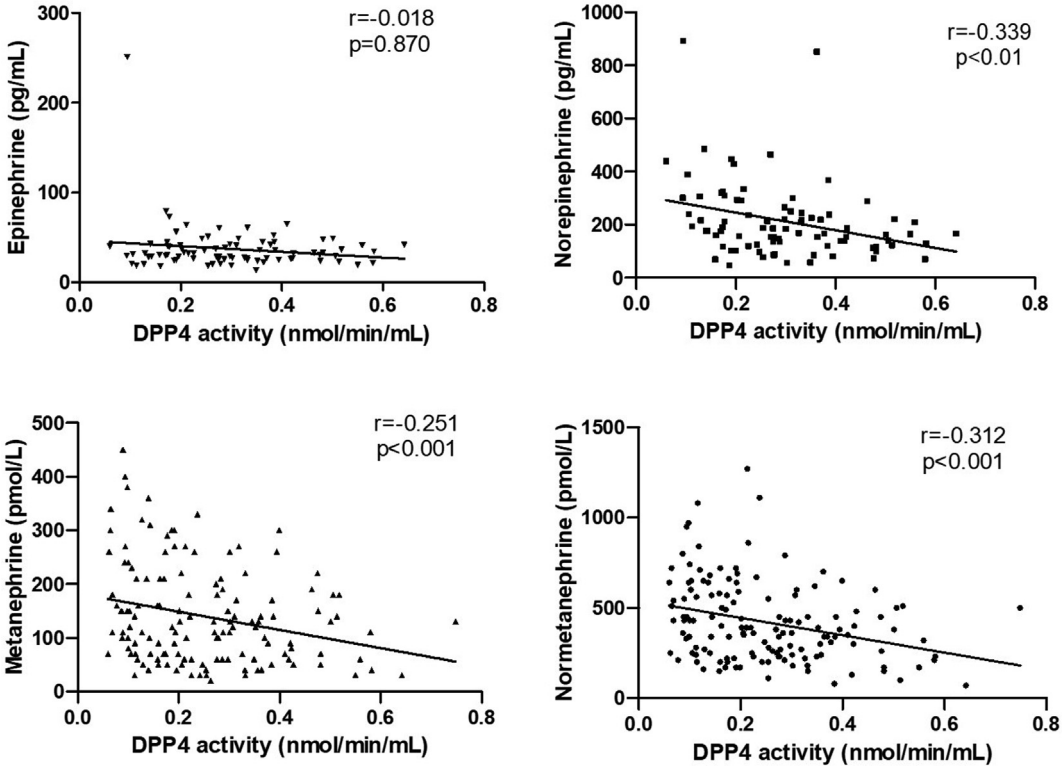

Fig. 3 – Scatter-plots showing the bivariate correlations between serum DPP4 activity and the levels of plasma catecholamines and their metabolites in DPP4I-treated T2DM patients.

levels or sympathetic activity are not clear, but probable explanations include the following: a) the increased level of neuropeptide Y_{1-36} after DPP4 inhibition led to the potentiation of NPY-Y1 receptor pathway [20]; b) the interaction of DPP4 inhibition and ACE inhibition affected plasma substance P levels [8,19].

Table 2 – Multiple linear regression analysis was performed using plasma NE as the dependent parameter and the other parameters as independent parameters in patients with T2DM.

Independent Factor	Combined T2DM group			Non-DPP4I group			DPP4I group		
	β	95% CI	p value	β	95% CI	p value	β	95% CI	p value
Age (years)	−1.409	−5.685, 2.867	0.515	0.961	−8.729, 10.650	0.840	0.543	−4.440, 5.856	0.839
Body weight (kg)	−2.605	−5.122, −0.089	**<0.05**	−0.742	−5.453, 3.968	0.748	−3.011	−6.042, 0.019	0.051
Fasting glucose (mg/dL)	0.047	−0.449, 0.543	0.852	−1.093	−2.122, −0.063	**<0.05**	0.423	−0.174, 1.019	0.162
T2DM duration (years)	1.072	−2.895, 5.039	0.593	1.126	−7.414, 9.667	0.788	−0.857	−5.527, 3.813	0.716
Total cholesterol (mg/dL)	0.251	−0.549, 1.050	0.535	0.372	−1.296, 2.041	0.650	0.312	−0.645, 1.268	0.518
eGFR (mL/min/1.73 m^2)	−2.938	−4.472, −1.404	**<0.01**	−1.563	−4.129, 1.003	0.221	−2.642	−4.736, −0.549	**<0.05**
DPP4 activity (nmol/min/mL)	−42.55	−169.35, 84.24	0.507	195.84	−235.72, 627.39	0.359	−284.15	−520.44, −47.86	**<0.05**

Abbreviations: T2DM, Type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; DPP4, Dipeptidyl peptidase 4.

In a large-scale clinical trial, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial, an increased risk of hospitalization due to HF was observed in DPP4I-treated patients, and the magnitude of this effect was attenuated in patients who were concomitantly treated with β-blockers [4,6]. Cardiac NPY and NE spillover rates were shown to be increased in patients with severe HF [21]. However, in the present study, there were no differences in the plasma levels of catecholamines and their metabolites between the DPP4I and non-DPP4I groups. We also observed significantly lower levels of catecholamines and their metabolites in T2DM patients than those in control subjects. In support of our observation, a previous study showed that the mean 24-h levels of heart rate variability and plasma noradrenaline in T2DM patients were significantly lower than in control subjects [22]. Diabetic neuropathy was shown to be an important factor associated with a decrease in plasma catecholamine concentration [23]. However, diabetic neuropathy was not evaluated systematically in the present study. Thus, we could not determine whether this specific microvascular complication affected our results, but this explanation could not be excluded, considering that the median duration of diabetes in our patients was 15.0 (10.0, 20.8) years. In addition, various other factors may also be associated with variations in the sympathetic hormones in patients with T2DM [24–26]. Thus, we analyzed the relationship between DPP4 activity and the levels of plasma catecholamines and their metabolites in DPP4I-treated T2DM patients after adjustments for multiple parameters. This analysis consistently showed a significant inverse association between DPP4 activity and the levels of plasma NE.

The clinical implications of our findings demonstrate that strong sustained suppression of DPP4 activity may be associated with sympathetic activation. In addition, previous studies suggested that the increased actions of NPY_{1-36}, substance P and stromal cell-derived factor 1 by DPP4 inhibition related with profibrotic pathways in the myocardium [4,27]. The combined effects of these pathophysiological changes during chronic DPP4 inhibition in vulnerable patients may contribute to cardiac pathology under high stress conditions.

The present study has its strengths and limitations. The strength of this study is that it is the first to simultaneously evaluate serum DPP4 activity and the levels of plasma catecholamines and their metabolites in DPP4I-treated T2DM patients, normal control subjects, and T2DM patients treated with other agents. Several limitations of our study need to be addressed and should be considered in future studies. First, we did not measure several important DPP4 substrates, including incretins, NPYs, and others. However, in a recent study that examined the effects of 7 days of treatment with sitagliptin versus placebo in patients with T2DM, the NPY_{1-36} levels were shown to be similar in both groups [20]. In that study, sitagliptin caused an elevation in NPY_{1-36} levels in the presence of ACE inhibitor compared with placebo [20]. Thus, even in DPP4I-treated patients, specific conditions such as ACE inhibitor therapy or a high level of stress may be required to produce a demonstrable elevation in the NPY_{1-36} level [11]. Second, variations in the stages of T2DM, comorbidities, and

polypharmacy in patients might affect the levels of plasma catecholamines and their metabolites and serum DPP4 activity and complicate the interpretation of the results. In particular, the levels of all of the plasma catecholamines and their metabolites in T2DM patients were lower than those in the healthy control group, which was in line with the results of a previous study [22]. Although multivariate analysis confirmed that there was an inverse correlation between plasma NE levels and DPP4 activity in the DPP4I group even after multiple adjustments, there were no differences in the proportion of patients with increased concentrations of catecholamines or their metabolites. More large-scale studies are required. Third, we could not evaluate the effect of ACE inhibitors on the basis of our results because few patients on ACE inhibitor therapy were included in the present study. A recent study showed the effect of the interaction of DPP4I, sitagliptin and an ACE inhibitor on NPY-induced vasoconstriction [20]. Fourth, the changes in the levels of plasma catecholamines and their metabolites over time were not determined in the present study. Fifth, although we observed the upper NMET tertile group among DPP4I-treated patients showed a lower DPP4 activity and more likely to have hypertension, further studies are required to see whether a moderate (2–3 folds) elevation in plasma catecholamines and their metabolites related with DPP4 inhibition has a causal relationship with hypertension and other CV diseases such as HF.

6. Conclusions

In conclusion, our results showed that although sympathetic activity was decreased in patients with T2DM, the greater the suppression of DPP4 activity by DPP4I therapy, the greater the increase in sympathetic activity was. Further studies are needed to evaluate whether this inverse relationship affects major CV-related outcomes in T2DM patients at high CV risk treated with DPP4Is.

Ethics approval and consent to participate

The study was approved by the Gachon University Gil Medical Center Institutional Review Board (#2016-195), and written informed consent was obtained from all participants.

Consent for publication

The participants were informed that their data would be shared and that their name and identity would be hidden, as per the informed consent.

Availability of data and materials

The datasets used and analyzed in our study are available from the corresponding authors upon reasonable request.

Authors' contributions

DHL, CSC, and THA contributed to the conception of the study and the writing of the manuscript. DHL, KYL, CSC, and IBP acquired and analyzed the data. THK analyzed the data and drafted the manuscript. All authors agree with the results and conclusions in the manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107832.

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