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Effect of Sitagliptin on Coronary Flow Reserve Assessed by Magnetic Resonance Imaging in Type 2 Diabetic Patients With Coronary Artery Disease

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Background: The present study was conducted to assess the cardiovascular effects of dipeptidyl peptidase-4 inhibitors (DPP4i) on coronary flow reserve (CFR), left ventricular (LV) function and endothelial function of the peripheral artery by comparison with those of α-glucosidase inhibitors (αGI) in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD).

Methods and Results: We randomly assigned 30 patients with T2DM and CAD to receive either sitagliptin or voglibose, and 28 patients (age 69±9 years, 75% male, hemoglobin A1c [HbA1c] 6.62±0.48%) completed the study (14 in each group). CFR and LV function, assessed by cardiac magnetic resonance imaging, and endothelial function, assessed by reactive hyperemia peripheral arterial tonometry (RH-PAT), were measured at baseline and 24 weeks after treatment. Clinical and laboratory parameters, including HbA1c level, plasma active glucagon-like peptide-1 concentrations, and biomarkers of inflammation, were unchanged in both groups after 24 weeks of treatment. CFR were unchanged in both the αGI group (3.01±0.98 at baseline and 3.06±0.8 after treatment, P=NS) and the DPP4i group (4.29±2.04 at baseline and 3.63±1.31 after treatment, P=NS), with no interaction effect. LV functional parameters and the reactive hyperemia index also remained unchanged after the 24-week treatment.

Conclusions: DPP4i did not improve CFR, LV function or endothelial function of the peripheral artery in patients with relatively well-controlled T2DM and CAD.

Key Words: Coronary flow reserve; Diabetes mellitus; Dipeptidyl peptidase-4 inhibitor

Diabetes mellitus (DM) is a major risk factor for cardiovascular (CV) disease,[1,2] but therapeutic strategies for the management of hyperglycemia to improve CV function in patients with DM are not well established. Dipeptidyl peptidase-4 inhibitors (DPP4i) enhance the physiological effects of incretins.[3] Previous reports showed that incretin had cardioprotective effects and a vasodilatory action.[4] Furthermore, DPP4i are reported to improve vascular endothelial function via an anti-inflammatory effect.[5] A recent clinical study using cardiac magnetic resonance imaging (cMRI) demonstrated that a 12-week treatment with DPP4i improved the coronary flow reserve (CFR) and left ventricular (LV) ejection fraction (EF).[6] However, sufficient clinical evidence has not been accumulated to confirm the cardioprotective effect of DPP4i.

The present study was conducted to assess the CV effects of DPP4i, including CFR, LV function and endothelial function of the peripheral artery, in comparison with those of a α-glucosidase inhibitor (αGI) in patients with type 2 DM (T2DM) and coronary artery disease (CAD).

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Methods

Study Design

This study was a prospective, single-center, 2-arm, randomized, open-label trial conducted between December 2013 and June 2016. The random assignment was performed by the Clinical Research Support Center of Mie University. The study was registered with the University Hospital Medical Information Network-Clinical Trials Registry

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(UMIN-CTR number: 000012562). The Ethics Committee of Mie University Hospital approved the study protocol (No. 2632) in accordance with the Declaration of Helsinki, and all patients gave written informed consent to participate.

Participants

Patients with T2DM who satisfied the following conditions were eligible: (1) hemoglobin A1c (HbA1c) between 6.1% and 8.9% without glucose-lowering drugs, or HbA1c between 6.5% and 8.9% with the use of fixed dosages of glucose-lowering drugs for more than 2 months, and (2) stable CAD with no ischemic symptoms and no stress-induced myocardial ischemia in the territories of the 3 major coronary arteries confirmed by cMRI. Exclusion criteria were: (1) severe renal dysfunction with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, (2) severe liver dysfunction, (3) unstable angina or acute myocardial infarction within 12 weeks before study enrolment, (4) atrial fibrillation, (5) use of DPP4i, glucagon-like peptide (GLP)-1 analog, αGI, or insulin before study enrolment, (6) severe heart failure with New York Heart Association class IV, and (7) allergies or contraindications to the study drugs.

Intervention

At randomization, 30 eligible study patients were assigned to receive either sitagliptin (50 mg once daily after breakfast) or voglibose (0.2 mg three times daily immediately before each meal) by a minimization method that took into account each patient's age (<75 years, ≥75 years) and HbA1c level (<7.5%, ≥7.5%). The study medications were initiated within 4 weeks of randomization. If glycemic control was insufficient 12 weeks after starting the study medication (HbA1c <6.2% in patients with baseline glucose-lowering drugs or HbA1c <6.0% in patients without baseline glucose-lowering drugs before randomization), sitagliptin was increased to 100 mg/day in the DPP4i group, and voglibose was increased to 0.9 mg/day in the αGI group. All patients underwent body weight, blood pressure and heart rate measurements, blood tests, reactive hyperemia peripheral arterial tonometry (RH-PAT) using an EndoPAT2000 (Itamar Medical, Caesarea, Israel) and MRI at baseline and after 24 weeks of treatment. All the participants consistently received lifestyle modification education including diet and exercise before and during the study period, and they were asked not to change their physical activity level during the study period.

Blood Tests and Biomarkers

Blood tests were performed while fasting in the morning. eGFR was calculated using the "Modified Diet in Renal Disease formula" modified by the Japanese Society of Nephrology (for males, 194×serum Cr levels$^{-1.094}$×age$^{-0.287}$; for females, 194×serum Cr levels$^{-1.094}$×age$^{-0.287}$×0.739).[7] Plasma levels of active GLP-1, high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor (TNF)-α, pentraxin (PTX)-3 and matrix metalloproteinase (MMP)-2 were measured by a clinical laboratory testing service (SRL, Tokyo, Japan).

RH-PAT

All patients underwent RH-PAT using an EndoPAT2000 (Itamar Medical, Caesarea, Israel) in the morning before breakfast and medications.[8] PAT probes were placed on the tip of each index finger. A blood pressure arm cuff was placed on the right arm, the other arm served as a control. After a 5-min equilibration period, the cuff was inflated to 200 mmHg, or 60 mmHg above systolic blood pressure, for 5 min and then deflated to induce reactive hyperemia. The PAT data were digitally analyzed using Endo-PAT2000 software. The RH index (RHI) reflects the endothelial vasodilator function.[8]

Echocardiography

Standard 2D Doppler echocardiography (Vivid 7, GE Medical Ultrasound, Horten, Norway or Artida, Toshiba Medical Systems, Tochigi, Japan) was performed for all patients by registered medical sonographers certified by the Japan Society of Ultrasonics in Medicine who were not involved in patient care. The peak early diastolic mitral annular velocity (E') of the lateral wall side was measured.

MRI

A 3.0-T MR system (Ingenia, Philips Medical Systems, Best, The Netherlands) with dS (dStream, Philips) anterior coils and dS posterior coils around the chest was used to acquire MR images. The cMRI study protocol included cine MRI, phase-contrast (PC) cine MRI during ATP stress and at rest, and late gadolinium-enhanced (LGE) MRI. Cine MR images were acquired with retrospective ECG gating, segmented steady-state free precession technique during brief periods of breath-holding at a shallow expiration in the LV vertical long-axis, horizontal long-axis and short-axis planes covering the entire LV under the following conditions: repetition time (TR) 3.2 ms; echo time (TE) 1.6 ms; flip angle (FA) 55°; field of view (FOV) 350×350 mm; acquisition matrix 174×306; reconstruction matrix 352×352; slice thickness 10 mm; sensitivity encoding (SENSE) factor 3; number of phases per cardiac cycle 20). The short-axis plane was the plane perpendicular to the horizontal and vertical long-axis views. Cine MR images on the axial planes were obtained through the atrioventricular groove to locate the coronary sinus (CS). The imaging plane for CS blood flow measurements by PC cine MRI was positioned perpendicular to the CS 2 cm from its ostium. PC cine MR images of the CS were acquired during suspended shallow breath-holding using an ECG-gated gradient echo sequence (TR 4.9 ms; TE 3.1 ms; FA 10°; FOV 250×208 mm; slice thickness 6 mm; acquisition matrix 176×97; reconstruction matrix 192×192; number of phases per cardiac cycle 25, velocity encoding ±80 cm/s). Pharmacological stress was achieved by injecting ATP (160 mg/kg/min) into the left antecubital vein for 4 min. PC cine MR images of the CS were acquired at rest and during ATP stress. All patients refrained from ingesting caffeine for at least 24 h before MRI. LGE MR images were acquired in the same LV short-axis planes as the cine images, covering the entire LV using a 3D inversion recovery TFE sequence (TR 4.8 ms; TE 2.3 ms; FA 15°; FOV 380×342×50 mm; acquisition matrix 240×192×5; reconstruction matrix 384×384×10; SENSE factor 4; TFE factor 28) 10 min after intravenous administration of 0.15 mmol/kg gadoterate meglumine (Magnescope, Guerbet Japan KK, Tokyo, Japan). The inversion time was adjusted for each patient to a null signal from the normal myocardium by using a look-locker sequence.

MRI Analysis

Cardiac MR images were analyzed using the cvi42 cMRI

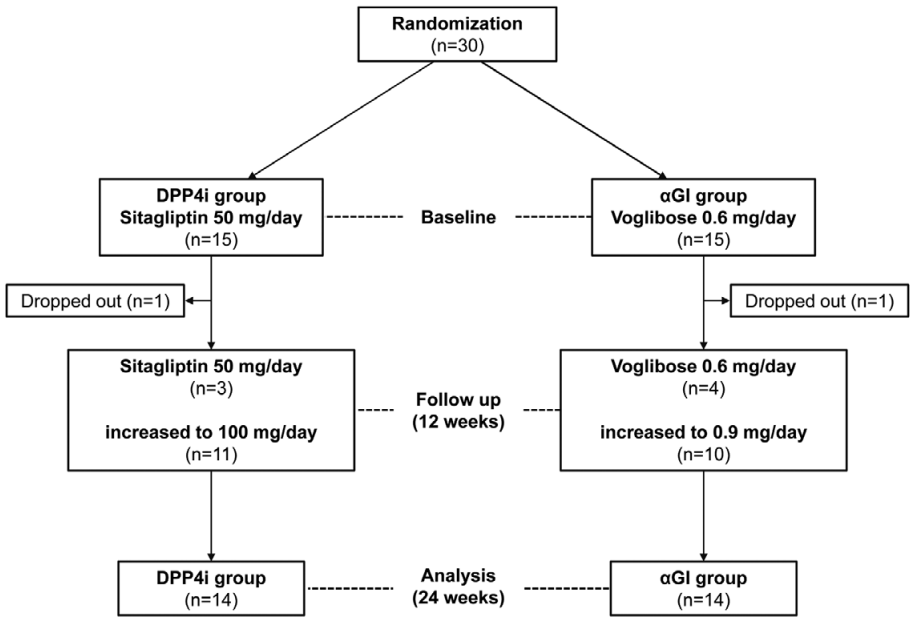

Figure 1. Study protocol. *α*GI, *α*-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin.

analysis software (Circle Cardiovascular Imaging Inc., Calgary, Canada) by an examiner not involved in patient care. On the short-axis cine MR images, the epi- and endocardial borders of the LV wall were manually traced at end-diastole and end-systole to measure the LV mass (LVM) and LV volume. LVM was calculated as the sum of myocardial areas multiplied by the slice thickness and the density (1.05 g/mL) of myocardial tissue.[9] To measure CS blood flow, the contour of the CS was manually traced on the magnitude images of the PC cine MRI at each cine frame throughout the cardiac cycle. The traced region of interest was applied on the corresponding phase image, and the cross-sectional area and mean velocity were recorded. Volumetric coronary venous flow was calculated as the product of the area and spatial average flow velocity. Mean volume flow was derived by means of integration of phasic flow over time. To compensate for the through-plane motion and phase offset error, a second region of interest was traced for each phase image on the adjacent CS tissue.[10] CFR was calculated by dividing the blood flow in the CS after injection of ATP by the baseline blood flow.

Endpoints

The primary endpoint was change in CFR at 24 weeks compared with baseline, and secondary endpoints included changes in LV end-diastolic and end-systolic volumes, LVM index and RHI at 24 weeks compared with baseline.

Sample Size Calculation

Because there has not been a previous study that evaluated the effects of sitagliptin on CFR by using cMRI when the protocol of the present study was finalized, sample size was estimated (α=0.05, β<0.20) based on previous data regarding GLP-1 receptor agonist; a synthetic GLP-1 receptor agonist improved myocardial blood flow from 0.69±0.097 to 0.86±0.09 mL/g·min,[11] while an *α*GI had no effects on coronary flow.[12] We assumed that sitagliptin may increase myocardial blood flow, thus CFR, by as much as 0.17 U with a SD of 0.15 and that voglibose may have no effect on CFR (by 0.0 U with a SD of 0.15). Thus, in order to detect this effect, in an unpaired comparison, this effect could be detected with 13 patients per group. With an expected drop-out of 2 patients in each group over 24 weeks of the program, we planned to enroll 15 patients per group.

Statistical Analysis

Continuous variables are presented as the mean±SD or median with interquartile range. They were compared by the unpaired t-test or non-parametric Mann-Whitney test, depending on the data distribution. Categorical data presented as percentages were compared by the chi-squared test. Two-way repeated measures analysis of variance was used to evaluate main (time; group) and interaction effects (time×group) for continuous variables at baseline and after 24 weeks. If significant results were identified, the Tukey post-hoc test was applied for pre–post comparisons where either the main or the interaction effect was statistically significant. Statistical significance was set at a value of P<0.05. All analyses were performed using SPSS 24.0 (SPSS Japan Inc., Tokyo, Japan).

Results

Baseline Clinical Characteristics

Two patients (1 in each group) dropped out because of poor compliance, and 28 patients (age 69±9 years, 75% men) completed the 24-week drug treatment. The study drugs were increased in 10 patients (71%) in the *α*GI group (voglibose 0.9 mg/day) and in 11 patients (79%) in the DPP4i group (sitagliptin 100 mg/day) (**Figure 1**). As shown in **Table 1**, there were no significant differences in demographic parameters, including age, height, body weight,

Table 1. Baseline Clinical Characteristics

	All (n=28)	DPP4i group (n=14)	αGI group (n=14)	P value
Demographic parameters				
Age, years	69±9	69±9	68±10	0.858
Male, n (%)	21 (75)	11 (79)	10 (71)	0.500
Height, cm	162±8	162±8	161±8	0.663
Body weight, kg	63±11	63±10	63±13	0.899
Systolic BP, mmHg	137±16	133±19	140±12	0.232
Diastolic BP, mmHg	73±11	72±13	74±9	0.611
Smoking, n (%)	2 (7)	1 (7)	1 (7)	0.759
Hypertension, n (%)	24 (86)	13 (93)	11 (79)	0.298
Dyslipidemia, n (%)	27 (96)	14 (100)	13 (93)	0.500
Previous MI, n (%)	19 (68)	12 (86)	7 (50)	0.052
Duration of DM, years	2.3 (1.1–6.0)	3.1 (2–5.7)	1.3 (0.6–5.6)	0.129
Medications				
β-blocker, n (%)	17 (61)	9 (64)	8 (57)	0.699
ACEI/ARB, n (%)	23 (82)	12 (86)	11 (79)	0.500
Diuretics, n (%)	7 (25)	2 (14)	5 (36)	0.192
Aldosterone antagonist, n (%)	2 (7)	1 (7)	1 (7)	0.759
Calcium-channel blocker, n (%)	14 (50)	6 (43)	8 (57)	0.450
Statin, n (%)	28 (100)	14 (100)	14 (100)	1.000
Ezetimibe, n (%)	7 (25)	4 (29)	3 (21)	0.500
Sulfonylurea, n (%)	4 (14)	2 (14)	2 (14)	0.702
Pioglitazon, n (%)	3 (11)	2 (14)	1 (7)	0.500
Biguanide, n (%)	1 (4)	0 (0)	1 (7)	0.500
Laboratory data				
HbA1c, %	6.62±0.48	6.64±0.51	6.60±0.46	0.817
Hemoglobin, g/dL	13.7±1.4	13.8±1.5	13.5±1.3	0.659
Albumin, g/dL	4.4±0.2	4.3±0.2	4.4±0.2	0.500
eGFR, mL/min/1.73 m^2	72±18	71±15	73±20	0.828
Total cholesterol, mg/dL	160±25	156±23	163±26	0.448
Triglyceride, mg/dL	113±59	100±49	125±66	0.271
HDL-C, mg/dL	56±13	53±7	58±17	0.307
LDL-C, mg/dL	91±21	90±22	91±20	0.879
Log BNP, pg/mL	1.34±0.45	1.41±0.44	1.27±0.47	0.418

ACEI, angiotensin-converting enzyme inhibitor; αGI, α-glucosidase inhibitor; ARB, angiotensin II receptor antagonists; BNP, B-type natriuretic peptide; BP, blood pressure; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

blood pressure and comorbidities, between the 2 groups. Of the 28 patients, 24 had a history of percutaneous coronary intervention. The median duration of DM was 2.3 years for all patients, and was not statistically different between groups. All patients were prescribed statins. Among the 28 patients, only 7 patients were prescribed hypoglycemic agents before randomization: 3 patients with sulfonylurea, 3 patients with pioglitazone, and 1 patient with sulfonylurea and biguanide. The average HbA1c level and eGFR were 6.62±0.48% and 72±18 mL/min/1.73 m^2, respectively, and were similar between groups.

Effects of DPP4i and αGI on Clinical and Laboratory Parameters

As shown in **Table 2**, the systolic and diastolic blood pressures remained unchanged over the 24-week treatment, but the changes in body weight were significantly different between groups. HbA1c levels were similarly and mildly decreased after the 24-week treatment. The changes in eGFR were significantly different between groups. As shown in **Table 3**, the plasma active GLP-1 concentrations did not significantly change in either group after the 24-week treatment. In addition, all measured biomarkers of inflammation and cardiac remodeling remained unchanged in both groups after the 24-week treatment.

Effects of DPP4i and αGI on CFR and Peripheral Endothelial Vasodilator Function

RHI was not assessed in 1 patient in the αGI group who took caffeine before RH-PAT after the 24-week treatment. In addition, no MRI parameters were obtained for 1 patient in the DPP4i group who developed atrial fibrillation after the 24-week treatment. RHI did not change after the 24-week treatment in either the DPP4i group (1.89±0.5 at baseline and 1.9±0.8 after treatment, P=NS), with no interaction effect, or in the αGI group (1.95±0.6 at baseline and 1.85±0.6 after treatment, P=NS) (**Figure 2**). In the MRI performed at baseline and after 24 weeks, the hemodynamic

Table 2. Comparisons of Clinical and Blood Parameters at Baseline and After 24 Weeks

	DPP4i group (n=14)	αGI group (n=14)	Group effect P value	Time effect P value	Interaction effect P value
Systolic BP, mmHg					
Baseline	133±19	140±12	0.127	0.856	0.661
After 24 weeks	132±17	142±15			
Diastolic BP, mmHg					
Baseline	72±13	74±9	0.574	0.421	0.931
After 24 weeks	74±12	76±9			
Body weight, kg					
Baseline	63±10	63±13	0.675	0.86	0.007
After 24 weeks	65±10*	61±13			
HbA1c, %					
Baseline	6.64±0.51	6.60±0.46	0.982	0.003	0.539
After 24 weeks	6.39±0.40*	6.43±0.44			
eGFR, mL/min/1.73 m^2					
Baseline	71±15	73±20	0.403	0.591	0.049
After 24 weeks	66±15	76±21			
Log BNP, pg/mL					
Baseline	1.41±0.44	1.27±0.47	0.597	0.672	0.299
After 24 weeks	1.38±0.47	1.34±0.50			

*P<0.05 vs. Baseline. Abbreviations as in Table 1.

Table 3. Comparisons of Biomarkers and Reactive Hyperemia Peripheral Arterial Tonometry at Baseline and After 24 Weeks

	DPP4i group (n=14)	αGI group (n=14)	Group effect P value	Time effect P value	Interaction effect P value
Active GLP-1, pmol/L					
Baseline	2.00 (2.00–2.00)	2.00 (2.00–2.18)	0.622	0.108	0.273
After 24 weeks	2.60 (2.00–3.15)	2.00 (2.00–2.23)			
hs-CRP, ng/mL					
Baseline	357 (163–814)	442 (297–1,203)	0.285	0.230	0.810
After 24 weeks	174 (125–1,050)	339 (246–1,850)			
TNFα, pg/mL					
Baseline	1.01±0.36	1.21±0.57	0.307	0.786	0.527
After 24 weeks	1.04±0.40	1.14±0.44			
PTX-3, ng/mL					
Baseline	1.98±0.81	1.74±0.88	0.780	0.462	0.196
After 24 weeks	1.91±0.62	1.99±0.98			
MMP-2, ng/mL					
Baseline	858 (830–928)	894 (787–962)	0.716	0.421	0.661
After 24 weeks	937 (800–993)	838 (776–949)			

CRP, C-reactive protein; GLP, glucagon-like peptide; hs, high-sensitivity; MMP, matrix metalloproteinase; PTX, pentraxin; TNF, tumor necrosis factor. Other abbreviations as in Table 1.

state induced by ATP infusion significantly changed in both groups (**Table 4**). Baseline CFR was 3.01±0.98 in the αGI group and 4.29±2.04 in the DPP4i group (P=0.08). Rest and stress CS flow did not change in either group, resulting in unchanged CFR after the 24-week treatment (**Figure 2**).

Effects of DPP4i and αGI on LV Morphology and Function

Table 5 and **Figure 2** show comparisons of the LV morphology and function at baseline and after the 24-week treatment. E' did not significantly change in both groups after the 24-week treatment (**Figure 2**). LV cavity volume indices, stroke volume, LVEF (**Figure 2**) and LVM index measured by MRI did not significantly change in both groups after the 24-week treatment, except for the LVESV index in the αGI group.

Discussion

The present study demonstrated that neither sitagliptin nor voglibose improved CFR, LV function or endothelial function of the peripheral artery in patients with T2DM and CAD after 24 weeks of treatment. Furthermore, neither treatment affected plasma biomarkers of inflammation and cardiac remodeling.

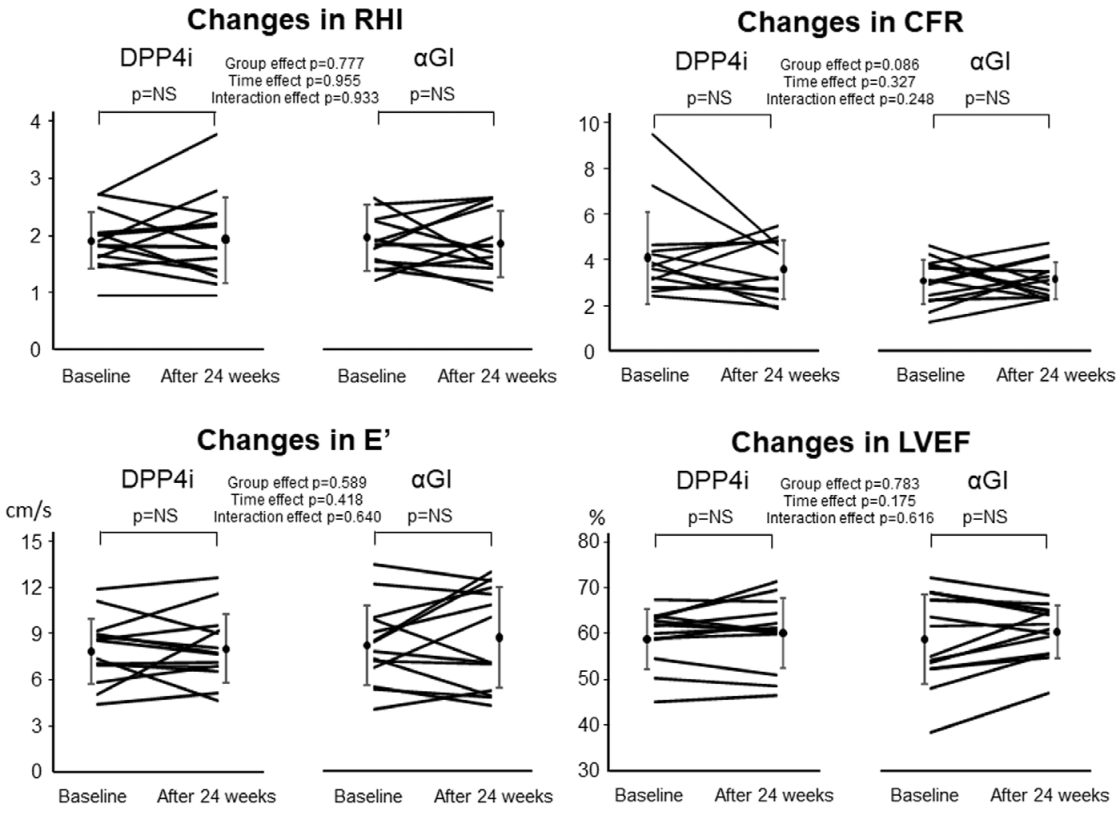

Figure 2. Comparisons of cardiovascular function at baseline and after 24 weeks of treatment. αGI, α-glucosidase inhibitor; CFR, coronary flow reserve; DPP4i, dipeptidyl peptidase-4 inhibitor; LVEF, left ventricular ejection fraction; RHI, reactive hyperemia index.

Table 4. Comparisons of Hemodynamic State Induced by ATP Infusion on MRI Between DPP4i and αGI Groups

	DPP4i group (n=13)		αGI group (n=14)	
	Rest	Stress	Rest	Stress
Baseline				
Systolic BP, mmHg	127±20	118±26*	141±12	126±12*
Diastolic BP, mmHg	69±8	61±9*	71±12	64±11*
Heart rate, beats/min	63±12	78±16*	65±10	78±11*
RPP, mmHg·beats/min	8,079±2,206	9,239±2,778*	9,109±1,633	9,908±2,111*
After 24 weeks				
Systolic BP, mmHg	123±13	111±13*	128±9	118±11*
Diastolic BP, mmHg	66±6	58±8*	66±9	60±10*
Heart rate, beats/min	64±11	75±14*	65±11	79±14*
RPP, mmHg·beats/min	7,804±1,637	8,287±1,947*	8,385±1,706	9,362±2,298*

*P<0.05 vs. at rest. MRI, magnetic resonance imaging; RPP, rate pressure product. Other abbreviations as in Table 1.

GLP-1 and GIP, known as incretins, increase insulin secretion and suppress glucagon secretion. GLP-1 receptors are expressed in the myocardium, vascular smooth muscle cells and the endothelium.[13–15] DPP4i, which enhance the physiological effects of incretin by increasing the half-life and bioavailability of active incretins, are thus thought to exert multiple effects on the CV system.[16] However, it has not been fully demonstrated whether these agents can improve or maintain endothelial cell function. Matsubara et al first showed that 6-month DPP4 inhibition with sitagliptin significantly improved the RHI compared with conventional therapy in patients with CAD and uncontrolled T2DM (HbA1c 7.4±1.0%), despite similar blood glucose-lowering effects (ΔHbA1c: −0.64±0.82% in the sitagliptin group and −0.65±0.68% in the conventional therapy group), and that sitagliptin was an independent

Table 5. Comparisons of LV Morphology and Function at Baseline and After 24 Weeks

	DPP4i group (n=13)	αGI group (n=14)	Group effect P value	Time effect P value	Interaction effect P value
LVEDV index, mL/m^2					
Baseline	133±34	126±31	0.336	0.107	0.292
After 24 weeks	131±27	117±26			
LVESV index, mL/m^2					
Baseline	55±19	52±20	0.408	0.037	0.286
After 24 weeks	53±17	47±15*			
Stroke volume, mL					
Baseline	78±19	74±19	0.420	0.490	0.436
After 24 weeks	78±17	71±15			
LVM index, g/m^2					
Baseline	44±6	42±5	0.285	0.807	0.999
After 24 weeks	44±9	43±8			

*P<0.05 vs. Baseline. EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular; LVM, left ventricular mass. Other abbreviations as in Table 1.

determinant of improved endothelial function.[5] Nakamura et al demonstrated that a 12-week treatment with sitagliptin or voglibose reduced HbA1c equally (ΔHbA1c: −0.39±0.60% in the sitagliptin group and −0.35±0.39% in the voglibose group) and improved flow-mediated dilatation (FMD) of the brachial artery in patients with T2DM (baseline HbA1c: 7.04±0.56% in the sitagliptin group and 6.94±0.45% in the voglibose group), despite no significant increases in GLP-1 activity after the treatment.[17] In contrast, a recent double-blind randomized study, which included patients with newly detected glucose perturbations (median HbA1c of 5.7 and 5.9% in the sitagliptin group and placebo group, respectively) and acute coronary syndrome, a 12-week sitagliptin or placebo treatment did not improve the RHI.[18] Similarly, neither sitagliptin nor voglibose improved RHI after the 24-week treatment in patients with CAD and T2DM (baseline HbA1c 6.62±0.48%) in the present study. Notably, the study participants in the 2 clinical studies showing no beneficial effects of sitagliptin therapy on endothelial function had relatively low HbA1c values at baseline compared with studies showing positive results. Because a higher baseline HbA1c is associated with greater efficacy of DPP4i therapy in lowering HbA1c,[19] the efficiency of antidiabetic treatment on the RHI may largely depend on the baseline levels of glycemic control and on the degree of reduction in glucose levels; in other words, DPP4i may improve peripheral vascular dysfunction via ameliorating hyperglycemia-induced oxidative stress and inflammatory processes. Indeed, Matsubara et al showed a significant correlation between changes in the RHI and hs-CRP levels after 6 months of treatment with sitagliptin.[5] The baseline values of inflammatory biomarkers, including hs-CRP and TNF-α, were close to normal levels in the present study, and neither voglibose nor sitagliptin treatment reduced these parameters. PAT was used in the present study whereas both FMD and PAT are commonly used methods for assessing endothelial function of the peripheral artery. FMD directly registers the dilatation capability of a large conduit artery, whereas PAT measures flow response hyperemia, which is related to the endothelial function of small arteries and to the endothelial function of the microcirculation. Although FMD may be a more validated technology, the PAT method is user-friendly because it is largely operator-independent and a computerized algorithm with an online system automatically calculates the RHI. In addition, PAT can minimize the effects of systemic circulation variation and the bilateral sympathetic nervous system by dividing the dilatation rate of the test side by that of the control side. Although a direct contribution of nitric oxide to both brachial artery FMD and the digital PAT values, the correlation between these methods varies according to the study design and spectrum of disease in the studied group.[20,21]

CFR values are affected by a number of factors such as hyperglycemia,[22] insulin resistance,[23] autonomic dysfunction,[24] and inflammation promoted by DM.[25] From the aspects of both hyperglycemia-induced oxidative stress and inflammatory process and of incretin-related molecular pathways in the regulation of endothelial function, DPP4i may have beneficial effects on CFR. Kato et al first demonstrated that a 12-week treatment with alogliptin but not glimepiride improved CFR assessed by cMRI in patients with T2DM and known or suspected CAD despite similar blood glucose-lowering effects (ΔHbA1c: −0.6±0.3% in the alogliptin group and −0.5±0.3% in the glimepiride group) in their very small study population.[6] In contrast, the present study failed to show a beneficial effect of chronic blood glucose-lowering therapy on CFR. Similar to the mechanisms of DPP4 inhibition on peripheral vascular dysfunction, patients with poorer glycemic control at baseline may show greater improvement in CFR because of the greater beneficial effect on hyperglycemia-induced and incretin-related molecular pathways in the regulation of endothelial function. In addition, the baseline values of CFR in the present study were relatively preserved when compared with those in the studies of Kato et al,[6] which may partially account for these inconsistent results.

It has been reported that chronic DPP4 inhibition improves LV functional parameters in experimental DM models. Shigeta et al reported that DPP4i reverse diastolic LV dysfunction via membrane-bound DPP4/stromal cell-derived factor-1α–dependent local actions on angiogenesis and circulating DPP4/glucagon-like peptide-1–mediated inotropic actions in DM rats.[26] Similarly, Hamdani et al showed that sitagliptin decreased LV passive stiffness and improved global LV performance in the absence of

hypoglycemic effects, and suggested that DPP4i reduce cardiomyocyte stiffness through a cGMP–PKG–titin phosphorylation pathway in obese T2DM mice.[27] Interestingly, Read et al demonstrated acute effects of DPP4i on LV function in both diabetic and non-diabetic humans.[28] However, recent clinical studies have provided inconsistent data regarding the chronic effects of DPP4i on LV systolic and diastolic function. Nogueira et al compared the effects of 24-week treatment with sitagliptin (n=18) and bedtime NPH insulin (n=17) on echocardiography-derived diastolic function in T2DM patients who were inadequately controlled with metformin plus glyburide (baseline HbA1c was 8.0±0.6% in the sitagliptin group and 8.1±0.7% in the NPH insulin group) in a prospective randomized study, and found that sitagliptin had a more beneficial effect on LV diastolic function than NPH despite their similar effects on glucose control and CRP.[29] Fujiwara et al retrospectively compared the changes in echocardiography-derived diastolic parameters between patients treated with DPP4i and non-DPP4i among patients with acute myocardial infarction (baseline HbA1c was 8.2±1.5% in the DPP4i group and 8.1±1.6% in the non-DPP4i group), and reported that the values of E/e' and e'/a' significantly decreased and increased, respectively, in the DPP4i group compared with the non-DPP4i group after 7.4±2.5 months of follow-up.[30] In contrast, neither sitagliptin nor voglibose improved LV systolic and diastolic function in the present study. Consistent with our results, a recent randomized multicenter study showed that treatment with sitagliptin or voglibose for 24 weeks did not change E' and E/e' in patients with T2DM (baseline HbA1c was 7.1±0.7% in the sitagliptin group and 6.9±0.5% in the voglibose group).[31] In that study, there were no changes in inflammatory markers in either group. Although the precise mechanisms responsible for these inconsistent data regarding the effects of DPP4i on LV function are unclear, the results of these clinical studies, including the present study, suggest that the efficiency of antidiabetic treatment on CV function largely depends on the baseline level of glycemic control and on the degree of reduction in glucose levels, and that DPP4i-specific effects via GLP-1 stimulation may be observed only under hyperglycemic conditions. Indeed, the active GLP-1 levels were not significantly increased, despite 79% of patients in the DPP4i group receiving the maximal dosage of 100 mg/day sitagliptin.

The changes in eGFR were statistically different between the 2 groups in the present study, indicating that sitagliptin treatment had a negative effect on eGFR compared with voglibose treatment. Similarly, Maeda et al reported that eGFR decreased significantly from 64.5±17.7 at baseline to 62.2±20.3 at 3 months.[32] Cornel et al also showed that the mean eGFR reduction over 4 years from baseline was greater in the sitagliptin treatment group than in the placebo treatment group in their Trial Evaluating Cardiovascular Outcomes with Sitagliptin.[33]

Several prospective, multicenter, randomized, double-blind clinical trials for evaluating the effect of DPP-4 inhibitors on CV outcomes have been published; the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) on sitagliptin,[29] the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial on saxagliptin,[34] and the Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE) trial on alogliptin.[35] All 3 trials revealed that DPP4i did not increase or decrease the rate of CV events, including CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or hospitalization for unstable angina, except for increases in the rate of hospitalization for heart failure with the use of saxagliptin compared with placebo treatment in the SAVOR-TIMI 53 trial. Therefore, DPP4i may have a largely neutral effect on CV outcomes in patients with T2DM at high CV risk. As DPP4i-based therapies when used alone or with metformin have a low risk of adverse effects including hypoglycemia, it is considered a useful second oral glucose-lowering agent.[36]

Study Limitations

Several limitations must be acknowledged. First, this was a single-center study with a small sample size. We planned to enroll 15 patients per group with the assumption that sitagliptin increased CFR by as much as 0.17 U with a SD of 0.15 and that voglibose would have no effect on CFR (by 0.0 U with a SD of 0.15). However, the change in CFR by sitagliptin was smaller than assumed. Given the small number of subjects and the large variability observed, we were powered to detect a true minimal difference of ±1.61 in CFR with a probability of type II error at <20% in the DPP4i group. The difference in CFR observed in the DPP4i group in the present study was 0.666 (n=13; SD, 1.896; 95% confidence interval, −0.48 to 1.81; power, 0.11). Second, the present study did not include control groups. The CV parameters including CFR in the DPP4i group and αGI group might be better than in control groups after 24 weeks of treatment, reflecting the preventive effects of these agents on the natural progression of CV dysfunction. A double-blind, placebo-controlled randomized clinical trial is needed to corroborate our findings. Third, differences in the various DPP4i effects on CV function were not assessed. Finally, the present study did not provide information about the long-term effects of DPP4i on CV function. We primarily evaluated the effect of DPP4i on CFR, as a surrogate for coronary artery endothelial function, which can be improved after short-term glucose-lowering therapy. Indeed, most studies have evaluated the effects of DPP4i on endothelial function of either the coronary or peripheral arteries during 12–24 weeks of treatment.[5,6,17,18] However, a longer follow-up period may also provide insight into the clinical effectiveness of DPP4i on CV function.

Conclusions

Chronic glucose-lowering therapy using DPP4i and αGI did not improve the endothelial function of the peripheral artery, CFR and LV function in patients with relatively well-controlled T2DM and CAD. These results indicate that DPP4i may have limited pleiotropic effects on the CV system beyond glycemic control.

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