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ORIGINAL ARTICLE

Effects of sitagliptin on exercise capacity and hemodynamics in patients with type 2 diabetes mellitus and coronary artery disease

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Abstract

Sitagliptin attenuates left ventricular (LV) dysfunction and may improve oxygen uptake in animals. The effects of sitagliptin on oxygen uptake (VO_2) and exercise hemodynamics have been unclear in patients with type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD). Thirty patients with T2DM and CAD were randomized into a sitagliptin (50 mg/day) or voglibose (0.6 mg/day) group. Patients underwent maximal cardiopulmonary exercise testing. VO_2 and hemodynamics were evaluated at rest, anaerobic threshold and peak exercise. Resting LV diastolic function (E', peak early diastolic mitral annular velocity) and geometry were evaluated by echocardiography, and endothelial function by reactive hyperemia peripheral arterial tonometry. A total of 24 patients (69 ± 9 years) completed 6 months of intervention. Peak VO_2 in the sitagliptin and voglibose groups (25.3 ± 7.3 vs. 24.0 ± 7.4, 22.7 ± 4.8 vs. 22.1 ± 5.2 ml/kg/min) was slightly decreased after 6 months (time effect $p = 0.051$; group × time effect $p = 0.49$). No effects were observed on LV ejection fraction, E', or reactive hyperemia index in either group. Heart rate during exercise was unaffected in both groups. Systolic blood pressure was unchanged by sitagliptin at rest and during exercise, but slightly lowered by voglibose at anaerobic threshold and peak exercise. In patients with T2DM and CAD, sitagliptin had little effect on resting LV and arterial function, exercise capacity, or exercise hemodynamics. Further studies need to be conducted with more patients as the number of the patients in this study was limited.

Keywords Sitagliptin · Exercise capacity · Type 2 diabetes mellitus · Left ventricular diastolic function

Introduction

Type 2 diabetes mellitus (T2DM) increases cardiovascular (CV) stiffening and impairs left ventricular (LV) function, resulting in increased risks for CV comorbidities, such as coronary artery disease (CAD) and heart failure, with or without preserved ejection fraction [1]. Arterial stiffening is associated with aging [2], and this stiffening may cause exaggerated blood pressure elevation and become particularly problematic during exercise, especially in older individuals, resulting in exercise intolerance [3]. Thus, older patients with T2DM and CAD could have exacerbated arterial and LV dysfunction during exercise, which may contribute to reduced exercise capacity.

Sitagliptin is one of the dipeptidyl peptidase-4 inhibitors (DPP4i) and inhibits the degradation of glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) [4]. Sitagliptin improves glycemic control and may exhibit favorable effects on CV function. For example, it was reported that DPP4 inhibition by sitagliptin reversed LV systolic dysfunction and attenuated LV diastolic stiffening in rats [5]. In addition, sitagliptin improved LV systolic function at peak stress in patients with coronary ischemia [6].

It is unclear whether LV and arterial dysfunction can be reversed by sitagliptin in patients with T2DM and CAD. It is also unclear whether possible improvements in LV and arterial function leads to increased exercise capacity. The objective of this study was to assess CV function, exercise hemodynamics, and exercise capacity before and after 6 months of sitagliptin in patients with T2DM and CAD. We hypothesized that advanced arterial and LV dysfunction are reversed by sitagliptin, resulting in improved exercise capacity in patients with T2DM and CAD.

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Materials and methods

Patient population

This was a sub-study from a prospective 6-month trial comparing the effects of sitagliptin or voglibose on coronary flow reserve in patients T2DM and CAD [7]. Thirty patients with CAD and T2DM who had not achieved their glycemic control target [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 glucose lowering drugs] were enrolled [7]. Patients were excluded from the study if they had type 1 diabetes mellitus, important coronary ischemia, acute myocardial infarction or unstable angina, prior coronary artery bypass graft surgery, artificial heart valves, severe valvular heart disease, atrial flutter/fibrillation, implanted pacemaker, or renal failure (estimate glomerular filtration rate < 30 ml/min/1.73 m^2). Patients were also excluded from the study if they were using DPP4i, alpha-glucosidase inhibitors, insulin, glynides, or GLP-1 receptor analogs. Baseline data including coronary flow reserve by cardiac magnetic resonance imaging from this patient population have been published [7]. This study now reports the effects of the 6 months of sitagliptin or voglibose on exercise hemodynamics and capacity.

Study protocol

Patients were stratified into additional treatment with either sitagliptin (50 mg/day) or voglibose (0.6 mg/day) for 6 months, so that HbA1c levels and patient ages were not different at baseline [7]. Patients received either 50 mg of sitagliptin, once a day, or 0.2 mg of voglibose, 3 times daily, for the first 3 months. The study medications were initiated within 4 weeks after randomization. If the glycemic control was inadequate, the dose of sitagliptin (up to 100 mg once daily) or voglibose (up to 0.3 mg three times daily) was increased according to the physician's discretion. No other antidiabetic drugs were added during the 6-month study period. Patients were asked not to change their physical activity level during the study. This study was registered with the University Hospital Medical Information Network-Clinical Trials Registry (https://www.umin.ac.jp/ctr/, UMIN-CTR number: UMIN000012562). The Ethics Committee of Mie University Hospital approved the study protocol (No. 2632) in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients, and the protocol was approved by the Human Studies Subcommittee of Mie University Graduate School of Medicine.

Echocardiographic assessment

Standard two-dimensional Doppler echocardiography (Vivid 7, GE Ultrasound, Horten, Norway; Artida, Toshiba Medical Systems) was performed before and after the program [7]. LV volumes and LV ejection fraction were assessed. Peak early transmitral filling velocity (E) and peak early diastolic mitral annular velocity (E') of the lateral wall side were measured [8]. The E/E' ratio was used to estimate LV end-diastolic pressure [9].

Cardiopulmonary exercise testing

A maximal symptom-limited exercise testing was performed using a cycle ergometer (StrengthErgo240, Mitsubishi Electric Engineering Company, Ltd.) with a ramp protocol with increments of 1 W per 6 s until exhaustion. The stress system was the ML-9000 (Fukuda Denshi Co. Ltd.). Heart rate was monitored, and blood pressure was measured every minute by an automatic-cuff blood pressure manometer. The expired breath-by-breath gas analysis was conducted (CPEX-1, Inter Reha Co. Ltd.). Minute ventilation, oxygen uptake (VO_2), and carbon dioxide production (VCO_2) were measured. Gas data were converted into time-series data every 3 s, and an 8-point moving average of data was applied to calculate heart rate and measured gas parameters. The peak respiratory exchange ratio (RER) was defined as peakVCO_2 divided by peakVO_2 to evaluate patients' effort. All patients were vigorously encouraged to exercise until exhaustion with a target peak RER ≥ 1.20 [10].

Assessment of peakVO_2, anaerobic threshold, and peak oxygen pulse

PeakVO_2 was defined by as the average value of VO_2 during the last 30 s before termination of exercise. Anaerobic threshold was determined by the V-slope method from the slopes of the VCO_2 vs. VO_2 plot [11]. Peak oxygen pulse (O_2 pulse) was defined as peakVO_2 divided by maximal heart rate, and was used as a surrogate for stroke volume [12]. As the ratio of end-systolic blood pressure to stroke volume, known as effective arterial elastance, has been shown to be a measure of arterial vascular load [13], the ratio of peak systolic blood pressure (SBP) to peak O_2 pulse (peak SBP/peak O_2 pulse) was used as a surrogate for arterial load at peak exercise.

Noninvasive assessment of arterial function

Endothelial function was non-invasively assessed in the fasting state by a peripheral arterial tonometry (PAT) device (Endo-PAT2000, Itamar Medical) [7, 14]. PAT probes were

placed on the tip of each index finger. A blood pressure arm cuff was placed on the right arm, and the left arm served as a control. The cuff was inflated to 200 mmHg or 60 mm Hg above the SBP for 5 min and deflated to induce reactive hyperemia. Obtained PAT data were digitally analyzed (Endo-PA2000 software). The reactive hyperemia PAT index (RH-PAT index) reflects endothelial vasodilator function [14].

Blood tests and biomarkers

Blood samples were collected before and after the program to measure HbA1c, blood glucose, complete blood counts, and plasma brain natriuretic peptide.

End points

The primary endpoint was the change in peakVO_2 at 24 weeks compared to baseline between 2 groups, and the secondary endpoints included changes in resting LV function, endothelial function, and exercise hemodynamics.

Sample size estimation

This study was a sub-study from a prospective 6-month trial comparing the effects of sitagliptin or voglibose on coronary flow reserve in patients with T2DM and CAD [7]. The sample size was estimated based on previous data regarding the effects of GLP-1 receptor agonist and an α-glucosidase inhibitor on myocardial blood flow. Fifteen patients per group were enrolled, as recently reported [7].

Statistical analysis

Statistical analyses were performed using SPSS 24.0. Data were expressed as mean ± SD in tables and mean ± SE in figures. Continuous data were compared by unpaired *t*-test or nonparametric Mann–Whitney rank sum test. Categorical data were assessed by chi-squared test. A two-way repeated measures ANOVA was used to evaluate main (group; time) and interaction effects (group × time). Post-hoc analysis was used for pre-post comparisons where either a main or interaction effect was significant. A p value less than 0.05 was considered significant.

Results

Patient characteristics

Twenty-four patients (18 men; 69 ± 9 years) out of 30 completed the 6-month intervention (Fig. 1). Two patients dropped out because of poor compliance. Four other patients were excluded due to no repeat exercise testing, an atrioventricular block during repeat exercise test, or proximal atrial fibrillation. There were no differences in patient characteristics, medications, laboratory data, or comorbidities except for a history of previous myocardial infarction (Table 1). No differences were observed in heart rate, SBP, VO_2 or O_2 pulse at rest and at peak exercise before the intervention ($p \geq 0.11$).

Anthropometric and biochemical variables

Body mass index, hemoglobin, and HbA1c were similar in the two groups at baseline (Table 1). The 6-month intervention significantly decreased HbA1c in the sitagliptin group (6.5 ± 0.4 vs. 6.3 ± 0.3%, $p = 0.02$), but not in the voglibose group ($p = 0.23$). Body weight was slightly increased in the sitagliptin group, but decreased in the voglibose group, resulting in a group × time interaction effect p value of 0.04.

Echocardiographic variables

No differences were observed in baseline LV ejection fraction, E wave velocity, E' or E/E' between the two groups (Table 1). E' was unaffected by the interventions with sitagliptin (8.1 ± 2.1 to7.9 ± 2.4 cm/s) and voglibose (8.2 ± 2.8 vs. 8.5 ± 3.3 cm/s), suggesting no improvement in LV early diastolic function (Table 2). LV ejection and E/E' ratio were unchanged after the intervention.

Arterial function

The 6-month intervention had no impacts on RH-PAT index measured by Endo-PAT in both groups [7] (Table 2). Arterial load at peak exercise assessed by the ratio of peak SBP to peak O_2 pulse was unchanged in both groups (Table 3).

Exercise capacity and exercise hemodynamics

The average peak RER values in both groups before intervention were greater than 1.20. As shown in Fig. 2a and b, peakVO_2 was slightly decreased after the intervention in both groups (group effect $p = 0.051$). The change in peak VO_2 in the sitagliptin group was not different from that in the voglibose group (− 1.2 ± 2.6 vs. − 0.6 ± 1.8 ml/kg/min, $p = 0.49$). SBP significantly decreased in the voglibose group at anaerobic threshold and at peak exercise (206 ± 27 vs. 194 ± 32 mmHg, $p = 0.01$), but not in the sitagliptin group ($p \geq 0.32$) (Table 3).

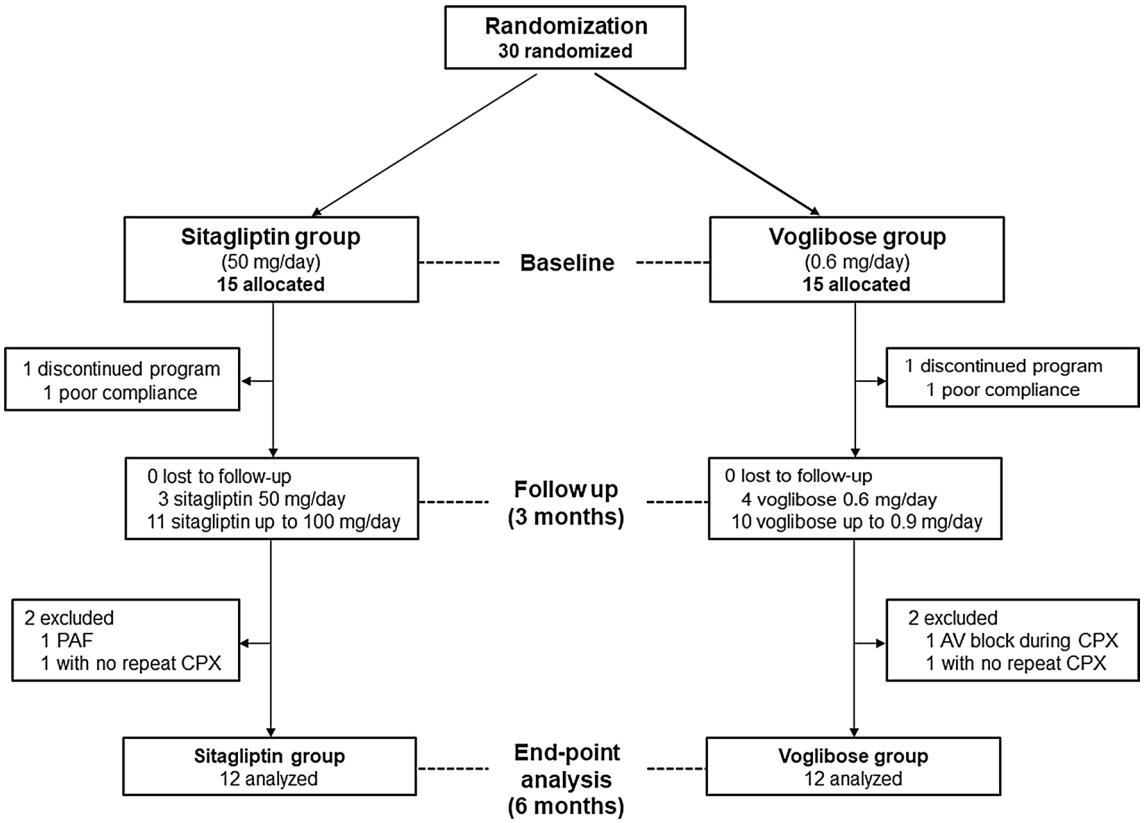

Fig. 1 Study protocol

Discussion

We demonstrated in T2DM patients with CAD that 6 months of treatment with sitagliptin failed to improve LV diastolic function, arterial function and exercise capacity. In addition, sitagliptin had no effects on exercise hemodynamics estimated noninvasively.

Effects of 6 months of sitagliptin on LV early diastolic function

DPP4i have been reported to exhibit CV pleiotropic effects in animal models [15]. Dos Santos et al. reported in rats with LV ablation-induced HF rats that DPP-4 inhibition by sitagliptin improved LV systolic dysfunction and attenuated LV diastolic stiffening [16]. This improvement in LV stiffness was confirmed by a lower apoptosis rate and smaller interstitial collagen deposition in remodeled myocardium away from the scar tissue [16]. Gomes et al. found that sitagliptin improved hemodynamics by lowering heart rate and increasing stroke volume [17]. Several mechanisms including stimulatory effects on the myocardial cGMP- protein kinase G pathway [18] or myocardial stromal cell-derived actions on angiogenesis [5] have been reported to be associated with improvements in LV function in animals. In patients with T2DM and CAD, we observed no changes in E' or E/e' after 6 months of sitagliptin. The present results, which indicate no improvement in LV diastolic function after sitagliptin, are consistent with the previous finding in T2DM patients treated with 6 months of sitagliptin [19]. As a line of research proposed that DPP4 was an adipokine produced in obesity and diabetes leading to CV damage [20, 21], any advantage of gliptin treatment would be the preventing the development of CV disease with little actions on the already established CV damage.

In contrast to these results, a small study reported that a year of sitagliptin increased E' in patients with uncontrolled T2DM, suggesting an improvement in LV early diastolic function [22]. In this study, the baseline HbA1c was substantially higher ($9.3 \pm 1.7\%$) and the reduction in HbA1c was greater than those in our study [23]. Although the precise mechanisms are unclear, differences in baseline glycemic control, duration of sitagliptin use, or improvement in diabetic control may be related to the discrepant results of the effects of sitagliptin on LV diastolic function.

Table 1 Patient characteristics

	Voglibose	Sitagliptin	*p* value
Number	12	12	
Female gender, *n* (%)	4 (33)	2 (17)	0.35
Age, years	68 ± 10	70 ± 9	0.55
Body mass index, kg/m^2	23.8 ± 3.9	23.5 ± 2.7	0.81
SBP, mmHg	137 (132, 150)	130 (116, 151)	0.52
DBP, mmHg	74 ± 9	71 ± 13	0.54
Heart rate, bpm	69 ± 9	67 ± 13	0.75
Comorbidities (%)			
Hypertension	10 (83)	11 (92)	0.54
Dyslipidemia	12 (100)	12 (100)	–
Diabetes mellitus	12 (100)	12(100)	–
Previous coronary intervention	8 (67)	11 (92)	0.13
Previous myocardial infarction	6 (50)	11 (92)	0.03
Medication, *n* (%)			
ARB/ACE-inhibitors	10 (83)	10 (83)	1.00
Calcium channel blockers	7 (58)	5 (42)	0.41
Beta-blockers	6 (50)	7 (58)	0.68
Statins	12 (100)	12 (100)	–
Hypoglycemic agents	2 (17)	1 (8)	0.54
Laboratory data			
Hemoglobin, g/dl	13.6 ± 1.4	13.5 ± 1.2	0.89
Glucose, mg/dl	122 ± 12	118 ± 11	0.41
HbA1c, %	6.4 (6.2, 7.1)	6.4 (6.2, 6.7)	0.86
eGFR, 60 ml/min/1.73m^2	76 ± 20	69 ± 12	0.29
BNP, pg/ml	12 (7, 54)	24 (12, 58)	0.30
LogBNP, pg/ml	1.24 ± 0.49	1.42 ± 0.47	0.39
Echocardiography			
Ejection fraction, %	67 ± 7	64 ± 6	0.28
E, cm/s	63 (49, 77)	69 (50, 77)	0.84
E', cm/s	8.2 ± 2.8	8.1 ± 2.1	0.88
E/E' ratio	6.9 (5.9, 10.9)	8.4 (6.5, 10.8)	0.75

SBP indicates systolic blood pressure, *DBP* diastolic blood pressure, *ARB* angiotensin II receptor antagonists, *ACE* angiotensin-converting enzyme, *HbA1c* glycated hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *BNP* brain natriuretic peptide, *E* peak early mitral inflow velocity, *E'* peak early mitral annular velocity, *E/E' ratio* the ratio of peak early mitral filling velocity-to-peak early mitral annular velocity

Effects of 6 months of sitagliptin on exercise capacity, arterial function, and exercise hemodynamics

Impairments in CV function occur along with healthy sedentary aging, resulting in a decline in peakVO_2 [24]. A further decline in peakVO_2 could be observed in patients with old myocardial infraction or heart failure [25]. Conversely, physical exercise, which improves LV and arterial function [26, 27], may reverse the age-associated decline in peakVO_2. When caloric restriction was combined with exercise training, the improvement in exercise capacity appeared to be greater [28]. In the present study, we asked our patients not to increase their physical activity level as our focus was on the effects of sitagliptin itself on CV function and exercise capacity. PeakVO_2 was slightly decreased in both groups in the present study. As we observed no changes in cardiac function or arterial function, the decrease in peakVO_2 could be explained by a time-associated decline in exercise capacity. Longer antidiabetic therapy with exercise training and caloric restriction may have been necessary to improve CV function and exercise capacity in our patients.

In a small study of patients with coronary stenosis, Read et al. reported that a single dose of 100 mg sitagliptin had no effects on LV global function at rest [6]. After administration of 100 mg sitagliptin, LV systolic function at ischemic segments improved during stress with no evidence of post-ischemic LV stunning [6]. Chang et al. also found that sitagliptin pretreatment attenuated myocardial injury by reducing apoptosis and oxidative damage [29]. In contrast to these studies, we observed no increase in peak O_2 pulse, a surrogate for peak stroke volume, with no change in peak heart rate after the intervention. These findings suggest that LV global function during exercise was unaffected by sitagliptin at peak exercise. We excluded patients with ischemia by use of stress cardiac magnetic resonance imaging. The results may have differed if we enrolled T2DM patients with significant coronary ischemia. Recently, favorable effect of other DPP4i such as teneligliptin on CV function were reported in T2DM [30]. As this DPP4i is in a new class of antidiabetic medication but structurally different, the effect on the CV system may not be uniform.

Effects of 6 months of voglibose on exercise hemodynamics and exercise capacity

A population-based cohort study exhibited a strong association between incident hypertension and increased visceral rat, especially retroperitoneal fat [31]. These authors speculated that local retroperitoneal fat surrounding the kidneys might be associated with blood pressure elevation over time. Alpha glucosidase inhibitors were reported to lower resting SBP, probably by the modification of lifestyle and visceral fat reduction [32, 33]. We observed a significant reduction in SBP during exercise only in the voglibose group. As body weight was slightly decreased in patients on voglibose after the intervention, we speculate that lifestyle modification along with a possible reduction in local visceral fat might result in favorable antihypertensive effects.

Table 2 Laboratory and echocardiographic data before and after the program

	Voglibose	Sitagliptin	Group effect *p*	Time effect *p*	Interaction effect *p*
SBP, mmHg					
Baseline	139 ± 11	132 ± 20	0.16	0.83	0.54
6 months	140 ± 13	132 ± 15			
Body weight, kg					
Baseline	62.4 ± 13.1	62.4 ± 10.2	0.83	0.93	0.04
6 months	61.4 ± 13.3	63.5 ± 9.8			
Hemoglobin, g/dl					
Baseline	13.6 ± 1.4	13.5 ± 1.2	0.94	0.47	0.85
6 months	13.7 ± 1.7	13.6 ± 1.3			
HbA1c, %					
Baseline	6.6 ± 0.5	6.5 ± 0.4	0.54	0.01	0.33
6 months	6.5 ± 0.4	6.3 ± 0.3*			
BNP, pg/ml					
Baseline	34.3 ± 49.1	48.5 ± 69.7	0.71	0.82	0.32
6 months	37.6 ± 60.6	43.3 ± 73.9			
RH-PAT index					
Baseline	2.0 ± 0.6	1.9 ± 0.5	1.00	0.99	1.00
6 months	1.9 ± 0.6	2.0 ± 0.8			
LV ejection fraction, %					
Baseline	67 ± 7	64 ± 6	0.43	0.36	0.28
6 months	67 ± 6	66 ± 5			
E', cm/s					
Baseline	8.2 ± 2.8	8.1 ± 2.1	0.73	0.84	0.60
6 months	8.5 ± 3.3	7.9 ± 2.4			
E/E' ratio					
Baseline	8.9 ± 4.4	8.8 ± 3.3	0.83	0.70	0.83
6 months	8.8 ± 3.0	8.4 ± 3.1			

* $p < 0.05$ vs. baseline

SBP indicates systolic blood pressure, *BNP* brain natriuretic peptide, *RH-PAT* reactive hyperthermia-peripheral arterial tonometry, *LV* left ventricular, *E'* peak early mitral annular velocity, *E/E' ratio* the ratio of peak early mitral filling velocity-to-peak early mitral annular velocity

Study limitations

There are a few limitations. First, the number of diabetic patients who were enrolled and completed repeat maximal cardiopulmonary testing after the 6 months of intervention was small, and peakVO_2 tended to decline in both groups. However, power analysis showed that the sample size in the present study in the sitagliptin group ($n = 12$, difference − 1.24; SD, 2.57) was sufficient to detect a true difference in the mean change of peakVO_2 of − 2.28 or 2.28 with a probability of type II error at less than 20% (power 0.8). Thus, we could be sure that sitagliptin had no favorable effects on exercise capacity in our patients. However, our observation needs to be tested in a larger population with different baseline glycemic control. Second, we did not measure cardiac output during exercise and no invasive assessment was performed to evaluate LV systolic and diastolic function. Thus, we were not completely sure how the 6-month intervention affect cardiac output and arteriovenous oxygen difference in our patients. While, we assessed LV global function during exercise testing by using peak O_2 pulse as a surrogate for peak stroke volume. The assessment of LV function was difficult and complicated, especially at peak exercise.

Conclusions

In patients with T2DM and CAD, six months of sitagliptin failed to improve LV diastolic function, arterial function and exercise capacity. In addition, sitagliptin had no effects on exercise hemodynamics such as blood pressure, heart rate, or stroke volume estimated noninvasively. Although voglibose exhibited no effects on LV function or exercise capacity, it did lower BP, especially during exercise.

Table 3 Patient characteristics during exercise test before and after the program

	Voglibose	Sitagliptin	Group effect *p*	Time effect *p*	Interaction effect *p*
Peak work load, watt					
Baseline	95 ± 30	111 ± 43	0.35	0.77	0.91
6 months	95 ± 38	110 ± 44			
VO_2 at AT, ml/kg/min					
Baseline	15.4 ± 2.1	15.1 ± 2.7	0.75	0.28	0.22
6 months	15.0 ± 2.0	15.3 ± 2.1			
PeakVO_2, ml/kg/min					
Baseline	22.7 ± 4.8	25.3 ± 7.3	0.38	0.051	0.49
6 months	22.1 ± 5.2	24.0 ± 7.4			
Resting HR, bpm					
Baseline	69 ± 9	67 ± 13	0.82	0.44	0.55
6 months	69 ± 8	69 ± 12			
HR at AT, bpm					
Baseline	103 ± 15	99 ± 17	0.95	0.45	0.32
6 months	100 ± 12	99 ± 13			
Peak HR, bpm					
Baseline	141 ± 19	141 ± 22	1.00	0.13	0.95
6 months	138 ± 23	138 ± 26			
Resting SBP, mmHg					
Baseline	148 ± 19	135 ± 18	0.37	0.43	0.15
6 months	139 ± 20	137 ± 26			
SBP at AT, ml/kg/min					
Baseline	184 ± 22	167 ± 28	0.92	< 0.01	< 0.03
6 months	166 ± 20*	165 ± 31			
Peak SBP, mmHg					
Baseline	206 ± 27	197 ± 32	0.97	0.25	0.02
6 months	194 ± 32*	202 ± 32			
Peak O_2 pulse, ml/ beat					
Baseline	10.1 ± 3.2	11.2 ± 2.8	0.36	0.33	0.65
6 months	9.8 ± 2.9	11.0 ± 3.1			
Peak SBP/O_2 pulse, mmHg·beat/ml					
Baseline	21.4 ± 4.3	18.8 ± 2.8	0.43	0.79	0.11
6 months	20.8 ± 4.5	19.8 ± 6.7			
VE/VCO_2 slope					
Baseline	28.3 ± 3.4.9	28.7 ± 2.7	0.95	0.07	0.14
6 months	30.1 ± 6.0	28.9 ± 2.7			

* $p < 0.05$ vs. baseline

VO_2 indicates oxygen uptake, *AT* anaerobic threshold, *HR* heart rate, *O_2* pulse, oxygen pulse defined as VO_2 divided by heart rate, *VE* minute ventilation, *VCO_2* carbon dioxide production

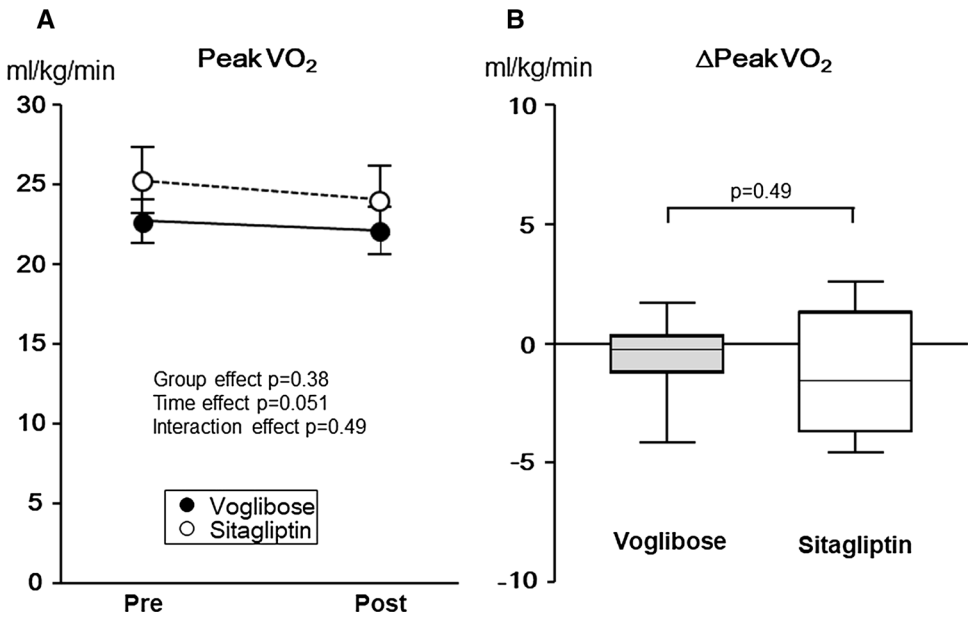

Fig. 2 Changes in peak VO_2 during the program

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Compliance with ethical standards

Conflict of interest Masaaki Ito received departmental research grant support ≥ 1,000,000 yen from Bristol-Myers Squibb K.K., MSD K.K., Shionogi & Co., Ltd., Otsuka Pharma Inc. and Takeda Pharmaceutical Company Limited in 2017. Masaaki Ito received lecture fees ≥ 500,000 yen from Daiichi Sankyo Company Limited, Bayer Holding Ltd. and Takeda Pharmaceutical Company Limited in 2017. Kaoru Dohi received lecture fees ≥ 500,000 yen from Otsuka Pharma Inc. in 2017. The other authors have no conflict of interest.

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