Effects of Dapagliflozin and Sitagliptin on Insulin Resistant and Body Fat Distribution in Newly Diagnosed Type 2 Diabetic Patients

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Data Collection B
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Background: The current study aimed to compare the effects of dapagliflozin and sitagliptin on insulin resistant and body fat distribution in newly diagnosed type 2 diabetic patients.

Material/Methods: This study was an open-label, parallel controlled study. Patients were included if they were newly diagnosed with type 2 diabetes (<6 months) and had been receiving dapagliflozin or sitagliptin for 12 weeks in combination with a stable dose of metformin in the last month. At baseline and 12 weeks, insulin resistant (homeostatic model assessment of insulin resistance [HOMA-IR]), body fat distribution (waist/hip ratio), fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), lipid profiles, and C-reactive protein (CRP) level were compared.

Results: There were 59 patients receiving dapagliflozin and 67 patients receiving sitagliptin. There was no significant between-group difference in baseline characteristics. After 12 weeks of treatment, compared to the sitagliptin group, the FBG (6.4±0.5 versus 6.7±0.7 mmol/L), HbA1c (7.0±0.4 versus 7.2±0.5%), HOMA-IR (1.6±0.5 versus 1.8±0.6), triglyceride (1.6±0.4 versus 1.8±0.3 mmol/L), and CRP (3.1±0.7 versus 3.3±0.5 mg/L) were slightly lower in the dapagliflozin group. Within each group, compared to baseline, FBG (dapagliflozin [6.4±0.5 versus 7.8±0.7 mmol/L]; sitagliptin [6.7±0.7 versus 7.7±0.6 mmol/L]), HbA1c (dapagliflozin [7.0±0.4 versus 8.0±0.5%]; sitagliptin [7.2±0.5 versus 8.1%±0.6%]), HOMA-IR (dapagliflozin [1.6±0.5 versus 2.4±0.4]; sitagliptin [1.8±0.6 versus 2.5±0.4]), triglyceride (dapagliflozin [1.6±0.4 versus 2.2±0.5 mmol/L]; sitagliptin [1.8±0.3 versus 2.1±0.5 mmol/L]), and CRP (dapagliflozin [3.1±0.7 versus 6.2±1.1 mg/L]; sitagliptin [3.3±0.5 versus 6.1±1.0 mg/L]) were significantly decreased.

Conclusions: Dapagliflozin and sitagliptin had comparable effects on improving insulin resistant and blood glucose control, and these benefits may be associated with improvement of systemic inflammation.

MeSH Keywords: Body Fat Distribution • Diabetes Mellitus • Insulin Resistance

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Background

Diabetes mellitus (DM) is a major risk factor for cardiovascular diseases (CVD) around the world including in China [1,2]. In the recent 2 decades, the prevalence and incidence of DM has continuously been increasing owing to the pandemic of obesity globally [3,4]. According to prior reports, only 14% of NHANES (National Health and Nutrition Examination Survey) and BRFSS (Behavioral Risk Factor Surveillance System Survey) individuals with DM achieved targeted HbA1c level, suggesting a huge challenge and great opportunities to improve the management of diabetes [4]. Indeed, better control of diabetes is beneficial for reducing the risk of CVD and mortality.

In recent decades, several novel anti-diabetic medications have been developed and applied for diabetic treatment in clinical practice. Among these novel anti-diabetic medications, sodium-glucose cotransporter-2 (SGLT-2) inhibitor and dipeptidyl peptidase-4 (DPP-4) inhibitor are the ones that are currently widely used [5–9]. Compared to prior anti-diabetic medications (e.g., sulfonylurea), these medications not only effectively reduce blood glucose level, but are also associated with lower risk of hypoglycemia and have reported better clinical outcomes [10,11]. The mechanisms underlying these benefits are likely multifactorial. Prior studies have shown that both SGLT-2 and DPP-4 inhibitors have efficacy on improving insulin resistant in animal diabetic models and human with diabetes [12–15]. However, most of these human studies were conducted in the Caucasian populations, and whether these benefits also existing in the Chinese populations are unknown. In addition, no studies have directly compared the effects of SGLT-2 inhibitor and DPP-inhibitor on insulin resistant and body fat distribution in diabetic patients. Further elucidation is needed as better management of diabetes is associated with lower risk of diabetes-related complication and better cost-effectiveness.

Metformin remains the first-line treatment of diabetes currently, therefore, in the current study, we enrolled newly diagnosed type 2 DM patients who were only treated with metformin and divided these patients into a SGLT-2 inhibitor group or DDP-4 inhibitor group. The aims of the current study were to: 1) compare the effects of SGLT-2 inhibitor and DPP-4 inhibitor on insulin resistant and body fat distribution in newly diagnosed type 2 diabetic patients; 2) analyze the change of glycated HbA1c level after 12 weeks of SGLT-2 inhibitor or DPP-4 inhibitor treatment.

Material and Methods

Participant enrollment and study design

The current study was approved by the Clinical Research Ethic Committee of the Third People's Hospital of Huizhou and written informed consent was obtained before participants' enrollment. This is an open-label, parallel controlled study. Participants were prospectively enrolled. The inclusion criteria were as follow: ≥18 years old; newly diagnosed type 2 DM in the past 6 months; only on metformin treatment in the last 3 months, with a stable dose in the last month; fasting blood glucose (FBG) ≥7 mmol/L or 2 hour postprandial blood glucose ≥10.0 mmol/L for at least 2 times in the past 2 weeks, or HbA1c ≥7.5% in the past 3 months. The exclusion criteria were as follow: type 1 DM; estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2; baseline alanine transaminase (ALT) or aspartate transaminase (AST) level ≥3 upper normal limit; pregnant or nursing women; severe CVD including unstable angina, myocardial infarction, congestive heart failure, ischemic or hemorrhagic stroke in the last 6 months; presence of malignancy disease; systemic rheumatic disease; or treating with corticosteroid. After enrollment, based on the last digit number of the telephone number, participant was divided into SGLT-2 inhibitor (dapagliflozin 10 mg/day) with odd number and DPP-4 inhibitor (sitagliptin 100 mg/day) with even number (Figure 1).

Baseline characteristic collection

Baseline characteristic included age, gender, weight in kilogram and height in meter, which was used to calculate body mass index (BMI, kg/m^2), and obesity was defined as BMI >27 kg/m^2, circumference of waist and hip in centimeter which was used to calculate waist/hip ratio, cigarette smoking history, exercise history, hypertension, dyslipidemia, prior CVD history and current medication used. All these data were extracted from electronic medical record and were collected by 2 independent investigators. In the current analysis, the definition of physical inactivity was based on American Heart Association recommendation, that is, patients who did not follow 30 to 60 minutes of aerobic exercise 3 to 4 times per week would be considered as physical inactivity.

Laboratory parameter assay

At baseline and after 12 weeks of treatment, participants were required to be fasting for 8 hours before venous blood were drawn for laboratory parameter assay. In specific, FBG, HbA1c, lipid profiles, creatinine, and ALT/AST level, as well as insulin, C-peptide and C-reactive protein (CRP) were measured in the core laboratory testing using the standardized methods as prescribed previously [16]. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated based on the formula (Insulin*Glucose=HOMA-IR) as described previously [16]. Herein, the unit of insulin was uIU/mL and the unit of glucose was mg/dL. The healthy rage of HOMA-IR is 1.0 (range 0.5–1.4), and the HOMA-IR value >1.9 indicates early insulin resistant and >2.9 indicates significant insulin resistant. Waist/hip ratio
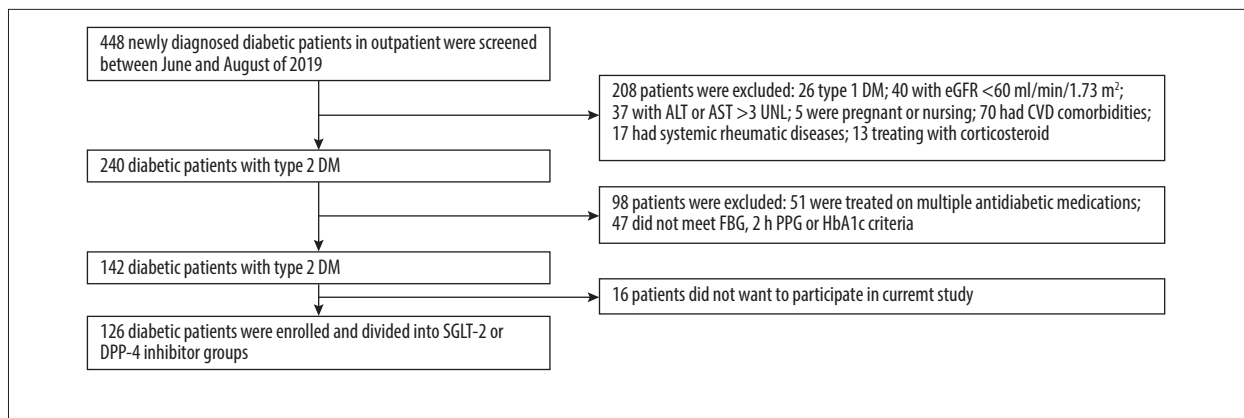
Figure 1. Study flowchart.

was used to evaluate body fat distribution and if waist/hip ratio >0.85 in women and >0.90 in men indicating abdominal obesity per the World Health Organization protocol [17].

Adverse effects reports

In the current study, the adverse effects included rash/allergy, fatigue, dizziness, headache, hypoglycemia, diarrhea, abdominal pain, liver function impairment, and urinary tract infection. All individuals were informed about the potential adverse effects of the medications before enrollment and were required to come to the clinic to confirm the potential adverse effects. All these adverse effects were adjudicated by 2 independent endocrinologists.

Statistical analysis

Due to lack of previous data on comparing the effects of dapagliflozin and sitagliptin on insulin resistant and body fat distribution in newly diagnosed type 2 diabetic patients in China, therefore, in the current analysis, we did not perform sample size calculation. Rather, we used a more pragmatic strategy; we screened all coming patients and then recruited consecutive eligible patients. Continuous variables were presented as mean±standard deviation (SD) and were compared by the Student's *t*-test; and categorical variables were presented by number and proportion and were compared by the chi-square or Fisher exact test. Univariate regression analysis was performed to evaluate factors associated with insulin resistant and abdominal obesity respectively, and factor with *P* value <0.1 were entered into multivariate regression analysis. The associations were reported as odds ratio (OR) and 95% confidence interval (CI). Statistical analysis was computed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). All statistical tests were 2-sided and considered statistically significant when a *P* value <0.05.

Results

A total of 126 newly diagnosed type 2 DM patients were enrolled in the current study and 59 patients were divided into the dapagliflozin group and 67 patients were divided into the sitagliptin group. The mean age of participants was 58.3±9.0 years old and female patients accounted for 44% (n=55). The mean duration of diabetes diagnosis was 5.1±0.6 months.

Baseline characteristics comparisons

As presented in Table 1, the mean age in both groups were 57.1±9.4 and 58.7±9.3 years old, and female patients accounted for 44.1% and 43.3%, respectively. The mean duration of diabetes was 5.0±0.7 and 5.2±0.6 months, and the prevalence of obesity and abdominal obesity was 79.7% versus 79.1% and 59.3% versus 58.2% respectively.

Comparisons of laboratory parameter at baseline and at 12 weeks follow-up

As presented in Table 2, no significant differences in laboratory parameter were observed between these 2 groups at baseline. After 12 weeks of treatment, it was noted that FBG, HbA1c, HOMA-IR, triglyceride, and CRP were slightly lower in the dapagliflozin group than that of the sitagliptin group. However, within each group, compared to baseline, FBG, HbA1c, HOMA-IR, triglyceride, and CRP levels were significantly decreased, strongly indicating that on top of metformin treatment, both dapagliflozin and sitagliptin had similar benefits on improving insulin resistant, triglyceride metabolism, and systemic inflammation. It is noted that no significant change of ALT/AST and creatinine levels were observed in both groups. Change from baseline to follow-up was also compared between both groups and as presented in Table 2, no significant difference in the change was observed.

Table 1. Baseline characteristics comparisons.

Variables	Dapagliflozin+metformin		Sitagliptin+metformin	
n	59		67	
Age (years)	57.1±9.4		58.7±9.3	
Female, n (%)	26	(44.1)	29	(43.3)
BMI, kg/m²	28.6±5.7		28.2±5.3	
Obesity, n (%)	47	(79.7)	53	(79.1)
Waist/hip ratio	0.88±0.14		0.87±0.13	
Abdominal obesity, n (%)	35	(59.3)	39	(58.2)
Current smoking, n (%)	32	(54.2)	36	(53.7)
Duration of diabetes (months)	5.0±0.7		5.2±0.6	
Physical inactivity, n (%)	42	(71.2)	48	(71.6)
Hypertension, n (%)	49	(83.1)	57	(85.1)
Dyslipidemia, n (%)	46	(78.0)	52	(77.6)
Prior CVD history, n (%)	12	(20.3)	14	(20.9)
Aspirin, n (%)	24	(40.6)	29	(43.2)
Statins, n (%)	31	(52.5)	36	(53.7)
Diuretic, n (%)	4	(6.8)	5	(7.5)
Anti-hypertensive medications, n (%)	29	(49.2)	32	(47.8)
Metformin dose				
500 mg/bid, n (%)	31	(52.5)	35	(52.2)
1000 mg/bid, n (%)	28	(47.5)	32	(47.8)

BMI – body mass index; CVD – cardiovascular disease; bid – twice daily.

Factors associated with insulin resistant and abdominal obesity

As presented in Table 3, in the univariate regression analysis, increased age, BMI, waist/hip ratio, and CRP level were associated with increased odds of insulin resistant, and use of dapagliflozin versus sitagliptin was associated with lower odds of insulin resistant. After multivariate regression analyses, increased age (OR 1.10 and 95% CI 1.0–31.32), waist/hip ratio (OR 1.24 and 95% CI 1.13–1.55), and CRP level (OR 1.15 and 95% CI 1.04–1.30) were still associated with increased odds of insulin resistant; while the association of dapagliflozin and lower odds of insulin resistant was attenuated to statistical insignificance (OR 0.97 and 95% CI 0.89–1.03).

As presented in Table 4, in the univariate regression analysis, increased BMI, CRP level, and HOMA-IR were associated with increased odds of abdominal obesity, and use of dapagliflozin versus sitagliptin was associated with lower odds of abdominal obesity. After multivariate regression analysis, increased BMI (OR 1.12 and 95% CI 1.01–1.31), CRP level (OR 1.24 and 95% CI 1.08–1.44), and HOMA-IR (OR 1.41 and 95% CI 1.26–1.73) were still associated with increased waist/hip ratio.

Comparisons of adverse effects

The rate of adverse effects was low in both the dapagliflozin group and the sitagliptin group and there were no significant between-group differences in the adverse effects observed. It was noted that urinary tract infection was most common in the dapagliflozin group (6.8%), and diarrhea was most common in the sitagliptin group (4.5%).

Discussion

To our knowledge, this is the first study to evaluate the effects of dapagliflozin and sitagliptin on insulin resistant and body fat distribution in newly diagnosed type 2 diabetic patients. There were 3 main findings of the current study: 1) on top of metformin therapy, the effects of dapagliflozin and sitagliptin on insulin resistant and body fat distribution were comparable; 2) both dapagliflozin and sitagliptin had similar efficacy on blood glucose control.

Diabetes is a leading cause of morbidity and mortality around the world. Diabetic patients are characterized by metabolic

Table 2. Change and comparison laboratory parameter.

Variables	Baseline	12 weeks follow-up	Change
FBG (mmol/L)			
Dapagliflozin+metformin	7.8±0.7	6.4±0.5*	1.3±0.4
Sitagliptin+metformin	7.7±0.6	6.7±0.7#	1.0±0.5
HbA1c (%)			
Dapagliflozin+metformin	8.0±0.5	7.0±0.4*	1.0±0.3
Sitagliptin+metformin	8.1±0.6	7.2±0.5#	0.9±0.2
HOMA-IR			
Dapagliflozin+metformin	2.4±0.4	1.6±0.5*	0.8±0.3
Sitagliptin+metformin	2.5±0.4	1.8±0.6#	0.7±0.3
Waist/hip ratio			
Dapagliflozin+metformin	0.88±0.14	0.84±0.14	0.04±0.01
Sitagliptin+metformin	0.87±0.13	0.85±0.15	0.02±0.01
Total cholesterol (mmol/L)			
Dapagliflozin+metformin	5.1±0.4	5.0±0.5	0.1±0.1
Sitagliptin+metformin	5.2±0.5	5.0±0.4	0.2±0.1
Triglyceride (mmol/L)			
Dapagliflozin+metformin	2.2±0.5	1.6±0.4*	0.6±0.3
Sitagliptin+metformin	2.1±0.5	1.8±0.3#	0.4±0.2
ALT (U/L)			
Dapagliflozin+metformin	32±15	36±16	−6±2
Sitagliptin+metformin	34±14	38±15	−4±2
AST (U/L)			
Dapagliflozin+metformin	34±14	37±15	−3±1
Sitagliptin+metformin	35±13	38±14	−3±2
Creatinine (umol/L)			
Dapagliflozin+metformin	1.0±0.3	1.0±0.4	0.1±0.1
Sitagliptin+metformin	1.1±0.4	1.1±0.4	0.1±0.1
C-reactive protein (mg/L)			
Dapagliflozin+metformin	6.2±1.1	3.1±0.7*	3.0±0.5
Sitagliptin+metformin	6.1±1.0	3.3±0.5#	2.8±0.3

FBG – fasting blood glucose; HbA1c – glycated hemoglobin A1c; HOMA-IR – homeostatic model assessment of insulin resistance;
ALT – alanine transaminase; AST – aspartate transaminase; Change – variable values from baseline to 12 weeks follow-up;
* $P<0.05$ versus baseline in dapagliflozin+metformin group; # $P<0.05$ versus sitagliptin+metformin group.

disorders including insulin resistant, abdominal obesity, dyslipidemia, and systemic inflammation [18–20]. Notably, metformin improves insulin resistant and has a good safety profile, rendering it as the first-line treatment for diabetes. In the past decades, several novel anti-diabetic medications have been tested in diabetic animal models and in diabetic patients. For example, Aschner et al. reported that compared to placebo, 24-weeks of sitagliptin monotherapy improved

glycemic control and β-cell function [12]. Compared to placebo, 12-weeks of vildagliptin monotherapy was also associated with better improvement of glycemic control and insulin resistant [21]. However, whether a DPP-4 inhibitor would improve body fat distribution in newly diagnosed type 2 diabetic patients was unclear. In a small sample size study (n=18), Merovci et al. reported that 2 weeks of dapagliflozin therapy improved muscle insulin resistant when compared to the

Table 3. Factors associated with insulin resistant.

	OR and 95% CI		OR and 95% CI	
	Univariate analysis	P value	Multivariate analysis	P value
Age (per 10 years increase)	1.28 (1.17–1.54)	<0.001	1.10 (1.03–1.32)	0.03
Gender (Female *vs.* Male)	1.06 (0.94–1.20)	0.17	NA	
BMI (per 5 kg/m² increase)	1.20 (1.07–1.33)	0.03	1.08 (0.97–1.11)	0.14
Waist/hip ratio (per 0.1 increase)	1.57 (1.36–1.92)	<0.001	1.24 (1.13–1.55)	0.008
Smoking (yes *vs.* no)	1.02 (0.89–1.12)	0.33	NA	
Physical inactivity (yes *vs.* no)	1.09 (0.97–1.24)	0.08	1.01 (0.92–1.06)	0.36
Hypertension (yes *vs.* no)	1.04 (0.91–1.17)	0.25	NA	
Dyslipidemia (yes *vs.* no)	1.11 (0.99–1.32)	0.06	1.03 (0.94–1.10)	0.21
Prior CVD history (yes *vs.* no)	1.01 (0.82–1.07)	0.46	NA	
Statin (yes *vs.* no)	0.92 (0.87–1.06)	0.09	0.94 (0.88–1.03)	0.19
Diuretic (yes *vs.* no)	1.05 (0.90–1.11)	0.14	NA	
Dapagliflozin *vs.* sitagliptin	0.94 (0.85–0.99)	0.04	0.97 (0.89–1.03)	0.11
CRP (per 1 mg/L increase)	1.31 (1.16–1.69)	<0.001	1.15 (1.04–1.30)	0.02

OR – odds ratio; CI – confidence interval; BMI – body mass index; CVD – cardiovascular disease; CRP – C-reactive protein.

Table 4. Factors associated with abdominal obesity.

	OR and 95% CI		OR and 95% CI	
	Univariate analysis	P value	Multivariate analysis	P value
Age (per 10 years increase)	1.07 (0.96–1.24)	0.09	1.01 (0.90–1.18)	0.22
Gender (Female *vs.* Male)	0.96 (0.90–1.07)	0.23	NA	
BMI (per 5 kg/m² increase)	1.29 (1.08–1.54)	0.01	1.12 (1.01–1.31)	0.04
Smoking (yes *vs.* no)	1.03 (0.90–1.14)	0.47	NA	
Physical inactivity (yes *vs.* no)	1.19 (1.08–1.37)	0.04	1.08 (0.98–1.16)	0.31
Hypertension (yes *vs.* no)	1.01 (0.93–1.10)	0.63	NA	
Dyslipidemia (yes *vs.* no)	1.13 (1.02–1.38)	0.03	1.06 (0.95–1.18)	0.18
Prior CVD history (yes *vs.* no)	1.04 (0.86–1.10)	0.35	NA	
Statin (yes *vs.* no)	0.90 (0.82–1.03)	0.08	0.95 (0.89–1.09)	0.11
Diuretic (yes *vs.* no)	1.05 (0.93–1.14)	0.17	NA	
Dapagliflozin *vs.* sitagliptin	0.92 (0.82–0.97)	0.02	0.96 (0.87–1.04)	0.25
CRP (per 1 mg/L increase)	1.40 (1.19–1.78)	<0.001	1.24 (1.08–1.44)	0.02
HOMA-IR (per 0.5 increase)	1.59 (1.33–1.94)	<0.001	1.41 (1.26–1.73)	0.01

OR – odds ratio; CI – confidence interval; BMI – body mass index; CVD – cardiovascular disease; CRP – C-reactive protein; HOMA-IR – homeostatic model assessment of insulin resistance.

placebo [16]. In the animal models, Han et al. also found that dapagliflozin not only improved glucose homeostasis in diabetic rats but also in normal rats [22]. Consistent to prior reports, our results demonstrated that compared to baseline, 12 weeks of dapagliflozin and sitagliptin treatment were associated with improved blood glucose control, which might be due to improvement of insulin resistant. Extending findings from prior reports, our results also show that both dapagliflozin and

sitagliptin slightly improved body fat distribution as reflected by decreased waist/hip ratio, although these differences did not achieve statistical significance. In addition, the triglyceride level was also reduced, which might be associated with improvement of insulin resistant. Amelioration of systemic inflammation as reflected by decreased serum CRP level after 12 weeks of dapagliflozin and sitagliptin treatment were also observed in our study. Indeed, prior experimental studies have demonstrated that both SLGT-2 inhibitor and DPP-4 inhibitor can activate the PI3K/AKT/eNOS signaling pathway, which in turn can improve endothelial function and inhibit inflammatory cells migration and activation [23].

Both SGLT-2 inhibitor and DPP-4 inhibitor have been broadly used in clinical practice, therefore it is clinically relevant to compare the effects of both these medications on insulin resistant and body fat distribution. Interestingly and importantly, we observed that after 12 weeks of treatment, FBG, HbA1c, triglyceride, and CRP levels and HOMA-IR were slightly lower in the dapagliflozin treatment group versus the sitagliptin treatment group. We noted that in the univariate regression analysis, compared to sitagliptin treatment, dapagliflozin treatment was associated with lower odds of insulin resistant and abdominal obesity. After adjusted for other potential covariates, this association was attenuated to statistical insignificance. However, these preliminary findings indicated that dapagliflozin might be superior to sitagliptin in improving insulin resistant and abdominal obesity in newly diagnosed type 2 diabetic patients. Further studies are needed to corroborate our preliminary findings. The current study did not observe any significant differences in adverse effects of dapagliflozin and sitagliptin treatment when combined with metformin treatment, suggesting a safe profile of these medications in newly diagnosed type 2 diabetic patients. The clinical implications of our findings were that in patients with newly diagnosed type 2 diabetes, initiating dapagliflozin or sitagliptin treatment may help to improve insulin resistant and body fat distribution in a short-term period. Based on our preliminary findings, future research direction should be focused on: 1) whether long-term use of dapagliflozin treatment would be superior to sitagliptin treatment; 2) whether these 2 novel anti-diabetic medications can prevent macro- and micro-cardiovascular events in newly-diagnosed type diabetic patients; and 3) the underlying mechanism such as improvement of systemic inflammation should also be assessed.

There were some limitations to our current study. First, this was a single center and open-label study, therefore, no causal-relationship could be drawn, and potential selection biases might exist due to the non-randomized design. Second, participants enrolled in our current analysis were newly diagnosed with type 2 DM and whether these findings can be extrapolated to long-term diabetic patients is unknown. Third, no statistically significant difference between dapagliflozin and sitagliptin treatment were observed, which might be due to the relatively small sample size. Further studies with more participants are needed to elucidate whether there is difference in efficacy of insulin resistant and abdominal obesity improvement between these 2 medications.

Conclusions

In conclusion, the current study, for the first time, shows that in combination with metformin, dapagliflozin and sitagliptin have comparable effects on improving insulin resistant and blood glucose control.

Conflict of interest

None.

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