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Effects of 6 Months of Dapagliflozin Treatment on Metabolic Profile and Endothelial Cell Dysfunction for Obese Type 2 Diabetes Mellitus Patients without Atherosclerotic Cardiovascular Disease

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Background: Sodium-glucose cotransporter 2 inhibitors reduce the risk of cardiovascular death in individuals with type 2 diabetes mellitus (T2DM) and cardiovascular disease, but the effect of these inhibitors on early cardiovascular disease remains unknown. This study evaluated the effect of dapagliflozin on the metabolic profiles and endothelial cell function in obese patients with T2DM without established cardiovascular disease.

Methods: We enrolled 140 patients with a mean age, weight, and body mass index (BMI) of 47 years, 83 kg, and 30.3 kg/m^2, respectively. Dapagliflozin (10 mg daily for 6 months) was administered to obese patients with T2DM without established cardiovascular disease. Participants' weight, BMI, body fat mass (BFM), muscle mass, glycosylated hemoglobin (HbA1c), lipid profile, waist to hip ratio (WHR), and pulse wave velocity (PWV) were measured at baseline and after 6 months.

Results: Participants experienced statistically significant reductions in their HbA1c, fasting plasma glucose, low-density lipoprotein cholesterol, total cholesterol, body weight, BMI, WHR, BFM, and aortic PWV, without a significant change in their muscle mass, extracellular fluid, or intracellular volume. Statistically significant reductions in aortic PWV were associated with a decrease in BFM, visceral fat, WHR, and homeostatic model assessment of insulin resistance.

Conclusion: Dapagliflozin may be beneficial in preventing early cardiovascular disease in obese patients with T2DM without established cardiovascular disease.

Key words: Sodium-glucose transporter 2 inhibitors, Body composition, Pulse wave velocity

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) patients are at a high risk for cardiovascular diseases. Atherosclerotic cardiovascular disease (ASCVD) is the major cause of morbidity and mortality in T2DM patients.[1] Although diabetes poses a substantial independent risk for ASCVD, most people with T2DM have numerous additional risk factors for ASCVD such as hypertension, dyslipidemia, obesity, chronic kidney disease, and smoking.[2] Body mass index (BMI) is a known predictor of all-cause mortality. A population-based cohort study of 3.6 million adults in the United Kingdom showed that life expectancy from 40 years of age was 4.2 years shorter in obese men (BMI ≥ 30.0 kg/m^2) and 3.5 years shorter in obese women (BMI ≥ 30.0 kg/m^2) than in individuals with a healthy weight (BMI, 18.5–24.9 kg/m^2).[3] Patients with T2DM who are overweight or have a high BMI have an increased risk of cardiovas-

cular disease and all-cause mortality.[4] The Look AHEAD (Action for Health in Diabetes) trial failed to show that lifestyle management alone reduces cardiovascular events in patients with T2DM.[5] Thus, medications associated with weight loss and other beneficial effects are recommended for patients with T2DM and a BMI > 27 kg/m^2.[4] Metabolic abnormalities such as hyperglycemia, excess free fatty acids, inflammation, and insulin resistance can lead to the suppression of nitric oxide production and activation of the renin-angiotensin-aldosterone system. This leads to oxidative stress and endothelial dysfunction that contribute to the development of cardiovascular diseases.[6] Endothelial dysfunction promotes the development of hypertension, contributing to cardiovascular damage. This may lead to increased arterial stiffness, related vascular calcification, or collagen accumulation.[7] Arterial stiffness, which can be assessed by measuring pulse pressure, is a powerful predictor of early cardiovascular disease.[8] Notably, early treatment of endothelial dysfunction can reverse the condition. Therefore, early treatment is crucial.

Cardiovascular disease is the main cause of mortality among patients with T2DM. Although strict glycemic control can reduce microvascular complications, the effect of glycemic control on macrovascular complications remains controversial.[9-12] The EMPA-REG OUTCOME study showed that empagliflozin, an inhibitor of sodium-glucose cotransporter 2 (SGLT-2), reduced the rate of primary composite cardiovascular outcomes among patients with T2DM who have a history of ASCVD.[13] Randomized controlled studies such as CANVAS-R and DECLARE showed some secondary preventative effects of SGLT-2 inhibitors in reducing the risk of myocardial infarction recurrence, cardiovascular death, and all-cause death in T2DM patients with a history of ASCVD.[14,15] However, limited data are available to verify whether any of the SGLT-2 inhibitors have a primary preventative effect on early cardiovascular disease in patients with T2DM who have no history of ASCVD. Further studies are needed to evaluate the primary preventative effects of SGLT-2 inhibitors.

Dapagliflozin is an oral selective SGLT-2 inhibitor. Since SGLT-2 is found exclusively in the proximal tubule of the kidney, the mode of action of dapagliflozin involves blocking glucose and sodium reabsorption. Dapagliflozin may affect blood glucose control, blood pressure, and body weight (BW), all of which are cardiovascular disease risk factors. Dapagliflozin induces glucose excretion in the urine and has been reported to induce weight loss by increasing calorie loss and reducing blood pressure through diuretic action. Many clinical trials have shown that SGLT-2 inhibitors reduce cardiovascular death in patients with both diabetes mellitus and cardiovascular disease. However, there is little evidence to demonstrate that SGLT-2 inhibitors affect body composition and systemic vascular function in obese T2DM patients with no established cardiovascular disease. The present study aimed to evaluate whether the short-term use of SGLT-2 inhibitors improves endothelial dysfunction, aortic stiffness, metabolic profile, and glycemic control in obese T2DM patients with no previous history of established cardiovascular disease.

METHODS

In this 6-month retrospective clinical study, T2DM patients without established cardiovascular disease were recruited from the diabetes outpatient clinic. All patients were treated with metformin. The groups were: the dapagliflozin group (receiving 10 mg daily) and the metformin group (1,000 mg). This study was approved by the Institutional Review Board of Konyang University Medical Center (IRB No. 2020 01 007). Owing to the retrospective design, the requirement for informed consent was waived.

Patients and treatment protocol

For inclusion in the study, patients needed to have a confirmed T2DM diagnosis and be between 30 and 65 years of age. Exclusion criteria included diagnosed heart failure, coronary heart disease, cerebrovascular disease, acute inflammation, infection (pneumonia, urinary tract infection and DM foot), hepatitis, malignancy, type 1 DM, kidney (estimated glomerular filtration rate below 60 mL/min/1.73 m^2) or liver failure or BMI below 25 kg/m^2.

Patients with T2DM and without established cardiovascular disease were recruited from the Diabetes Center at Konyang University Hospital. Participants with a BMI ≥ 25 kg/m^2 were treated with a combination of dapagliflozin and metformin. Dapagliflozin (10 mg) was administered to patients with T2DM daily for 6 months.

Data collection

Height (cm), BW (kg), and waist circumference (WC; cm)

were measured; BMI was calculated by dividing weight (kg) by height squared (m^2). WC was measured midway between the lowest rib and iliac crest while the subjects were standing. To determine factors contributing to BW and BMI, skeletal muscle mass (kg, %) and body fat mass (kg, %) were estimated using bioelectrical impedance values measured with the Inbody 720 (Biospace, Seoul, Korea). The participants were instructed to stand upright and grasp the handles of the analyzer, placing both palms, thumbs, and the anterior and posterior aspects of the soles of their feet in contact with the electrodes. Impedance values were measured at frequencies of 1, 5, 20, 50, 500, and 1,000 Hz.

Blood samples were collected to measure metabolic and biochemical parameters after fasting overnight for 8–10 hours. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using the Hitachi 747 chemistry analyzer (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula. Glycosylated hemoglobin (HbA1c) was measured using high performance liquid chromatography.

Pulse wave velocity (PWV), an indicator of arterial stiffness, was measured using a pulse wave unit (PP-1000; Hanbyul Meditech, Jeonju, Korea) with the participants resting in a supine position. Six signals were collected from electrocardiograph, phonocardiograph and pressure sensors strapped to four different arterial sites (carotid, radial, femoral, and dorsalis pedis). Patients waited approximately 10 seconds for the recording of pulse waves. Pressure pulse waves were measured using a pressure sensor in combination with a traveling wave and the reflected wave that passes along the artery wall. Brachial-ankle PWV and carotid-femoral PWV offer the simplest, most reproducible and noninvasive evaluation of regional stiffness. In this study, PWV was calculated as the mean of the left and right values, corresponding to the brachial-ankle PWV and carotid-femoral PWV.

Statistical analysis

Statistical analyses were conducted using R version 3.2 (R Foundation, Vienna, Austria), and a Cronbach's alpha value of $P < 0.05$ was considered statistically significant. Clinical and anthropometric data are expressed as the mean and standard deviation. The values at baseline and after 6 months of treatment were compared using paired t-tests. To evaluate the PWV aorta factors, we used linear regression analysis.

Table 1. Characteristics of study subjects (n = 140) with obesity and type 2 diabetes mellitus at baseline

Characteristics	Mean ± SD
Age (yr)	47.0 ± 10.6
Diabetes mellitus duration (yr)	6.0 ± 3.1
Weight (kg)	83.01 ± 16.42
Body mass index (kg/m²)	30.26 ± 4.69
Percent body fat (%)	36.75 ± 7.56
WHR	0.96 ± 0.05
Skeletal muscle mass (kg)	28.95 ± 6.31
Body fat mass (kg)	31.09 ± 9.90
HbA1c (%)	7.56 ± 1.25
Fasting blood glucose (mg/dL)	152.87 ± 57.27
Microalbuminuria (mg/dL)	108.73 ± 49.21
eGFR (mL/min/1.73 m²)	102.21 ± 15.41

SD, standard deviation; WHR, waist to hip ratio; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate.

RESULTS

Baseline characteristics

The demographic characteristics and baseline metabolic parameters of the 140 study subjects are shown in Table 1. The mean age of the subjects was 47.0 ± 10.6 years, and the mean duration of diabetes was 6.0 ± 3.1 years, with a mean HbA1c of 7.56% ± 1.25%.

Effects of 6 months of dapagliflozin treatment on glycemic values and metabolic profiles

After 6 months of dapagliflozin treatment, HbA1c levels significantly decreased from 7.56% ± 1.25% at baseline to 7.14% ± 1.02% at 6 months ($P < 0.01$). FPG levels also decreased ($P < 0.01$) (Table 2). There were significant decreases in the levels of TC and LDL-C, but levels of TG and HDL-C did not significantly change.

There was also a significant decrease in BMI from 30.3 ± 4.7 kg/m^2 to 29.1 ± 4.7 kg/m^2 ($P < 0.001$), and mean BW significantly decreased by 3.3 kg ($P < 0.01$). After 6 months of dapagliflozin treatment, body fat percentage and body fat mass also decreased significantly from 36.76% ± 7.56% to 35.12% ± 7.19% ($P < 0.001$) and from 31.09 ± 9.90 kg to 28.31 ± 9.91 kg ($P < 0.001$), respectively, without any reduction in muscle mass. There was also a significant improvement in the waist to hip ratio (WHR; $P < 0.001$) (Table 3).

Table 2. Changes in glycemic values and blood chemistry findings after 6 months of dapagliflozin treatment

Variable	Baseline	After 6 months	*P**
HbA1c (%)	7.56 ± 1.25	7.14 ± 1.02	0.001
FPG (mg/dL)	152.87 ± 57.27	134.97 ± 34.55	0.001
TC (mg/dL)	167.25 ± 46.16	157.04 ± 38.06	0.013
TG (mg/dL)	165.05 ± 67.63	151.99 ± 80.02	0.092
LDL-C (mg/dL)	112.27 ± 40.41	103.39 ± 34.66	0.019
AST (mg/dL)	29.76 ± 15.01	26.57 ± 13.49	0.013
ALT (mg/dL)	33.37 ± 21.85	29.59 ± 20.31	0.091
BUN (mg/dL)	14.66 ± 4.54	16.34 ± 4.63	0.001
Cr (mg/dL)	0.77 ± 0.19	0.77 ± 0.20	0.792
eGFR (mL/min/1.73 m^2)	102.21 ± 15.41	102.07 ± 16.15	0.858
C-peptide (ng/mL)	3.06 ± 1.67	2.72 ± 1.27	0.019
Microalbuminuria (mg/dL)	108.73 ± 49.21	60.04 ± 24.24	0.001

Values are presented as mean ± standard deviation.
*Comparison between baseline and 6 months using paired t-tests.
HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate.

Comparison between body-fat-lost and body-fat-gained groups and effects of 6 months of dapagliflozin treatment on vascular variables in the body-fat-lost group (n=80)

After 6 months of treatment with dapagliflozin, an improvement in arterial stiffness was observed along with a reduction in BW. We also investigated the difference between arterial stiffness, regional fat distribution and insulin resistance according to body fat changes. PWV, body fat mass, and homeostatic model assessment of insulin resistance scores were analyzed by dividing participants into two groups based on body fat changes after 6 months of dapagliflozin treatment: those who lost body fat (n = 80) and those who gained body fat (n = 20). Significant improvements were shown for aortic PWV, regional fat distribution, and insulin resistance in the group that lost body fat ($P < 0.01$). However, there was no significant relation between a reduction in aortic PWV and body fat mass or insulin resistance in the body-fat-gained group. Re-analysis according to BMI showed the same result.

Among the study participants, aortic PWV significantly improved from 7.33 ± 1.48 m/sec at baseline to 6.76 ± 1.51 m/sec after 6 months of treatment ($P < 0.01$) in only the BW reduction group. However, there was no significant improvement in PWV in the extremities (PWV ext) and PWV aorta (Table 4).

Table 3. Changes in body composition and endothelial cell function after 6 months of dapagliflozin treatment

Variable	Baseline	After 6 months	*P**
Weight (kg)	83.01 ± 16.42	79.70 ± 16.13	< 0.001
BMI (kg/m^2)	30.26 ± 4.69	29.05 ± 4.72	< 0.001
Percent body fat (%)	36.75 ± 7.56	35.12 ± 7.19	< 0.001
Body fat mass (kg)	31.09 ± 9.90	28.31 ± 9.91	< 0.001
Muscle mass (kg)	28.95 ± 6.31	28.57 ± 6.04	0.065
WHR	0.96 ± 0.05	0.94 ± 0.05	< 0.001
ICW (L)	23.59 ± 5.11	23.55 ± 4.77	0.856
ECW (L)	14.67 ± 2.90	14.56 ± 2.88	0.399
BMR	1,489.20 ± 286.06	1,497 ± 233.28	0.641
PWV ext (m/sec)	7.39 ± 1.47	7.44 ± 1.55	0.850
PWV aorta (m/sec)	7.36 ± 1.58	6.74 ± 1.52	< 0.001

Values are presented as mean ± standard deviation.
*Comparison between baseline and 6 months using paired t-tests.
BMI, body mass index; WHR, waist to hip ratio; ICW, intracellular water; ECW, extracellular water; BMR, basal metabolic rate; PWV, pulse wave velocity; PWV ext, PWV in the extremities.

Association between PWV aorta and metabolic parameters

The association between PWV aorta and metabolic parameters are in Table 5. PWV aorta is significantly dependent on BW, body fat mass and WHR and slightly, but not significantly, dependent on BMI. This association is not significantly dependent on PWV ext.

DISCUSSION

Our study findings show the effects of dapagliflozin in reducing cardiovascular disease risk in obese T2DM patients with no history of cardiovascular disease. This 6-month trial of patients with T2DM who did not develop cardiovascular disease showed that daily oral dapagliflozin treatment reduced arterial stiffness and improved metabolic profiles as well as glycemic control. Over the duration of our clinical trial, dapagliflozin significantly reduced HbA1c by a mean absolute amount of 0.42 (data not shown).

Obesity is associated with hypertension, dyslipidemia, and cardiovascular disease as well as DM. Studies have shown a sustained reduction in cardiovascular risk when obese adults maintained weight loss of 10%–15%.[16] Among obese patients with T2DM, sustained weight loss has also been shown to improve glycemic control. However, several classes of anti-hyperglycemic agents are associated with weight gain or no change in weight. Therefore, weight loss medications are considered effective adjuncts to life-

Table 4. A statistical comparison between groups (reduction in body fat vs. no reduction in body fat) according to body fat change after 6 months of dapagliflozin treatment

Variable	Reduction in body fat group (n=80)			No reduction in body fat group (n=20)		
	Baseline	After 6 months	*P**	Baseline	After 6 months	*P**
HbA1c (%)	7.59±1.17	7.2±1.1	0.001	7.89±1.90	7.3±0.72	0.126
FPG (mg/dL)	154.14±50.15	136.21±36.38	0.001	155.0.83±50.62	132.22±25.41	0.518
TG (mg/dL)	167.21±71.05	145.31±69.30	0.008	157.22±55.92	212.52±143.02	0.218
TC (mg/dL)	166.66±46.73	156.79±39.51	0.033	166.55±38.85	157.11±38.85	0.499
LDL-C (mg/dL)	111.52±41.01	102.82±34.50	0.040	111.90±31.72	110.92±45.42	0.071
Weight (kg)	81.99±15.73	78.21±15.12	0.000	91.01±20.17	91.44±19.43	0.443
BMI (kg/m^2)	30.02±4.22	28.63±4.12	0.000	32.42±7.19	0.079±7.15	0.303
WHR	0.96±0.04	0.94±0.05	0.000	0.96±0.06	0.957±0.065	0.635
Muscle mass (kg)	28.63±6.24	28.19±5.98	0.051	31.04±6.99	30.61±6.24	0.051
Body fat mass (kg)	30.56±9.17	27.24±8.76	0.000	30.56±9.17	27.24±8.76	0.180
HOMA-IR	2.65±1.29	2.29±1.26	0.008	1.84±0.85	2.08±0.65	0.460
PWV ext (m/sec)	7.38±1.48	7.48±1.52	0.703	7.65±1.52	7.21±1.89	0.698
PWV aorta (m/sec)	7.33±1.48	6.76±1.51	0.000	7.51±1.59	6.27±1.59	0.079

Values are presented as mean±standard deviation.
*Comparison between baseline and 6 months using by paired t-tests.
HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist to hip ratio; HOMA-IR, homeostatic model assessment of insulin resistance; PWV, pulse wave velocity; PWV ext, PWV in the extremities.

Table 5. Linear regression analysis (results) evaluating independent factors of changes in arterial stiffness

Variable	Change of PWV aorta	*P*	Change of PWV ext	*P*
	Coefficient		Coefficient	
ΔHbA1c (%)	0.12	0.511	–0.35	0.780
ΔFPG (mg/dL)	0.035	0.780	–0.021	0.518
ΔTG (mg/dL)	–0.472	0.632	0.052	0.218
ΔTC (mg/dL)	–0.282	0.062	0.052	0.499
ΔLDL-C (mg/dL)	0.230	0.193	0.60	0.071
ΔWeight (kg)	0.035	0.041	0.039	0.061
ΔBMI (kg/m^2)	0.032	0.052	0.023	0.303
ΔWHR	0.15	0.05	0.021	0.635
ΔMuscle mass (kg)	0.103	0.476	–0.034	0.872
ΔBody fat mass (kg)	0.393	0.044	0.046	0.071
ΔHOMA-IR	0.021	0.038	0.012	0.460

PWV, pulse wave velocity; PWV ext, PWV in the extremities; Δ, delta value; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist to hip ratio; HOMA-IR, homeostatic model assessment of insulin resistance.

style modifications in obese patients with T2DM.[4]

To maintain healthy conditions while losing weight and reducing body fat, especially visceral fat, improving the metabolic profile such as blood glucose levels, blood pressure, and endothelial cell function is important.[17] SGLT-2 inhibitors are a class of glucose-lowering drugs with proven efficacy for lowering the risk of cardiovascular events in patients with T2DM. In a large-scale pooled analysis assessing the effects of SGLT-2 inhibitors on cardiovascular outcomes, there was an improvement in MACE (the composite of cardiovascular death, myocardial infarction, or stroke) among patients with previous ASCVD.[13] However, the mechanism of action for the reduction in cardiovascular outcomes is not fully understood. One suggestion is that suppression of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, and improvement in nitric oxide bioactivity could explain this cardiovascular protection.[18] However, some studies have shown that these neurohormonal pathways remain unchanged in response to SGLT-2 inhibitors.[18-20] Therefore, we suggest that a decrease in arterial stiffness with dapagliflozin plays a crucial role in explaining its cardiovascular benefit. Weight loss independently reduces arterial stiffness.[21] Aortic stiffness is associated with visceral adiposity, a key driver of cardiometabolic risk. Increased WC and TG levels are predictors of excess visceral adiposity. Several studies have explored positive relationships between PWV and WC; these are indicators of visceral fat, as well as WHR. Dapagliflozin was associated with a significant reduction in weight (an average loss of 3.8 kg) in our study. Since WC and WHR were also significantly reduced, this reduction in weight was probably due to central fat loss. As the result, significant improvements were shown for only aortic PWV, not PWV ext, so we supposed that the weight loss effect by SGLT-2 inhibitors is due to the fat loss effect rather than the muscle. This is more specific in abdominal fat and appears as a decrease in the cir-

cumference of the abdomen, improving the elasticity of the abdominal aorta. Thus, we speculated that dapagliflozin might be beneficial in preventing early CVD in obese subjects with T2DM without established CVD.

To evaluate other factors that can explain the cause of weight loss, we analyzed extracellular and intracellular fluid volume (extracellular fluid and intracellular fluid, respectively) because dapagliflozin affects osmotic diuresis. There were no changes in ECF and ICF volumes. With dapagliflozin treatment, body fat loss occurred without a reduction in skeletal muscle mass. This is important in T2DM patients with obesity because muscle mass is typically reduced while ectopic fat mass increases. Skeletal muscle plays an important role in maintaining systemic glucose metabolism. Loss of muscle may lead to a reduced response to insulin in target tissues, resulting in insulin resistance and metabolic syndrome. Research has shown an association between the highest portion of the skeletal muscle index (ratio of total skeletal muscle mass to total BW) with improved insulin resistance and decreased risk of transitional or overt diabetes.[22] Insulin sensitivity is determined by body fat distribution; those with a more peripheral distribution have more insulin sensitivity than those whose fat distribution is more central.[23] WHR is a marker of insulin resistance.[24] Visceral adipocytes have elevated lipolytic activity; this results in increased free fatty acid release in the portal vein with an accumulation in the liver and muscles, contributing to insulin resistance.[25] In this study, the weight loss group showed significant improvements in insulin resistance according to HOMA as compared with the weight gain group.

A series of studies have also demonstrated a positive relationship between the amount of visceral fat and PWV.[26] Aortic PWV is a predictor of cardiovascular disease. Cardiovascular events and all-cause mortality are greater in patients with high aortic PWV than in those with low aortic PWV.[8] Several studies also show evidence that increased PWV indicates adverse macrovascular and microvascular outcomes in T2DM patients.[27] The present study had certain limitations that need to be acknowledged. First, as a retrospective study, this study has selection bias. Second, the study period was too short to evaluate the effects of dapagliflozin in primary prevention of a cardiovascular event. Third, the number of participants in the fat gain group was less than that in the fat loss group. Thus, further studies are required for the evaluation of the long-term effects of dapagliflozin treatment on overweight or obese T2DM patients.

In summary, we demonstrated that dapagliflozin administration for 6 months in T2DM patients with no history of cardiovascular disease resulted in improved glycemic control, lower aortic stiffness, and reduced BW and body fat, especially visceral fat without a loss in body muscle mass. When used in obese diabetic patients with no evidence of vascular disease, SGLT-2 inhibitors may help with initial vascular disease in addition to blood sugar control.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: DML; analysis and interpretation of data: DML, WMH; drafting of the manuscript: JYH; critical revision of the manuscript: JDK, KYP; statistical analysis: WMH.

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