Comparison of the effects of empagliflozin and glimepiride on endothelial function in patients with type 2 diabetes: A randomized controlled study

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Abstract

Background : Patients with type 2 diabetes at high risk of cardiovascular events and receiving empagliflozin have a lower rate of primary composite cardiovascular outcomes and death from any cause. Alternatively, treatment with sulfonylurea reduces microvascular complications in diabetes but appears to increase cardiovascular hospitalization or mortality in combination with metformin. In the present study, we therefore assessed the effects of empagliflozin and glimepiride, a sulfonylurea, on endothelial function using flow-mediated dilation (FMD) to estimate arteriosclerosis and cardiovascular events in patients with type 2 diabetes. **Methods :** In this prospective, randomized, parallel-group comparison, 58 patients with type 2 diabetes were administered metformin and glargine before bedtime for 12 weeks, followed by the random addition of 10 mg empagliflozin or 0.5 mg glimepiride for 12 weeks. The primary outcome was FMD changes (Δ FMDs), which were measured prior to and following 12 weeks of additional treatment. Secondary outcomes comprised changes in metabolic markers and body composition. **Results :** Analysis of the empagliflozin group (n = 30) and glimepiride group (n = 28) showed no significant differences in Δ FMDs (empagliflozin, $-0.19 \pm 2.34\%$; glimepiride, $-0.37 \pm 2.77\%$; P = 0.79); likewise, HbA1c changes were similar between the groups. Body weight changes significantly differed (empagliflozin, -0.59 ± 2.5 kg; glimepiride, 1.2 ± 3.0 kg; P = 0.02). However, analysis of body composition revealed that body fluid volume significantly decreased only after empagliflozin treatment (baseline, 35.8 ± 6.8 L; after 12 weeks, -0.33 ± 0.72 L; P = 0.03). **Conclusions :** Empagliflozin did not improve endothelial function compared with glimepiride in patients with type 2 diabetes, but decreased body fluid volume. This suggested that the coronary protective effect of empagliflozin is not derived by protecting endothelial function but rather from reducing heart failure.

Background

Patients with diabetes are at high risk of cardiovascular events. For example, the risk of myocardial infarction in diabetic patients without cardiovascular disease is identical to that of nondiabetic patients with cardiovascular disease [1]. Accordingly, reports on the safety of new antidiabetic drugs with regard to cardiovascular death, myocardial infarction, or ischemic stroke are a requirement of the US Food and Drug Administration [2].

In the treatment of coronary artery disease, the assessment of coronary endothelial vasoreactivity has important diagnostic and prognostic implications. Specifically, an estimate of arteriosclerosis and cardiovascular events can be made by measuring endothelial dysfunction [3]; thus, this metric may be useful for assessing cardiovascular risk in diabetes as well. Flow-mediated dilation (FMD) constitutes a method that is used to assess endothelial function in a noninvasive manner, which is based on the intrinsic ability of blood vessels to respond to blood flow [4]. FMD involves high-frequency ultrasonographic imaging of the brachial artery and reflects nitric oxide production. As FMD can independently predict cardiovascular events, it has been utilized in numerous investigations of arteriosclerosis [5-8]. However, variables such as age, systolic blood pressure, body mass index (BMI), sex,

diabetes mellitus, lipid-lowering medication, smoking, and a decrease in visceral adipose tissue mass can impact FMD [8-10].

Blood glucose levels in diabetes can be decreased by preventing proximal tubular glucose reabsorption and increasing urinary glucose excretion using an inhibitor of sodium glucose cotransporter 2 (SGLT2). Notably, such inhibitors can also reduce blood pressure [11] and body weight [11, 12]. A meta-analysis of SGLT2 inhibitors showed that these had the effect of reducing myocardial infarction, stroke, or cardiovascular death, albeit only in patients with existing atherosclerotic cardiovascular disease. In addition, hospitalization consequent to heart failure was reduced with SGLT2 inhibitor treatment regardless of the presence of atherosclerotic cardiovascular disease or heart failure at baseline [13]. However, the anti-atherosclerotic mechanism of SGLT2 inhibitors remains unclear.

Furthermore, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) revealed that treatment with empagliflozin, an inhibitor of SGLT2, reduced the risk of cardiovascular outcomes and death from all causes. However, the incidence of myocardial infarction or stroke did not significantly differ between empagliflozin and placebo[14].

In the UK Prospective Diabetes Study (UKPDS) 33 Group, microvascular complications but not macrovascular disease were reduced with sulfonylurea therapy [15]. However, of concern was the observation that combination therapy of sulfonylureas and metformin was found to increase cardiovascular hospitalization or mortality [16]. We thus hypothesized that glimepiride, a sulfonylurea, may not improve endothelial function. Consequently, in this study we used FMD to compare endothelial function in patients with type 2 diabetes treated with empagliflozin or glimepiride.

Methods

Study design

This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000024001) as a prospective, randomized, parallel-group comparison study. Approval for this study was obtained from the ethics committee of Chigasaki Municipal Hospital, approval No. 2016-04. The study protocol conforms to the provisions of the Declaration of Helsinki as revised in 2013.

Written, informed consent was obtained from all patients. Patients were advised that they would not be disadvantaged by participating in the study and could withdraw on agreement.

Inclusion and exclusion criteria

This study enrolled patients with type 2 diabetes between >20 and <80 years of age who were hospitalized at Chigasaki Municipal Hospital and who had given written consent to be study participants

during hospitalization. Such patients underwent metformin and basal insulin therapy prior to discharge and had a BMI ≤ 45 kg/m².

Patients were excluded if they showed severe renal (estimated glomerular filtration rate [eGFR] < 45 mL min⁻¹ 1.73 m⁻²) or liver dysfunction; were on steroid therapy; experienced cardiovascular disease and a cerebral infarction within 24 weeks of the study; had cancer, a severe infection, or were traumatized; were or could become pregnant; were allergic to empagliflozin, glargine, glimepiride, or metformin; or the supervising doctor decided they could not participate in this study.

Treatment and interventions

Patients treated with metformin and glargine for 12 weeks were randomized to receive 10 mg empagliflozin or 0.5 mg glimepiride daily. Randomization was stratified by age, glycated hemoglobin (HbA1c), and FMD. The blood sample was obtained in a fasting state. Postprandial plasma glucose was measured by self-monitoring blood glucose (ONE TOUCH Verio IQ; Johnson and Johnson Co., New Brunswick, NJ). First time measurements of FMD were made prior to additional treatment and randomization. Second time measurements were made following additional treatment for 12 weeks. Treatment was not changed in general after randomization, although glargine was decreased by one unit, once weekly, if the fasting plasma glucose was maintained under 90 mg/dL. Hypoglycemia (i.e., blood glucose < 70 mg/dL) was ascertained using the values recorded by the patients.

Endpoints and assessments

The primary outcome was a change in FMD and was measured prior to and following 12 weeks of additional treatment (Fig. 1). Secondary outcomes were measured prior to and following 12 weeks and were related to changes in the following: fasting plasma glucose, HbA1c, glycated albumin (GA), postprandial plasma glucose, fasting C-peptide immunoreactivity, renal function, urinary albumin, liver-type fatty acid binding protein, uric acid (UA), waist circumference, body weight, BMI, body composition components, heart rate, blood pressure, lipids (high-density lipoprotein cholesterol [HDL-C], triglycerides [TG], and low-density lipoprotein cholesterol [LDL-C]), and adverse events. Body composition components, such as skeletal muscle and total fat mass, and body fluid volume were assessed using a Multifrequency Bioelectrical Impedance Analyzer (BIA) (InBody720; InBody Co., Ltd., Seoul, Korea). An eight-polar BIA was shown to accurately estimate total and appendicular body composition regardless of age and sex [17].

Sample size and statistical analysis

The effect of SGLT2 inhibitors on endothelial function as measured using FMD was unknown at the time this protocol was developed. Glimepiride administration for 6 months was shown to produce a Δ FMD of $+0.14 \pm 1.09\%$, whereas that for pioglitazone was $+2.02 \pm 2.05\%$, with a difference of $1.88 \pm 0.96\%$ [18]. Another study showed that sitagliptin for 12 weeks led to a Δ FMD of $+0.76 \pm 2.42\%$, whereas that for voglibose, was $+0.98 \pm 2.41\%$ [19]. Glimepiride therefore did not improve endothelial function. We estimated that the Δ FMD with empagliflozin treatment for 12 weeks would be $1.5 \pm 2.0\%$. Based on a two-sided *P*-value of 5% and a power of 80%, we needed 58 patients to detect a significant difference in comparisons of the two groups.

Results

Patients

Between June 2016 and 2018, 69 patients with type 2 diabetes agreed to participate in this study. A total of 63 patients were randomized to an empagliflozin or glimepiride group. Ultimately, 30 patients in the empagliflozin group and 28 patients in the glimepiride group were analyzed (Fig. 2). Table 1 shows baseline characteristics indicating that both groups were almost similar. The average ages were 58.6 ± 8.5 and 54.3 ± 12.2 years, and HbA1c values were $6.9 \pm 1.1\%$ and $6.6 \pm 0.7\%$ for empagliflozin and glimepiride groups, respectively.

Endothelial function

Average baseline FMD values were $5.49 \pm 2.05\%$ and $5.46 \pm 2.2\%$ for empagliflozin and glimepiride groups, respectively (Tables 1 & 2). FMD values following treatment with empagliflozin and glimepiride were $5.3 \pm 2.28\%$ and $5.09 \pm 1.86\%$, respectively (Table 2). Changes in FMD were $-0.19 \pm 2.34\%$ and $-0.37 \pm 2.77\%$ for empagliflozin and glimepiride groups, respectively, without a significant difference observed (*P* = 0.79). This indicated that empagliflozin and glimepiride treatment did not affect FMD.

Metabolic markers

We measured metabolic parameters in patients with type 2 diabetes in response to treatment with empagliflozin or glimepiride. Fasting plasma glucose remained unchanged, with no significant difference evident in the Δ fasting plasma glucose between the two groups following treatment (Table 3). However, HbA1c and GA levels were significantly decreased following treatment, with the Δ HbA1c and GA showing no significant difference between the two groups.

Renal function as measured by the eGFR of cystatin C was significantly reduced following additional treatment for 12 weeks with empagliflozin ($P < 0.001$). UA was significantly decreased in the empagliflozin group ($P < 0.001$) albeit significantly increased in the glimepiride group ($P = 0.01$). A significant difference between the two groups was also noted in the Δ UA ($P < 0.001$). Systolic and diastolic blood pressures along with heart rate were not changed significantly between the two groups. Empagliflozin treatment significantly increased LDL-C ($P < 0.001$), whereas TG and HDL-C were not significantly changed between the two groups. Glimepiride treatment led to a significantly increased body weight ($P < 0.05$), with a significant difference observed in the Δ body weight between the two groups ($P = 0.02$). However, for the subgroup showing decreased body weight, FMD was not significantly different between the two groups (empagliflozin; $P = 0.52$, glimepiride; $P = 0.26$). Glimepiride also led to a significantly increased waist circumference ($P = 0.004$). A significant difference was also observed in the Δ waist circumference between the two groups ($P = 0.008$). With regard to body composition, glimepiride led to a significantly increased total fat mass ($P = 0.02$). In comparison, empagliflozin significantly decreased body fluid volume ($P = 0.03$).

Fasting CPR, Homeostasis Model Assessment 2 steady state beta cell (%B) function, Homeostasis Model Assessment 2 insulin sensitivity (%S), and Homeostasis Model Assessment 2 insulin resistance were not significantly changed between the two groups. In this study, empagliflozin and glimepiride did not affect insulin secretion, insulin sensitivity, pancreatic β cell function, or insulin resistance. Δ HbA1c, Δ body weight, Δ HDL-C, and Δ TG were related to the Δ FMD. Additionally, the Δ FMD may have been greater if the baseline FMD was lower (Tabel 4).

Discussion

Endothelial function in patients with type 2 diabetes was assessed using FMD following treatment with empagliflozin and glimepiride, a sulfonylurea. We found that although FPG, HbA1c, and GA were equally improved in both empagliflozin and glimepiride treated patient groups, the Δ FMD did not show a significant difference. Empagliflozin had no effect toward improving endothelial function irrespective of glucose level improvement in this study. To observe changes in endothelial function induced by drugs that lacked the ability to improve the glucose level, this study was conducted with patients in a steady glucose-controlled state. Although baseline HbA1c was targeted in this study, severe hypoglycemia did not occur after reducing glargine if the fasting plasma glucose was maintained under 90 mg/dL. Additionally, GA improved significantly in both groups. It is possible that any glucose variation was improved by the additional treatment. The insulin dose was also decreased significantly for both groups and this may have reduced any increase in body weight observed. Although Δ HbA1c, body weight, HDL-C, and TG had an effect on the change of FMD and at least HbA1c was improved significantly in the empagliflozin group, FMD showed no significant change in this study. These findings suggested that empagliflozin had no effect toward improving FMD although empagliflozin was effective for improving HbA1c.

Renal function was found to be worse in the empagliflozin group. However, our study was conducted over a relatively short observation period, whereas empagliflozin was previously shown to stably maintain the eGFR during long term administration [20]. In a recent study, canagliflozin reduced the risk of kidney failure at a median follow up of 2.62 years [21], whereas an SGLT-2 inhibitor decreased hyperfiltration by diuresis [22]. Therefore, empagliflozin would be expected to prevent the progression of kidney disease over an extended period of time.

UA was significantly decreased in the empagliflozin compared to the glimepiride treated group. Hyperuricemia is a known risk factor for developing end stage renal disease [23] and the serum UA level constitutes an independent predictor of future cardiovascular mortality [24]. A reduced serum UA may affect kidney function and cardiovascular events in the future. Notably, increased fractional excretion of UA was shown to be related to reduced serum UA following canagliflozin treatment [25].

In previous studies, empagliflozin was found to decrease body weight [11, 26]. We also observed a change in body weight of -0.59 ± 2.5 kg in the present study, which was less than that described in previous reports; this discrepancy may be due to a lack of patient compliance with the diet. However, for the subgroup showing decreased body weight, FMD was found not to be significantly different between the two groups. This suggested that a change in body weight only may not affect the FMD.

In another study, empagliflozin together with basal insulin for 18 weeks led to a significant decrease in body weight (-1.7 ± 0.6 kg; $P = 0.035$) [27]. Additionally, empagliflozin combined with multiple titrated daily injections of insulin for 18 weeks also led to a significantly decreased body weight (-0.97 ± 0.18 kg) [28]. Our study examined the effect of empagliflozin together with basal insulin and metformin. The dose of glargine used was not related to a change in body weight and FMD, and was found to be significantly decreased for both groups; however, the Δ dose of glargine showed no significant difference. In comparison, insulin therapy was found by others to induce weight gain in the absence of a well-controlled diet [29]; however, in the present study, the use of insulin was not related to the lack of a significantly decreased body weight with empagliflozin treatment.

Abdominal adiposity is linked to a risk of cardiovascular disease, as shown by assessments made noninvasively using waist measurements [30]. Empagliflozin was found to have decreased the waist circumference of patients, as also observed in a previous report [31]; however, glimepiride increased it significantly. This suggested that empagliflozin may have decreased abdominal adiposity compared to glimepiride and is therefore expected to contribute to the prevention of cardiovascular disease. To confirm this effect, it will be necessary to follow up with abdominal computed tomography studies to assess visceral fat with more accuracy.

The body fluid volume was also found to have significantly decreased following 12 weeks of empagliflozin treatment. However, the two groups did not show a significant difference in Δ body fluid volume. Additionally, it was unclear whether the effect of empagliflozin on decreasing the body fluid volume was greater than that of glimepiride. Empagliflozin has been shown to improve hospitalization rates after heart failure [32] and is thought to ameliorate this disease by decreasing body fluid volume. In

the observational period, heart failure was not observed for patients in either treatment group. This suggested that empagliflozin may have had a coronary protective effect that is not derived from any impact on endothelial function.

The FMD may be improved when the baseline FMD is low. However, in the subgroup showing a lower than median baseline FMD, the FMD was not significantly changed by additional treatments and the Δ FMD did not significantly differ between the two groups in both subgroup (empagliflozin; $P = 0.59$, glimepiride; $P = 0.64$) and overall analyses. Notably, SGLT2 inhibitors have a secondary preventive role in adverse cardiovascular events but lack a primary preventive role [13]. Although SGLT2 inhibitors have a greater effect on the improvement of FMD in patients with a history of cardiovascular events than on those without such a history, no patients in the present study had such a background; it therefore would be necessary to undertake a secondary intervention.

In particular, the effects of other oral hypoglycemic agents along with glucagon like peptide 1 (GLP-1) analogs on endothelial function have been previously reported; e.g., pioglitazone improved endothelial function [18, 33]. In comparison, a dipeptidyl peptidase (DPP) 4 inhibitor improved [34], had no effect [35], or worsened [36] endothelial function but did not affect cardiovascular events [37, 38]. Moreover, GLP-1 treatment itself enhanced [39, 40] or had no effect on [41] endothelial function. However, in patients with type 2 diabetes, liraglutide, a GLP-1 analog, was successful in preventing nonfatal myocardial infarction or stroke along with death from cardiovascular causes [42]. Consistent with these inconsistent findings, significant heterogeneity existed between a meta-analysis study of a DPP4 inhibitor and GLP-1 [43]. The size of the study, the duration of intervention, and the age or sex of participants enrolled did not affect the mean difference in FMD [43]. Rather, a change in FMD was found to be dependent on the baseline FMD. As the baseline FMD of our study was less than that in reports of improved FMD by additional treatment [19, 33, 34], this may have affected our findings. In our study, the baseline blood glucose was well controlled. However, empagliflozin may not improve endothelial function in patients with moderately controlled blood glucose and no history of cardiovascular events.

In the empagliflozin group, blood glucose, serum UA, body weight, and waist measurement improved significantly, whereas the lipid profile, blood pressure, and insulin resistance remained unchanged for the observation period. Changes in these risk factors are required to improve endothelial function as assessed by FMD. However, empagliflozin would be expected to help prevent heart failure if metabolic risk factors remained unchanged. With regard to body composition, empagliflozin significantly decreased body fluid, which supports the idea of the potential of empagliflozin to reduce heart failure. However, any change in FMD is required to be assessed for longer periods than evaluated in the present study to more fully evaluate any coronary protective effect by empagliflozin.

Several limitations were evident in this study. First, as the study participants were outpatients, it may not have been possible to completely exclude patients who smoked or had a meal before the FMD was examined. Some patients may also not have been very compliant with their diet, which may have affected the change in body weight observed. Second, the number of patients examined was small and

the study observation period was relatively short. A larger patient cohort and longer study period to monitor any adverse events are both required in any future studies.

Overall, we found that empagliflozin did not improve endothelial function compared with glimepiride in patients with type 2 diabetes. However, empagliflozin significantly reduced body fluid volume. Thus, the coronary protective effect of empagliflozin may be derived not from preventing endothelial dysfunction but rather from reducing heart failure.

Abbreviations

ARB/ACE-I, angiotensin type II receptor blocker/angiotensin converting enzyme I; BMI, body mass index; Cr, serum creatinine; CRP, C-reactive protein; CysC, cystatin C; dBp, diastolic blood pressure; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; eGFR_{cys}, estimated glomerular filtration rate by cystatin C; F-CPR, fasting C-peptide immunoreactivity; FMD, flow-mediated dilation; FPG, fasting plasma glucose; GA, glycated albumin; GLP, glucagon-like peptide; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; HOMA2%B, Homeostasis Model Assessment 2 steady state beta cell (%B) function; HOMA2%S, Homeostasis Model Assessment 2 insulin sensitivity (%S); HOMA2IR, Homeostasis Model Assessment 2 insulin resistance (IR); HR, heart rate; LDL, low-density lipoprotein; L-FABP, liver-type fatty acid binding protein; sBP, systolic blood pressure; TG, triglycerides; UA, uric acid; U-Alb, urine albumin

Declarations

Ethics approval and consent to participate

Approval for this study was obtained from the ethics committee of Chigasaki Municipal Hospital, approval No. 2016-04. Written, informed consent was obtained from all patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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We have not accepted any financial support for this study.

Authors' contributions

YK provided advice on study design; HT and YK designed the study. HT collected and analyzed the data. HT performed statistical analysis. HT, KI, and MH interpreted the data. HT wrote the manuscript. YK, SS, and YTDrafted the work or substantively revised it. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics of patients

	Empagliflozin group (±SD)	Glimepiride group (±SD)	P value
Age [years]	58.6±8.5	54.3±12.2	0.13
Gender (male/female)	18 / 12	18 / 10	0.74
Duration [years]	6.1±7.2	4.9±4.9	0.44
Past smoker [%]	60.0	60.7	0.96
Current smoker [%]	20.0	39.3	0.11
FMD [%]	5.49±2.05	5.46±2.2	0.96
HbA1c [%]	6.9±1.1	6.6±0.7	1.0
FPG [mg/dL]	136.9±65.2	127.1±52.6	0.37
GA [%]	17.0±3.7	16.3±3.4	0.48
Body weight [kg]	70.0±11.3	69.6±17.1	0.92
BMI [kg/m ²]	26.1±3.7	25.9±5.4	0.9
Skeletal muscle mass [kg]	26.7±5.7	27.1±7.1	0.81
Total fat mass [kg]	21.1±6.8	20.5±11.0	0.8
Waist circumference [cm]	91.6±9.2	91.2±15.7	0.27
Cr [mg/dL]	0.76±0.16	0.73±0.16	0.54
eGFR [mL min ⁻¹ 1.73 m ⁻²]	74.9±12.9	81.9±19.7	0.11
CysC [mg/L]	0.8±0.12	0.79±0.16	0.78
eGFR _{cys} [mL min ⁻¹ 1.73 m ⁻²]	96.4±20.1	99.3±21.6	0.59
F-CPR [ng/mL]	3.1±1.7	2.5±1.9	0.23
Log U-Alb	2.9±1.7	2.5±1.6	0.34
Log L-FABP	0.96±0.85	0.6±0.85	0.11
UA [mg/dL]	5.6±1.2	5.4±1.4	0.96
LDL-C [mg/dL]	95.7±26.4	88.1±30.1	0.51
HDL-C [mg/dL]	54.4±16.7	56.4±16.2	0.52
TG [mg/dL]	202.6±106.2	181.8±139.8	0.2
CRP [mg/dL]	0.17±0.11	0.23±0.39	0.54
sBP [mmHg]	130.1±14.1	131.0±19.7	0.9
dBp [mmHg]	81.4±10.7	77.5±7.6	0.28
HR [bpm]	80.3±15.1	77.0±14.1	0.65
Metformin [mg]	883.3±375.6	991.1±473.8	0.34
Glargine [U]	9.4±4.6	11.7±9.0	0.6
ARB/ACE-I [%]	23.3	32.1	0.46
Statin [%]	40.0	53.6	0.31

Values are shown as the means $\pm$ standard deviation (SD). Paired Student's *t*-tests were used to compare values between different groups.

FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; GA, glycated albumin; BMI, body mass index; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; CysC, cystatin C; eGFRcys, estimated glomerular filtration rate by cystatin C; F-CPR, fasting C-peptide immunoreactivity; U-Alb, urine albumin; L-FABP, liver-type fatty acid binding protein; UA, uric acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; CRP, C-reactive protein; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; ARB/ACE-I, angiotensin type II receptor blocker/angiotensin converting enzyme-I

Table 2 FMD (% $\pm$ SD) with treatment

	Empagliflozin	Glimepiride	
FMD (0)	5.49 $\pm$ 2.05	5.46 $\pm$ 2.2	<i>P</i> = 0.96
FMD (12)	5.3 $\pm$ 2.28	5.09 $\pm$ 1.86	<i>P</i> = 0.71
	<i>P</i> = 0.66	<i>P</i> = 0.49	
Δ FMD (12) – (0)	-0.19 $\pm$ 2.34	-0.37 $\pm$ 2.77	<i>P</i> = 0.79

Values are shown as the means $\pm$ standard deviation (SD). Paired Student's *t*-tests were used to compare values between groups or baseline and week 12.

FMD, flow-mediated dilation

Table 3 Changes in metabolic markers

	Empagliflozin	Glimepiride	
Fasting plasma glucose (mg/dL) [mean ± SD]			
Baseline	136.9±65.2	127.1±52.6	<i>P</i> = 0.37
Week 12	124.5±52.1	119.9±49.1	<i>P</i> = 0.5
	<i>P</i> = 0.11	<i>P</i> = 0.47	
ΔFPG	-12.4±44.4	-7.3±52.0	<i>P</i> = 0.69
Postprandial plasma glucose (mg/dL) [mean ± SD]			
Baseline	181.2±76.2	162.6±53.9	<i>P</i> = 0.43
Week 12	169.6±87.0	165.1±61.1	<i>P</i> = 0.87
	<i>P</i> = 0.07	<i>P</i> = 0.26	
ΔPPG	-16.5±43.9	-9.5±27.6	<i>P</i> = 0.63
HbA1c (%) [mean ± SD]			
Baseline	6.9±1.1	6.6±0.73	<i>P</i> = 0.66
Week 12	6.7±1.1	6.4±0.78	<i>P</i> = 0.23
	<i>P</i> = 0.001	<i>P</i> = 0.01	
ΔHbA1c	-0.22±0.36	-0.26±0.5	<i>P</i> = 0.75
GA(%) [mean ± SD]			
Baseline	17.0±3.7	16.3±3.4	<i>P</i> = 0.48
Week 12	16.0±3.2	15.7±3.1	<i>P</i> = 0.69
	<i>P</i> < 0.001	<i>P</i> = 0.05	
ΔGA	-0.97±1.3	-0.65±1.6	<i>P</i> = 0.42
Fasting CPR (ng/mL) [mean ± SD]			
Baseline	3.1±1.7	2.5±1.9	<i>P</i> = 0.23
Week 12	3.1±2.2	2.8±1.6	<i>P</i> = 0.61
	<i>P</i> = 0.99	<i>P</i> = 0.34	
ΔF-CPR	-0.003±2.1	0.3±1.6	<i>P</i> = 0.55
Renal function			
Cr (mg/dL) [mean ± SD]			
Baseline	0.76±0.16	0.73±0.16	<i>P</i> = 0.48
Week 12	0.79±0.15	0.74±0.16	<i>P</i> = 0.24
	<i>P</i> = 0.03	<i>P</i> = 0.8	
eGFR (mL min ⁻¹ 1.73 m ⁻²) [mean ± SD]			
Baseline	74.9±12.9	81.9±19.7	<i>P</i> = 0.11
Week 12	72.1±11.7	81.5±20.2	<i>P</i> = 0.03
	<i>P</i> = 0.02	<i>P</i> = 0.8	
CysC (mg/dL)[mean ± SD]			
Baseline	0.8±0.12	0.79±0.16	<i>P</i> = 0.78
Week 12	0.84±0.13	0.82±0.17	<i>P</i> = 0.52
	<i>P</i> < 0.001	<i>P</i> = 0.03	
eGFRcys (mL min ⁻¹ 1.73 m ⁻²) [mean ± SD]			
Baseline	96.4±20.1	99.3±21.6	<i>P</i> = 0.59
Week 12	89.4±17.3	95.9±20.4	<i>P</i> = 0.19
	<i>P</i> = 0.01	<i>P</i> = 0.04	
Log U-Alb			
Baseline	2.9±1.7	2.5±1.6	<i>P</i> = 0.34
Week 12	2.7±1.4	2.5±1.5	<i>P</i> = 0.51
	<i>P</i> = 0.31	<i>P</i> = 0.72	
Log L-FABP			
Baseline	0.96±0.85	0.6±0.85	<i>P</i> = 0.11
Week 12	0.94±0.7	0.69±0.79	<i>P</i> = 0.21
	<i>P</i> = 0.85	<i>P</i> = 0.66	
UA (mg/dL) [mean ± SD]			
Baseline	5.5±1.2	5.4±1.5	<i>P</i> = 0.96
Week 12	4.8±1.2	5.7±1.4	<i>P</i> = 0.01
	<i>P</i> < 0.001	<i>P</i> = 0.01	

ΔUA	-0.64±0.9	0.26±0.5	<i>P</i> < 0.001
Body weight (kg) [mean ± SD]			
Baseline	70.0±11.3	69.6±17.1	<i>P</i> = 0.92
Week 12	69.4±12.0	70.8±18.2	<i>P</i> = 0.73
	<i>P</i> = 0.22	<i>P</i> < 0.05	
ΔBody weight	-0.59±2.5	1.2±3.0	<i>P</i> = 0.02
Waist circumference (cm) [mean ± SD]			
Baseline	91.6±9.2	91.2±15.7	<i>P</i> = 0.27
Week 12	90.9±8.9	92.3±15.3	<i>P</i> = 0.68
	<i>P</i> = 0.07	<i>P</i> = 0.004	
ΔWaist circumference	-0.64±1.8	1.1±2.8	<i>P</i> = 0.008
BMI (kg/m ²) [mean ± SD]			
Baseline	26.1±3.7	25.9±5.4	<i>P</i> = 0.9
Week 12	25.8±3.8	26.4±5.6	<i>P</i> = 0.65
	<i>P</i> = 0.14	<i>P</i> = 0.04	
Blood pressure (mmHg) [mean ± SD]			
sBP			
Baseline	129.6±14.9	130.1±20.5	<i>P</i> = 0.9
Week 12	130.2±14.2	128.9±19.3	<i>P</i> = 0.76
	<i>P</i> = 0.79	<i>P</i> = 0.62	
ΔsBP	0.69±13.7	-1.3±13.5	<i>P</i> = 0.59
dBP			
Baseline	80.8±10.0	78.0±9.3	<i>P</i> = 0.28
Week 12	80.6±7.6	78.6±12.0	<i>P</i> = 0.47
	<i>P</i> = 0.91	<i>P</i> = 0.72	
ΔdBP	-0.24±10.8	0.64±9.3	<i>P</i> = 0.74
Heart rate			
Baseline	79.4±14.8	77.5±14.3	<i>P</i> = 0.64
Week 12	80.1±15.4	79.0±12.8	<i>P</i> = 0.78
	<i>P</i> = 0.76	<i>P</i> = 0.55	
Lipids (TG, HDL-C, LDL-C) (mg/dL) [mean ± SD]			
LDL-C			
Baseline	94.0±26.7	89.2±28.1	<i>P</i> = 0.51
Week 12	107.5±33.0	93.9±29.6	<i>P</i> = 0.1
	<i>P</i> < 0.001	<i>P</i> = 0.33	
ΔLDL-C	13.5±19.3	4.7±25.2	<i>P</i> = 0.14
HDL-C			
Baseline	54.7±16.0	57.4±16.4	<i>P</i> = 0.52
Week 12	56.0±12.5	56.4±13.1	<i>P</i> = 0.92
	<i>P</i> = 0.43	<i>P</i> = 0.61	
ΔHDL-C	1.4±9.4	-1.1±10.9	<i>P</i> = 0.37
TG			
Baseline	197.7±101.1	176.0±131.5	<i>P</i> = 0.2
Week 12	177.1±86.9	185.7±123.7	<i>P</i> = 0.76
	<i>P</i> = 0.29	<i>P</i> = 0.8	
ΔTG	-20.6±103.8	9.6±121.5	<i>P</i> = 0.31
Body fluid volume (L) [mean ± SD]			
Baseline	35.8±6.8	36.6±8.6	<i>P</i> = 0.69
Week 12	35.4±6.9	36.3±8.7	<i>P</i> = 0.7
	<i>P</i> = 0.03	<i>P</i> = 0.32	
ΔBody fluid volume	-0.33±0.72	-0.35±1.8	<i>P</i> = 0.94
Skeletal muscle mass (kg) [mean ± SD]			
Baseline	26.7±5.7	27.1±7.1	<i>P</i> = 0.81
Week 12	26.4±5.7	27.1±7.2	<i>P</i> = 0.71
	<i>P</i> = 0.08	<i>P</i> = 0.72	
ΔSkeletal muscle mass	-0.21±0.6	0.05±0.7	<i>P</i> = 0.15

Total fat mass (kg) [mean ± SD]			
Baseline	21.1±6.8	20.5±11.0	<i>P</i> = 0.8
Week 12	20.6±6.8	21.7±11.6	<i>P</i> = 0.68
	<i>P</i> = 0.16	<i>P</i> = 0.02	
ΔTotal fat mass	-0.58±2.1	1.2±2.3	<i>P</i> = 0.006
Adverse events (%)			
	rash on both arms (3.3%)	hypoglycemia (3.6%)	
Glargine (U) [mean ± SD]			
Baseline	9.4±4.6	11.7±9.0	<i>P</i> = 0.6
Week 12	8.4±5.1	9.6±8.9	<i>P</i> = 1.0
	<i>P</i> = 0.02	<i>P</i> < 0.001	
ΔGlargine	-1.0±2.4	-2.1±3.5	<i>P</i> = 0.16
HOMA2%B			
Baseline	217.8±92.3	205.4±105.1	<i>P</i> = 0.63
Week 12	237.8±116.1	274.1±194.4	<i>P</i> = 0.39
	<i>P</i> = 0.32	<i>P</i> = 0.05	
HOMA2%S			
Baseline	21.5±28.5	25.5±16.2	<i>P</i> = 0.07
Week 12	21.9±18.1	21.3±14.2	<i>P</i> = 0.86
	<i>P</i> = 0.54	<i>P</i> = 0.14	
HOMA2IR			
Baseline	8.8±8.9	6.5±6.1	<i>P</i> = 0.07
Week 12	8.2±8.3	6.8±4.4	<i>P</i> = 0.88
	<i>P</i> = 0.44	<i>P</i> = 0.21	

Values are shown as the means ± standard deviation (SD).

FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; GA, glycated albumin; F-CPR, fasting C-peptide immunoreactivity; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; CysC, cystatin C; eGFR_{cys}, estimated glomerular filtration rate by cystatin C; U-Alb, urine albumin; L-FABP, liver-type fatty acid binding protein; UA, uric acid; BMI, body mass index; sBP, systolic blood pressure; dBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; HOMA2%B, Homeostasis Model Assessment 2 steady-state beta cell (%B) function; HOMA2%S, Homeostasis Model Assessment 2 insulin sensitivity (%S); HOMA2IR, Homeostasis Model Assessment 2 insulin resistance (IR)

Table 4 Relationship between arteriosclerosis markers and ΔFMD in all patients (n = 58)

	Raw β	Std β	<i>P</i> value
Age	0.01	0.05	0.7
Gender	-0.02	-0.004	0.98
Duration	0.02	0.06	0.67
FMD (0)	-0.74	-0.61	0.0001***
HbA1c (0)	-0.47	-0.18	0.18
FPG (0)	-0.005	-0.11	0.4
GA (0)	-0.17	-0.24	0.07
BW (0)	0.03	0.18	0.18
BMI (0)	0.12	0.2	0.15
UA (0)	0.31	0.16	0.22
LDL (0)	-0.02	-0.23	0.09
HDL (0)	-0.04	-0.26	0.05
TG (0)	0.004	0.2	0.11
Past smoker	-0.79	-0.15	0.25
sBP (0)	-0.03	-0.18	0.17
dBP (0)	-0.06	-0.21	0.11
Δ HbA1c	-1.85	-0.31	0.02*
Δ GA	-0.16	-0.1	0.48
Δ FPG	-0.005	-0.09	0.49
Δ BW	-0.33	-0.38	0.003**
Δ LDL-C	0.01	0.11	0.43
Δ HDL-C	0.08	0.31	0.02*
Δ TG	-0.009	-0.38	0.003**
Δ sBP	0.01	0.06	0.63
Δ dBP	0.05	0.18	0.18
ARB/ACE-I	0.41	0.07	0.59
Statin	0.34	0.07	0.62

Values are shown as the means. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ indicate a significant association between arterial sclerosis markers and Δ FMD.

(0), baseline; FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; GA, glycated albumin; BMI, body mass index; UA, uric acid; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; sBP, systolic blood pressure; dBP, diastolic blood pressure; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; ARB, angiotensin receptor blocker; ACE-I, angiotensin converting enzyme inhibitor

Figures

Figure 1

Study flow chart. Patients who took metformin and glargine were randomized to empagliflozin or glimepiride groups. Flow-mediated dilation (FMD), blood examination, body weight, and blood pressure were checked at study baseline and endpoint

Figure 2

Consort 2010 flow diagram of patient selection. Ultimately, 25 patients in the empagliflozin group and 24 patients in the glimepiride group were analyzed