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Effect of sodium-glucose co-transporter-2 inhibitors on coronary blood flow in patients with type 2 diabetes mellitus

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Abstract. – OBJECTIVE: Type 2 diabetes mellitus (T2DM) is known to be associated with endothelial dysfunction (ED). Reducing ED can attenuate the occurrence of cardiovascular diseases. One of the indicators of ED is decreased coronary blood flow (CBF). Sodium-glucose co-transporter 2 inhibitors (SGLT-2is) are known to directly improve ED in both euglycemic and hyperglycemic conditions and have been shown to decrease the incidence of major cardiovascular events. We aimed to investigate whether SGLT-2is improves CBF in patients with T2DM, who have angiographically normal or nearly normal coronary arteries.

PATIENTS AND METHODS: In this single-center retrospective study, all patients who underwent coronary angiography between January 2017 and September 2022 were screened. We designed the study by dividing the patients into two groups – those who used conventional antidiabetic medications (CAM) together with SGLT-2is (patients using an SGLT-2 inhibitor for at least 3 months) and those who used only conventional antidiabetic medications. Of the 18,205 patients who underwent coronary angiography, 5,040 patients had T2DM. After exclusion, 288 patients were divided into two groups – those who used CAM together with SGLT-2is and those who used only CAM. CBF was assessed by thrombolysis in myocardial infarction (TIMI) frame counting.

RESULTS: Two hundred eighty-eight patients who had T2DM and met the inclusion criteria were included in our study. The patients were divided into two groups – those who used CAM together with SGLT-2is (n = 75) and those who used only CAM (n = 213). The median age in the group that used CAM together with SGLT-2is was 55 (51-64), where 52 (69.3%) patients were female. The mean TIMI frame count (TFC) was 23.5 in the group using CAM + SGLT-2is and 27.5 in the group using only CAM. In the multivariable linear regression analysis, the mean TFC was significantly lower in the group using CAM together with SGLT-2is compared to the group using only CAM [β-coefficient = -12.766, 95% CI: -5.304; -3.887, $p < 0.001$]. Moreover, there was a statistically significant correlation between an increase in BMI and hemoglobin with an increase in the mean TFC [β-coefficient = 3.018, 95% CI 0.037-0.175, $p = 0.003$ and β-coefficient = 2.316, 95% CI 0.033-0.405, $p = 0.021$, respectively].

CONCLUSIONS: We have demonstrated that the use of SGLT-2is improves coronary artery blood flow in patients with T2DM who have normal or nearly normal coronary angiography.

Key Words:
Coronary blood flow, Endothelial dysfunction, SGLT-2 inhibitors.

Introduction

Type 2 diabetes mellitus (T2DM) is a well-known independent risk factor for atherosclerotic cardiovascular diseases (CVD), which are the main causes of morbidity and mortality worldwide. It is also known to be associated with microvascular disease and endothelial dysfunction (ED). ED is the precursor to the development and progression of atherosclerosis. Hence, reducing ED can attenuate the occurrence of CVD. One of the indicators of ED is decreased coronary blood flow (CBF)[1]. SGLT-2is are known to directly ameliorate ED, independent of hyperglycemia, and have been shown to reduce the incidence of major cardiovascular events[2,3].

CBF can be assessed by thrombolysis in myocardial infarction (TIMI) frame counting, which is a simple, reproducible, and quantitative index of coronary blood flow. It is calculated by counting the number of cineangiographic frames from the initial contrast opacification of the proximal coronary artery to the opacification of the distal reference point[4].

We aimed to investigate whether SGLT-2is improves coronary blood flow in T2DM patients who have angiographically normal or nearly normal coronary arteries.

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Patients and Methods

Study Population

In this single-center retrospective study, all patients who underwent coronary angiography at the Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey, between January 2017 and September 2022 were screened. Of 18,205 patients who underwent coronary angiography during this period, 5,040 patients had T2DM. Patients diagnosed with T2DM and receiving treatment, as well as those with normal or nearly normal coronary arteries, were included in the study. We designed the study by dividing the patients into two groups – those who used conventional antidiabetic medications (CAM) together with SGLT-2is (patients using an SGLT-2 inhibitor for at least 3 months) and those who used only conventional antidiabetic medications.

The following were the exclusion criteria – patients with acute coronary syndrome or other cardiac diseases with positive troponin [such as myocarditis, myocardial infarction with nonobstructive coronary arteries (MINOCA)], a previous history of Percutaneous coronary intervention (PCI), a history of coronary bypass, a previous valve operation or severe valvular disease, stenosis in any main coronary artery ≥ 50%, left ventricular systolic dysfunction (ejection fraction < 50%), a history of COVID-19 in the last 1 month before coronary angiography, low glomerular filtration rate [GFR < 50 ml/min with the Modification of Diet in Renal Disease (MDRD) formula], angiographically unsuitable patients (such as poorly or inadequate image, rudimentary, vasospasm, myocardial bridge, and ectasia of any main coronary artery) and those who lacked data [such as body mass index (BMI) and smoking]. The exclusion criteria are shown in Figure 1.

After exclusion, a total of 288 patients were divided into two groups – those who used CAM together with SGLT-2is (n = 75) and those who used only CAM (n = 213). Among the 288 patients, 40 were using dapagliflozin, and 35 were using empagliflozin in the group that used CAM together with SGLT-2is.

Based on coronary angiography time, the demographic data, laboratory parameters, comorbidities, and drugs used were obtained from the electronic medical records of the hospital and the national electronic medical record system. All angiographic images were recorded at a rate of 30 frames/s. The first frame was defined as the complete filling of the opaque proximal artery lumen, the last frame was defined when the dye first entered a certain distal landmark branch. For the left anterior descending artery (LAD), the distal reference point was used as the distal bifurcation or moustache. For the left circumflex artery (LCX), the most distal bifurcation of the obtuse marginal branch farthest from the coronary ostium was used as the distal reference point. Then, for the right coronary artery (RCA), the first branch of the posterolateral segment was used as the distal reference point. The angiograms were evaluated, and the coronary flow measurement was performed using the corrected TIMI frame count (CTFC) method described by Gibson et al[4]. The TIMI frame counts for the LAD artery were divided by 1.7 to derive the CTFC, and the mean TFC was calculated by summing the TFCs of the three coronary arteries and dividing them into three. The assessment was performed by two cardiologists who were blinded to the data of the study population. The intra- and inter-observer coefficients of variation for mean TFC were 3.52% and 4.38%, respectively.

The study was approved by the local institutional ethics committee. The study protocol conformed to the Declaration of Helsinki.

Statistical Analysis

The continuous variables were presented as a median interquartile range (IQR) (25-75%) owing to their non-normal distribution. A histogram and the Shapiro-Wilks test were used to verify the normal distribution of the data. The categorical variables were expressed as percentages. A Chi-square test was used to compare the categorical variables between the groups, and the continuous variables were compared using Mann-Whitney U tests. Univariable and multivariate linear regression analyses were performed to determine the parameters affecting the mean TFC. Variables with a p-value < 0.2 in univariable analysis were added to the multivariable analysis. The value $p < 0.05$ in multivariable analysis was considered to be statistically significant. The data analysis was carried out using SPSS statistical software version 24.0 (IBM Corp., Armonk, NY, USA).

Results

The median age in the group using CAM together with SGLT-2is was 55 (51-64), where 69.3% of the patients were female. The median age in the group using only CAM was 59 (54-68), where 58.7% of the patients were female. The BMI of the

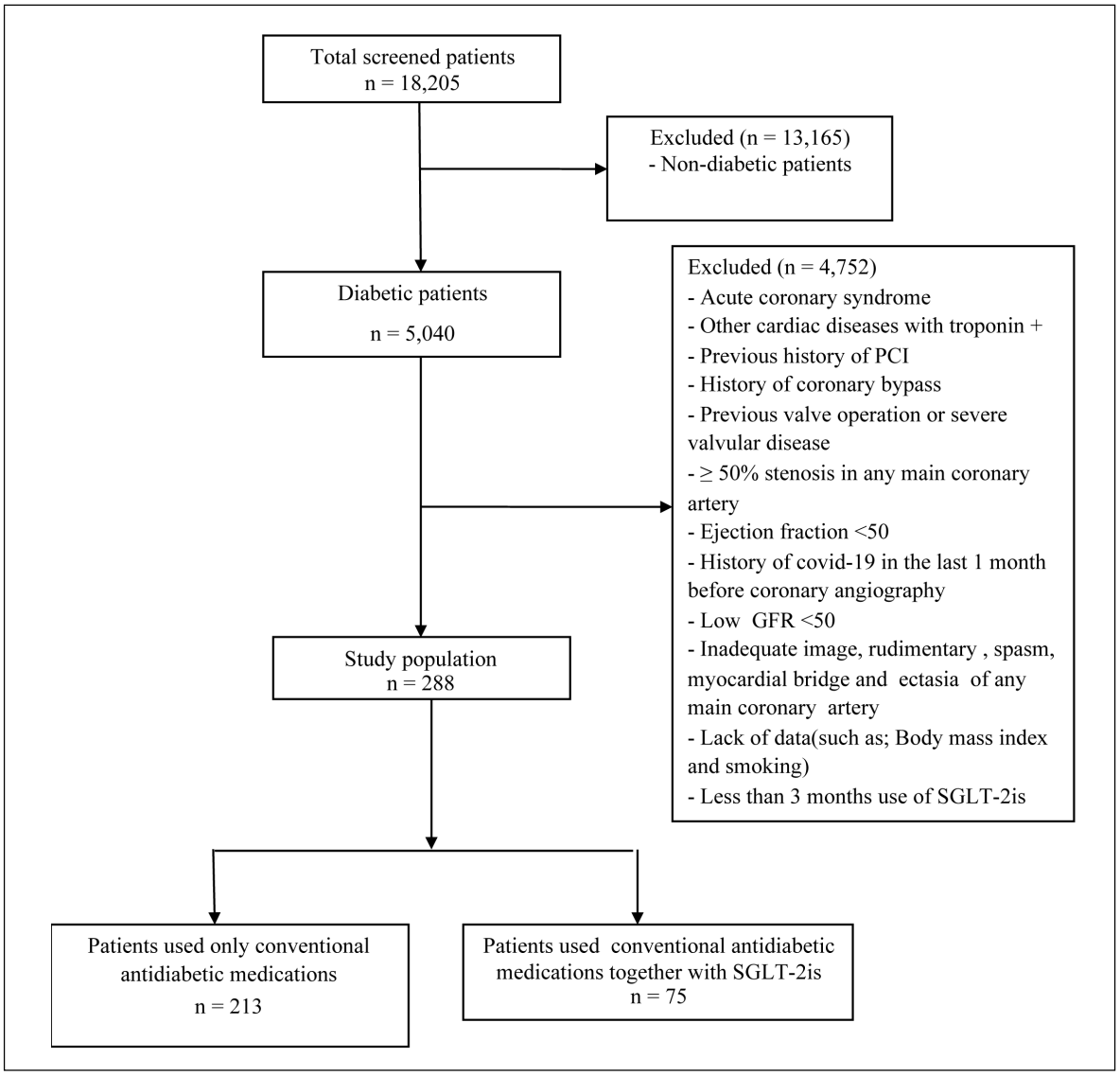

Figure 1. Flowchart of patient selection.

patients using CAM together with SGLT-2is was 32, and that using only CAM was 28. The mean TFC was 23.5 in the group using CAM together with SGLT-2is, whereas the mean TFC was 27.5 in the group using CAM only. Demographic, laboratory, angiographic, and used drug characteristics of the study population are shown in Table I.

In multivariable linear regression analysis, the mean TFC was significantly lower in the group using CAM together with SGLT-2is compared to the group using only CAM. That is to say, there was a statistically significant correlation between SGLT-2is use and low mean TFC [β-coefficient = -12.766, 95% Cl: -5.304; -3.887, $p < 0.001$] (Table II). In addition to this, there was a statistically significant correlation between an increase in BMI and hemoglobin with an increase in the mean TFC [β-coefficient = 3.018, 95% Cl 0.037–0.175, $p = 0.003$ and β-coefficient = 2.316, 95% Cl 0.033–0.405, $p = 0.021$, respectively]. A multivariable regression analysis for the mean TFC is shown in Table III.

Discussion

To our knowledge, this is the first angiographical study to investigate the effect of SGLT-2is on CBF. In our study, we observed that the mean TFC was significantly lower in diabetic patients who used SGLT-2is than in those who did not use SGLT-2is.

Table I. Demographic, laboratory, angiographic, and used drugs characteristics of the study population.

Parameters	CAM+SGLT-2is group (n=75)	CAM group (n=213)	*p*-value
Age (years)	55 (51-64)	59 (54-68)	<0.001
Gender (female), (n) (%)	52 (69.3)	125 (58.7)	0.104
Hypertension ,(n) (%)	38 (55.9)	119 (50.7)	0.437
Smoking, (n) (%)	24 (33.8)	72 (32)	0.776
BMI, (kg/m^2)	32.0 (28.0-34.0)	28.0 (26.5-30.0)	<0.001
Psychiatric disorder, (n) (%)	8 (10.7)	23 (10.8)	0.975
COPD, (n) (%)	14 (18.7)	43 (20.2)	0.777
LV ejection fraction, (%)	60 (55-60)	60 (55-60)	0.863
Acetylsalicylicacid/Clopidogrel, (n) (%)	41 (54.7)	107 (50.2)	0.510
ACE-I/ARB, (n) (%)	33 (44)	112 (52.6)	0.202
Thiazide diuretic, n (%)	24 (32)	69 (32.4)	0.950
Calcium channel blocker, n (%)	10 (13.3)	51 (23.9)	0.051
β-Blockers, (n) (%)	8 (10.7)	38 (17.8)	0.145
Statin, (n) (%)	35 (46.7)	68 (31.9)	0.022
Fenofibrate, (n) (%)	7 (9.3)	16 (7.5)	0.625
HbA1C, (%)	8.7 (7.5-10.5)	8.1 (7.0-9.5)	0.014
GFR, ml/min/1.73 m^2	90 (84-90)	90 (76-90)	0.021
Calcium, mg/dL	9.3 (9.0-9.6)	9.4 (9.0-9.7)	0.618
Albumin, g/L	42.0 (38.0-45.0)	42.0 (39.0-45.0)	0.509
Triglycerides, mg/dL	202 (110-246)	185 (116-283)	0.574
Total Cholesterol, mg/dL	185 (159-220)	189 (158-224)	0.715
High density lipoprotein, mg/dL	39.8 (33-53)	40.4 (33-48)	0.460
Low density lipoprotein, mg/dL	113 (88-138)	112 (90-138)	0.799
Alanin Aminotransferase, IU/L	17 (14-23)	22 (16-31)	0.001
Aspartat Aminotransferase, IU/L	16 (14-22)	21 (16-28)	0.001
Sodium, mmol/L	137 (136-139)	138 (136-140)	0.190
Potassium, mmol/L	4.4 (4.2-4.7)	4.4 (4.1-4.7)	0.344
C-reactive protein, mg/dL	2.0 (2.0-6.9)	2.0 (2.0-7.5)	0.443
White blood cell, 10^3/uL	9.3 (8.0-10.3)	8.7 (7.3-10.6)	0.310
Hemoglobin, gr/dL	13.7 (12.7-15.3)	13.5 (12.6-14.6)	0.229
Platelet, 10^3/uL	305 (269-344)	266 (228-317)	<0.001
Mean platelet volume, fL	10.2 (9.5-11.0)	10.3 (9.7-11.1)	0.317
Red cell distribution width, fL	43.0 (41.0-46.4)	43.0 (41.0-45.6)	0.892
LAD CORRECT TFC	25.2 (22.4-26.6)	28.0 (26.6-29.4)	<0.001
LCX TFC	24.0 (22.0-26.0)	28.0 (26.0-30.0)	<0.001
RCA TFC	22.0 (20.0-24.0)	26.0 (24.0-30.0)	<0.001
MEAN TFC	23.5 (22.1-25.6)	27.5 (26.0-28.9)	<0.001

COPD: Chronic obstructive pulmonary disease; BMI: Body mass index; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; LV: left ventricle; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; TFC: TIMI frame count; SGLT-2is: Sodyum-Glucose Co-Transporter-2 inhibitors; CAM: conventional antidiabetic medications.

Aetiology and Pathogenesis of Decreased Coronary Blood Flow

Decreased CBF or coronary slow flow (CSF) is defined as delayed opacification of the distal coronary artery despite the absence of significant coronary artery obstruction. It has been most frequently found in those who have components of metabolic syndromes, such as hypertension, diabetes mellitus, obesity, hyperlipidemia and hypercholesterolemia, and smokers. These are all risk factors for damage to the endothelium[5-9]. Several theories and hypotheses have been proposed regarding the coronary slow-flow mechanism, but endothelial and microvascular dysfunction are highly suspected. Coronary vascular tone is regulated by the endothelium. Normally, the resistance of the coronary artery to blood flow is low[5]. ED occurs when the endothelium fails to serve its normal physiologic functions and when endothelial nitric oxide (NO) availability and endothelium-dependent vascular tone are impaired[10]. Endothelium secretes numerous modulators of vascular tone, the most important of which is NO. Lower NO levels have been demonstrated in several studies of CSF patients[5]. In addition to the risk factors mentioned above, oxidative stress and

Table II. Univariable regression analysis for mean TFC.

	β- coefficient	CI 95%	*p*-value
Gender(Female)	3.212	0.466 − 1.939	0.001
Age	0.736	-0.23 − 0.051	0.462
Hypertension	-0.532	-0.939 − 0.534	0.595
Smoking	0.790	-0.463 − 1.084	0.430
BMI	-1.331	-0.136 − 0.026	0.184
COPD	-0.521	-1.158 − 0.673	0.603
Lipid lowering drugs	-1.866	-1.445 − 0.038	0.063
Acetylsalicylicacid/Clopidogrel	-1.285	-1.203 − 0.253	0.200
ACE-I/ARB	0.471	-0.555 − 0.904	0.638
Calcium channel blocker	-0.679	-1.203 − 0.586	0.498
β-Blockers	1.114	-0.431− 1.557	0.266
GFR	0.280	-0.28 − 0.037	0.280
Triglycerides	1.602	<0.001 − 0.005	0.110
Total Cholesterol	0.841	-0.004 − 0.010	0.401
Low density lipoprotein	0.204	-0.008 − 0.010	0.838
High density lipoprotein	-0.528	-0.043 − 0.025	0.598
Potassium	-2.362	-1.849 − -0.168	0.019
HbA1C	-1.610	-0.364 − 0.036	0.108
Hemoglobin	2.104	0.014 − 0.419	0.036
Platelet	-2.669	-0.012 − -0.002	0.008

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; ACE-I: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; GFR: Glomerular filtration rate; TFC: TIMI frame count.

inflammation can cause CSF. In many studies[11-13], it has been demonstrated that the levels of the C-reactive protein (CRP), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), nuclear factor-κB (NF-κB), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, which are indicators of inflammation, increase in patients with CSF.

Pathogenesis of ED in Diabetes

Physiologically, endothelial cells (ECs) serve to maintain cardiovascular function by providing the production of endothelium-derived vasoactive factors. The release of NO by endothelial NO synthase (eNOS) performs a crucial task in preserving vascular health. NO regulates blood flow and blood pressure by inhibiting vascular tone. It also induces antithrombotic and anti-inflammatory effects by inhibiting the aggregation and adhesion of platelets within the vessel wall[2]. ED is an abnormal vascular condition characterized by disequilibrium in the synthesis and/or discharge of various endothelial signaling molecules. When ED develops, the level and bioavailability of NO decrease. The main cause of ED is an increase in reactive oxygen species (ROS) in ECs. In patients with diabetes, hyperglycemia, along with inflammatory reaction, oscillatory

Table III. Multivariable linear regression analysis for mean TFC.

	β-coefficient	CI 95%	*p*-value
Age	-0.595	-0.040 − 0.021	0.553
Gender (female)	1.295	-0.228 − 1.106	0.196
BMI	3.018	0.037 − 0.175	0.003
Triglycerides	0.269	-0.002 − 0.002	0.788
HbA1C	-0.126	-1.172 − 0.151	0.900
Hemoglobin	2.316	0.033 − 0.405	0.021
Platelet	-0.785	-0.006 − 0.002	0.433
Potassium	-1.951	-1.366 − 0.006	0.052
Acetylsalicylicacid/Clopidogrel	-0.334	-0.794 − 0.564	0.739
Lipid lowering drugs	-0.431	-0.853 − 0.547	0.667
SGLT-2is	-12.766	-5.304 − -3.887	<0.001

BMI: Body mass index; SGLT-2is: Sodyum-Glucose Co-Transporter-2 inhibitors; TFC: TIMI frame count.

shear stress, and enhanced cyclic stretch, increases the production of ROS in ECs. Studies[14,15] have focused on four main hyperglycemia-dependent mechanisms related to the overproduction of ROS-mitochondrial dysfunction, increased intracellular formation of advanced glycation end products (AGEs), activation of the polyol pathway, and activation of protein kinase C (PKC). First, hyperglycemia leads to the mitochondrial overproduction of ROS via more oxygen use, high redox potential, and mitochondrial fission. Hyperglycemia also upregulates both the abundance and activity of sodium-hydrogen exchangers (NHE) within ECs[14]. As ROS increases, it stimulates the production of proinflammatory cytokines, such as IL-6, monocyte chemotactic protein-1 (MCP-1), and adhesion molecules, such as ICAM-1, VCAM-1, and E-selectin[15]. Second, as a precursor of the majority of advanced glycation end products (AGE), methylglyoxal is increased in hyperglycemia. Then, the expression of AGE, receptors for AGEs (RAGE), and RAGE ligands are promoted. AGE-RAGE binding activates multiple signal transduction pathways that increase the expression of VCAM-1, ICAM-1, NF-κB, TNF-α and IL-1β and decrease NO level and bioavailability[16]. Third, in the polyol pathway, excess glucose is converted to sorbitol and then to fructose. The polyol pathway also produces ROS by using NADPH (Nikotinamid adenin dinukleotid phosphate) and glutathione as co-factors and increasing subsequent NADH oxidation during the conversion of sorbitol to fructose. Aldose reductase (AR) is the first enzyme in the polyol pathway. As a key rate-limiting enzyme of the polyol pathway, AR facilitates the expression of inflammatory cytokines, such as TNF-α and NF-κB. Lastly, PKC becomes active with hyperglycemia as a result of ROS production. ROS induces vascular inflammation via activating multiple downstream pathways, including the kinases extracellular signal regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK). As a result, an increase in adhesion molecules and decreases in bioavailability of nitrite oxide occurs[15,16].

Sodium-Glucose Co-Transporter 2 Inhibitors' Effect on Endothelial Dysfunction

SGLT-2is improves endothelial dysfunction through many mechanisms – a decrease of oxidative stress and inflammatory reactions in endothelial cells, restoration of endothelium-related vasodilation, inhibition of the overactive sodium–hydrogen exchanger, alleviation of mitochondrial injury, suppression of inflammation-related signaling pathways and repair of impaired NO bioavailability[2,16].

In many stages of endothelial dysfunction, there is an excessive increase in intracellular ROS, which stimulates the production of proinflammatory cytokines and adhesion molecules. Many studies have shown that SGLT-2is reduce excessive intracellular ROS production. *in vitro* studies with human coronary artery endothelial cells (HCAEC) and cardiac microvascular endothelial cells (CMEC) have indicated that empagliflozin reduces the amount of cytoplasmic ROS, mitochondrial ROS, and mitochondrial fragmentation[17-21]. In a study conducted by Li et al[22] with HCAEC, dapagliflozin was shown to reduce the amount of intracellular ROS. In another study[17] with human umbilical vein endothelial cells (HUVEC), dapagliflozin was shown to reduce intracellular ROS. Moreover, one of the anti-oxidative effects of SGLT-2is is hypothesized to be NHE inhibition. Uthman et al[18] obtained direct evidence that empagliflozin inhibited ROS production in ECs via NHE inhibition since empagliflozin treatment lowered NHE activity and Na+ concentration in human ECs. However, some studies[21,23] have shown that empagliflozin has a neutral effect on NHE inhibition.

Many studies[24-26] have been performed on the effect of SGLT-2is to improve endothelial dysfunction due to its anti-inflammatory effects. A recent clinical trial[24] determined that 24-week treatment with empagliflozin significantly reduced serum ICAM-1 levels and hindered leukocyte-endothelium interactions in patients with DM. An *in vitro* study conducted by Cooper et al[25] demonstrated that dapagliflozin reduced the increased ICAM-1 and VCAM-1 secretion of HUVECs exposed to TNF-α or hyperglycemia. Another *in vitro* study conducted by Ortega et al[26] revealed that empagliflozin attenuated the increased leukocyte-endothelium interactions, ICAM-1 and VCAM-1 secretion of human aortic endothelial cells (HAECs) exposed to ang-2. Other vitro studies[27-29] carried out with HUVEC demonstrated that dapagliflozin reduced the increased NF-Kb.

Recently, several studies[7,20,21] have been performed on the effect of SGLT-2is to improve endothelial dysfunction due to the restoration of NO. Some *in vitro* studies with HCAECs and CMECs have indicated that empagliflozin increases NO bioavailability[17,20,21]. Another study conducted by Uthman et al[17] with HUVECs indicated

that dapagliflozin increases NO bioavailability. Moreover, many studies[30-34] have indicated that SGLT-2is improves nitric oxide production and vasodilation. Flow-mediated dilatation (FMD) has been used before and after shear stress induction to reflect NO-mediated vasodilation. In these studies with empagliflozin and dapagliflozin in patients with type 2 diabetes mellitus, SGLT-2is has been shown to increase FMD.

The possible causes of the mean TFC being lower in the group using SGLT-2is, as mentioned above, can be attributed to decreased oxidative stress and inflammatory reactions to the restoration of NO and increased NO levels in ECs by SGLT-2is. It can also be attributed to the inhibition of the overactive sodium-hydrogen exchanger and the alleviation of mitochondrial injury in ECs by SGLT-2is. In sum, SGLT-2is results in the recovery of endothelial dysfunction and, possibly for this reason, may improve coronary artery blood flow. Moreover, in our study, an increase in BMI was found to be an independent parameter for increased mean TFC. Clinical studies[35-38] have shown that there are lower levels of NO bioavailability in obese patients, which leads to the disruption of endothelium-dependent vasodilation. These studies have also demonstrated that the decreased expression of the eNOS enzyme in the endothelium, which is responsible for NO production, is the most important cause of ED. Obesity has additionally been shown to trigger several cellular stresses that deteriorate ED, which involve oxidative stress, endoplasmic reticulum stress, and inflammation, leading to decreased NO bioavailability during obesity[35-38]. Recently, *in vivo* and *in vitro* studies[39-43] have shown that an increase in microRNAs downregulates eNOS expression, leading to lower NO production in obese people.

Another independent parameter of our study was the increase in hemoglobin levels. We found a significant correlation between the rise in hemoglobin and the increased mean TFC. Although the reason for this is unknown, a significant relationship has been found between the two parameters in other studies[44,45].

The most important limitation of our study is its single-center, retrospective design.

Conclusions

We have demonstrated that the use of SGLT-2 inhibitors improves coronary artery blood flow in diabetic patients. Our study should be followed by larger and prospective studies in order to add SGLT-2is as a treatment in T2DM patients who have normal or nearly normal coronary angiography.

Conflict of Interest
The authors have nothing to declare.

Informed Consent
Informed consent was obtained from all individual participants included in the study.

Availability of Data and Materials
The data supporting this study's findings are available from the corresponding author, [E.T.], upon reasonable request.

Ethics Approval
Ethical approval was obtained from the Local Ethical Committee of Gazi Yaşargil Training and Research Hospital. (Approval number: 257, Date: 09.12.2022).

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Authors' Contributions
E.T.: design of the study, collection of data, statistical analysis, writing, critical revision. S.S.: design of the study, approval of the final version of the manuscript. A.D.C.: collection of data. M.A.: collection of data. R.T.: collection of data C.Ö.: collection of data. A.A.: statistical analysis. F.I: collection of data. M.Ç.: manuscript preparation. Ö.B.: statistical analysis and writing. M.S.: approval of the final version of the manuscript. M.O.: reviewing the final version.

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