Eskisehir Medical Journal
Eskişehir Tıp Dergisi

Eskisehir Med J. 2023; 4(1): 73-79
doi: 10.48176/esmj.2023.108

Original Article / Araştırma Makalesi

EFFECT OF SODIUM GLUCOSE CO-TRANSPORTER 2 INHIBITORS ON LIPID LEVELS IN NEWLY DIAGNOSED HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES MELLITUS

TİP 2 DİABETES MELLİTUSU OLAN YENİ TANI HİPERTANSİF HASTALARDA SODYUM GLUKOZ KO-TRANSPORTER 2 İNHİBİTÖRLERİNİN LİPİD DÜZEYLERİ ÜZERİNE ETKİSİ

BİRSEN DOGANAY[1] **OZLEM OZCAN CELEBİ**[1]

[1]Department of Cardiology, Ankara City Hospital, Ankara, Turkey.

ABSTRACT

Aim: This study aimed to examine the effects of sodium glucose cotransporter 2 inhibitors (SGLT-2i) on lipid levels at 12 weeks of follow-up in newly diagnosed hypertensive (NDHT) patients with type 2 diabetes mellitus (T2DM).

Methods: This retrospective study, 236 NDHT patients with T2DM were included. The SGLT-2i group consisted of patients who received SGLT-2i (empagliflozin or dapagliflozin) in addition to stable triple combination treatment. The control group was selected over NDHT patients with T2DM who did not receive SGLT-2i and matched with the SGLT-2i group in terms of baseline risk factors by propensity score. The laboratory findings of the patients were compared retrospectively at the time of diagnosis of NDHT (baseline) and at 12-month follow-up.

Results: The decrease in fasting blood glucose and hemoglobin A1C levels was higher in the SGLT-2i group than control group. Although both groups received similar antihypertensive therapy, the improvement in lipid profile was higher in the SGLT-2i group. Glycemic control and side effects were similar in empagliflozin and dapagliflozin groups. However, greater improvement in lipid profiles was detected in dapagliflozin users.

Conclusions: In NDHT patients with T2DM, the addition of SGLT-2i to treatment management in cases where glycemic control is not achieved is associated with more improvement of the lipid profile without significant side effects. However, the effects of various SGLT-2i agents on this improvement may be different.

Key words: sodium glucose cotransporter 2 inhibitors, diabetes mellitus, empagliflozin, dapagliflozin, lipid panel.

ÖZET

Giriş: Bu çalışma, tip 2 diabetes mellitus (T2DM) olan yeni tanı konmuş hipertansif (YTHT) hastalarında 12 haftalık takipte sodyum glukoz kotransporter 2 inhibitörlerinin (SGLT-2i) lipid düzeyleri üzerindeki etkilerini incelemeyi amaçladı.

Yöntemler: Bu retrospektif çalışmaya, T2DM olan 236 YTHT hastası dahil edildi. SGLT-2i grubu, stabil üçlü kombinasyon tedavisine ek olarak SGLT-2i (empagliflozin veya dapagliflozin) alan hastalardan oluştu. Kontrol grubu, SGLT-2i almayan ve başlangıç risk faktörleri açısından SGLT-2i grubu ile eşleşen T2DM'li YTHT hastaları üzerinden propensity skoru ile seçildi. Hastaların laboratuvar bulguları, YTHT tanısı anında (başlangıç) ve 12 aylık takipte retrospektif olarak karşılaştırıldı.

Bulgular: Açlık kan şekeri ve hemoglobin A1C düzeylerindeki düşüş SGLT-2i grubunda kontrol grubuna göre daha yüksekti. Her iki grup da benzer antihipertansif tedavi almasına rağmen, lipid profilindeki iyileşme SGLT-2i grubunda daha yüksekti. Empagliflozin ve dapagliflozin gruplarında glisemik kontrol ve yan etkiler benzerdi. Ancak, dapagliflozin kullananlarda lipit profillerinde daha fazla iyileşme saptandı.

Sonuç: T2DM'li YTHT hastalarında, glisemik kontrolün sağlanamadığı durumlarda tedavi yönetimine SGLT-2i eklenmesi, önemli yan etkiler olmaksızın lipid profilinde daha fazla iyileşme ile ilişkilidir. Ancak çeşitli SGLT-2i ajanlarının bu iyileşme üzerindeki etkileri farklı olabilir.

Anahtar kelimeler: Diabetes mellitus; dapagliflozin; empagliflozin; lipid; sodyum glukoz kotransporter 2 inhibitörleri.

INTRODUCTION

Diabetes mellitus (DM) and hypertension remain significant health burden worldwide. The coexistence of these two diseases, which are closely related to each other, carries a high risk of target organ damage and cardiovascular events (1, 2). In the treatment of type 2 DM (T2DM), the use of sodium glucose cotransporter-2 inhibitors (SGLT-2i) as anti-hyperglycemic drugs has high efficacy and safety (3). SGLT-2i also offer renoprotective or cardioprotective effects (4). Therefore, they may play prognostic roles in cases of T2DM accompanied by hypertension.

The atherogenic effect of impaired lipid metabolism contributes to the development and acceleration of atherosclerosis, target organ damage and the development of cardiovascular diseases (5, 6). Increasing evidence indicated that SGLT-2i may affect lipid metabolism (7). Some clinical studies have reported that SGLT-2i cause rises in low-density lipoprotein cholesterol (LDL) levels despite their renoprotective or cardioprotective effects (8, 9). Conversely, there is some evidence that SGLT-2i may improve high-density lipoprotein cholesterol (HDL) levels and regulate lipid metabolism or accumulation (10, 11). These conflicting results may be due to the efficacy of different SGLT-2i agents. However, the short-term effects of SGLT-2i on lipid levels in newly diagnosed hypertensive (NDHT) patients with T2DM has not yet been investigated.

Corresponding author: Birsen Doganay, Department of Cardiology, Ankara City Hospital, University District Bilkent Street No: 1, 06800, Ankara, Turkiye.
Telephone: +905336852322
E-mail: doganay.brsn@gmail.com
ORCID: https://orcid.org/0000-0003-4659-3596
Received date: 09.02.2023 **Accepted date:** 06.03.2023

Cite as: Doganay B, Celebi OO. Effect of Sodium Glucose Co-Transporter 2 Inhibitors on Lipid Levels in Newly Diagnosed Hypertensive Patients with Type 2 Diabetes Mellitus. Eskisehir Med J. 2023; 4(1): 73-79
doi: 10.48176/esmj.2023.108

Table 1. Baseline characteristics of newly diagnosed hypertensive patients with Type 2 diabetes mellitus

Variables	All population n=236	Control group n=118	SGLT-2i group n=118	p
Age, years	56.3±6.4	56.4±6.1	56.3±6.5	0.999[a]
Male gender, n (%)	142 (60.2)	71 (60.2)	71 (60.2)	0.999[b]
BMI, kg/m^2	27.1±2.9	27.3±2.6	26.9±5.2	0.518[a]
Office BP				
Systolic BP, mmHg	159.6±13.5	159.2±14.3	160.1±12.8	0.611[a]
Diastolic BP, mmHg	98.8±9.4	98.3±9.5	99.2±9.3	0.463[a]
24-hours BP				
Systolic BP, mmHg	152.7±11.7	152.2±11.9	153.2±11.4	0.510[a]
Diastolic BP, mmHg	95.8±8.5	95.2±8.2	96.4±8.7	0.277[a]
Smoking, n (%)	120 (50.8)	57 (48.3)	63 (53.4)	0.435[b]
Hyperlipidemia, n (%)	119 (50.4)	58 (49.2)	61 (51.7)	0.702[b]
Oral antidiabetic drugs, n (%)				
Metformin	209 (88.6)	104 (88.1)	105 (89.0)	0.999[b]
Sulfonylurea	66 (28.0)	33 (28.0)	33 (28.0)	0.999[b]
DPP4	127 (53.8)	64 (54.2)	63 (53.4)	0.999[b]
Glitazone	15 (6.4)	7 (5.9)	8 (6.8)	0.999[b]
Insulin	99 (41.9)	52 (44.1)	47 (39.8)	0.598[b]
Discharge antihypertensive therapy, n (%)				
ACEi/ARBs	219 (92.8)	110 (93.2)	109 (92.4)	0.999[b]
CCB	93 (39.4)	45 (38.1)	48 (40.7)	0.683[b]
Statin	73 (30.9)	35 (29.7)	38 (32.2)	0.678[b]

Data are mean±standard deviation, median (IQR), or number (%). [a] Student T test, [b] Chi-square tests.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase-4 inhibitor.

We hypothesized that SGLT-2i could cause changes in lipid levels in relation to differences in the pharmacokinetic properties of SGLT2/SGLT1 receptor selectivity. Therefore, this study aimed to examine the effects of SGLT-2i and its agents on lipid levels at 12 weeks of follow-up in NDHT patients with T2DM.

METHODS

This study was planned as a single-center retrospective study between June 2019 and June 2021 in Cardiology Clinic from Ankara City Hospital. Sample size was calculated based on a previous study of patients with Type 2DM reporting a decrease in mean total cholesterol after 2 weeks of SGLT-2i treatment (baseline: 169±48 vs. after 2 weeks: 148±34 mg/dL, p=0.05) (12). Accordingly, the effect size was found to be 0.49, and the sample size was determined as at least 47 patients with a 5% margin of error and 95% power. The study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Decision Date/No: 11.2022/E2-22-3007).

Study population

The study population included T2DM patients between 18 and 80 years old who had been NDHT. Alongside lifestyle changes, these patients had been receiving treatment regimens comprising stable triple combination anti-diabetic therapy with metformin (maximum tolerated dose or 2000 mg/day), glimepiride (maximum tolerated dose or 8 mg/day), and dipeptidyl peptidase 4 inhibitors (maximum doses according to country-specific labels) for 12 weeks without achieving glycemic control (hemoglobin A1c (HbA1c) value of >7%) before an SGLT-2i was prescribed. Exclusion criteria were gestational or type 1 or steroid-induced DM, history of SGLT-2i therapy, systemic inflammatory or autoimmune disease, a previous documented history of hypertension and antihypertensive drug use, diabetic ketoacidosis, thyroid dysfunction, acromegaly, active hepatitis, Cushing's syndrome, malignancy, heart and renal

Table 2. Changes in laboratory parameters in patients added to SGLT-2i treatment

Variables	Control group			SGLT-2i group			p[1]	Δp
	Baseline	12 weeks	p	Baseline	12 weeks	p		
WBC, x10^3 /mL	8.3±2.3	8.2±2.1	0.610 *	8.1±2.4	8.0±2.1	0.237 *	0.509[a]	0.664[e]
Neutrophil, x10^3 /mL	4.9 (3.8-6.3)	4.8 (3.6-6.2)	0.444 †	4.7 (3.7-6.2)	4.6 (3.7-5.8)	0.343 †	0.561[c]	0.924[e]
Lymphocyte, x10^3 /mL	2.2±0.7	2.1±0.7	0.107 *	2.3±0.8	2.2±0.7	0.103 *	0.741[a]	0.249[e]
Platelet, x10^3 /mL	248.7±62.8	255.6±60.4	0.114 *	253.1±59.1	255.4±58.7	0.481 *	0.590[a]	0.607[e]
FPG, mg/dL	171 (137.5-207.5)	154 (130-166)	0.025 †	178 (138-214)	132 (117-160)	<0.001†	0.982[c]	<0.001[e]
HbA1c, %	8.8±1.4	8.4±1.3	<0.001*	8.7±1.4	8.0±1.3	<0.001*	0.478[a]	<0.001[e]
Urea, mg/dL	38.0±9.5	40.1±10.6	0.098 *	38.5±9.6	43.5±17.2	0.004 *	0.692[a]	0.039[e]
Creatinine, mg/dL	0.8±0.2	0.8±0.3	0.530 *	0.9±0.3	1.0±0.2	0.030 *	0.936[a]	0.044[e]
Uric acid, mg/dL	4.9±1.3	4.8±1.5	0.755 *	4.8±1.3	4.7±2.0	0.680 *	0.935[a]	0.891[e]
Albumin, g/dL	4.4±0.4	4.5±0.4	0.143 *	4.5±0.4	4.4±0.5	0.211 *	0.418[a]	0.789[e]
AST, U/L	19 (17-27)	19 (16-24.5)	0.774 †	20 (16-26)	19 (15-23)	0.410 †	0.884[c]	0.946[e]
ALT, U/L	24.5 (19-35)	23.5 (19-29)	0.726 †	24 (19-31)	22 (17-29)	0.443 †	0.767[c]	0.991[e]
Total cholesterol, mg/dL	217 (170-248)	180 (134-182)	0.046 †	224 (175-253)	166 (130-198)	0.023 †	0.645[c]	0.030[e]
Triglyceride, mg/dL	228 (143-269)	188 (136-235)	0.048 †	237 (138-275)	172 (130-225)	0.037 †	0.727[c]	0.027[e]
HDL-C, mg/dL	41.0±11.5	43.4±10.1	0.040 *	40.5±11.1	44.7±9.8	0.043 *	0.734[a]	0.050[e]
LDL-C, mg/dL	134.9±34.6	130.1±30.3	0.049 *	136.5±30.7	126.4±33.8	0.042 *	0.707[a]	0.040[e]
Calcium, mg/dL	9.5±0.6	9.6±0.8	0.221 *	9.5±0.6	9.7±0.5	0.016 *	0.901[a]	0.048[e]
Magnesium, mg/dL	1.8±0.2	1.9±0.3	0.340 *	1.8±0.2	1.9±0.3	0.250 *	0.867[a]	0.961[e]
Phosphorus, mg/dL	3.6±0.6	3.6±0.8	0.405 *	3.7±0.6	3.8±0.6	0.004 *	0.346[a]	0.025[e]
Sodium, mmol/L	139.1±2.5	139.3±3.0	0.422 *	138.9±2.9	139.2±3.1	0.264 *	0.564[a]	0.561[e]
Potassium, mmol/L	4.6±0.5	4.6±0.7	0.221 *	4.6±0.5	4.4±0.4	0.003 *	0.972[a]	0.017[e]
eGFR, mL/dk/1.73 m^2	87.6±14.8	86.2±18.1	0.368 *	87.0±15.1	86.8±17.2	0.283 *	0.747[a]	0.885[e]

Data are mean±standard deviation, median (IQR), or number (%). [a] Student T test, [c] Mann-Whitney U test, [e] repeated measures for ANOVA test, * Paired T test, † Wilcoxon Sign Test, p[1], baseline laboratory findings in SGLT-2i (-) *vs.* SGLT-2i (+); Δp, change of laboratory findings in SGLT-2i (-) *vs.* SGLT-2i (+).

Abbreviations: WBC, white blood count, FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ALT, alanin aminotransferaz; AST, aspartate aminotransferase.

Table 3. Distribution of demographic characteristics by SGLT-2i types

Variables	SGLT-2i		p
	Empagliflozin group n=75	Dapagliflozin group n=43	
Age, years	56.6±7.2	55.8±6.1	0.541[a]
Male gender, n (%)	48 (64.0)	23 (53.5)	0.329[b]
BMI, kg/m^2	26.8±5.6	27.1±4.8	0.769[a]
Office BP			
Systolic BP, mmHg	161.2±11.4	158.2±13.5	0.201[a]
Diastolic BP, mmHg	99.8±10.2	98.2±9.1	0.396[a]
24-hours BP			
Systolic BP, mmHg	153.4±11.3	152.8±11.8	0.785[a]
Diastolic BP, mmHg	96.7±8.5	95.8±8.9	0.587[a]
Smoking, n (%)	39 (52.0)	24 (55.8)	0.706[b]
Hyperlipidemia, n (%)	37 (49.3)	24 (55.8)	0.568[b]
Discharge antihypertensive drugs, n (%)			
ACEi/ARBs	69 (92.0)	40 (93.0)	0.999[b]
CCB	31 (41.3)	15 (34.9)	0.559[b]
Statin	26 (34.6)	12 (27.9)	0.455[b]

Data are mean±standard deviation, median (IQR), or number (%). [a] Student T test, [b] Chi-square tests.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase-4 inhibitor.

failure, liver diseases, pregnancy or delivery within the last 90 days, glomerular filtration rate less than 45 mL/min, and missing clinical data.

There were 458 patients who met these initial inclusion criteria. It was determined that SGLT-2i treatment (10 mg once a day) was added to the existing anti-diabetic treatment in 118 of these patients, and these patients were classified as the SGLT-2i group. Out of the remaining 440 patients, a control group matched with the SGLT-2i group for some baseline parameters was formed by propensity match score, in which 1:1 nearest neighbor matching method. The matching parameters were as follows: age, gender, body mass index, comorbidities, oral antidiabetic drugs, baseline fasting blood glucose (FBG), baseline HbA1c, baseline lipid profile and discharge antihypertensive therapy. Thus, 118 NDHT patients with T2DM who did not receive SGLT-2i treatment were included in the control group.

The hospital's electronic information system and patient files were used to gather demographic and clinical data. In addition, SGLT-2i's were classified according to use of empagliflozin or dapagliflozin. All patients' fasting blood samples were taken at the time of admission and at the 12th week.

Laboratory parameters

The blood samples obtained from the patients was subsequently divided into serum and plasma components with centrifugation at 2500xg for 10 min. The enzymatic ultraviolet hexokinase method was then used to obtain values of serum glucose, liver function parameters, and electrolytes with the help of a Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA). An automated glycohemoglobin analyzer (ARKRAY ADAMS A1c HA8180, ARKRAY Global Business Inc., Kyoto, Japan) was used for the evaluation of HbA1c by cation-exchange high-performance liquid chromatography. A bromocresol green method was applied for albumin measurements. Lipid

Table 4. Changes in laboratory parameters by SGLT-2i types

Variables	Empagliflozin group			Dapagliflozine group			p[1]	Δp
	Baseline	12 weeks	p	Baseline	12 weeks	p		
WBC, x10^3 /mL	8.1±2.4	8.0±2.0	0.782*	8.0±2.5	7.9±2.3	0.847*	0.830[a]	0.915[c]
Neutrophil, x10^3 / mL	4.8 (3.8-6.2)	4.7 (3.6-5.8)	0.648†	4.6 (3.4-5.7)	4.5 (3.2-5.9)	0.695†	0.753[b]	0.943[c]
Lymphocyte, x10^3 / mL	2.3±0.7	2.2±0.6	0.349*	2.2±0.8	2.1±0.7	0.539*	0.480[a]	0.988[c]
Platelet, x10^3 /mL	252.2±52.9	256.9±59.6	0.610*	254.5±60.6	254.9±53.1	0.961*	0.829[a]	0.452[c]
FPG, mg/dL	174 (135-217)	130 (121-162)	<0.001†	185 (145-220)	138 (115-155)	<0.001†	0.315[b]	0.715[c]
HbA1c, %	8.6±1.6	8.0±1.8	<0.001*	8.7±1.1	8.1±1.2	<0.001*	0.717[a]	0.673[c]
Urea, mg/dL	37.8±9.5	42.1±14.3	<0.001*	39.7±9.8	45.9±21.4	<0.001*	0.303[a]	0.692[c]
Creatinine, mg/dL	0.9±0.2	1.0±0.3	0.018*	0.9±0.2	0.9±0.4	0.672*	0.320[a]	0.038[c]
Uric acid, mg/dL	4.8±1.2	4.7±2.1	0.721*	4.9±1.3	4.8±1.7	0.760*	0.637[a]	0.562[c]
Albumin, g/dL	4.5±0.4	4.4±0.5	0.178*	4.6±0.3	4.5±0.4	0.193*	0.157[a]	0.711[c]
AST, U/L	20 (17-26)	19 (16-24)	0.460†	19 (15-27)	17 (15-23)	0.380†	0.815[b]	0.359[c]
ALT, U/L	25 (19-34)	23 (18-30)	0.518†	24 (18-30)	21 (17-27)	0.675†	0.415[b]	0.402[c]
Total cholesterol, mg/dL	202 (163-220)	164 (143-208)	0.028†	248 (184-289)	168 (154-215)	<0.001†	0.037[b]	<0.001[c]
Triglyceride, mg/dL	209 (123-224)	168 (125-197)	0.014†	248 (147-296)	185 (137-230)	<0.001†	0.040[b]	<0.001[c]
HDL-C, mg/dL	41.8±9.6	44.7±8.5	0.046*	37.7±11.8	44.1±10.2	<0.001*	0.028[a]	<0.001[c]
LDL-C, mg/dL	132.0±30.2	128.0±32.4	0.435*	144.3±33.4	125.8±30.7	<0.001*	0.042[a]	<0.001[c]
Calcium, mg/dL	9.5±0.5	9.7±0.5	<0.001*	9.4±0.8	9.6±0.5	<0.001*	0.405[a]	0.517[c]
Magnesium, mg/dL	1.8±0.3	1.9±0.4	0.185*	1.8±0.4	1.8±0.3	0.193*	0.999[a]	0.351[c]
Phosphorus, mg/dL	3.7±0.5	3.9±0.6	0.039*	3.8±0.7	3.8±0.6	0.478*	0.370[a]	0.044[c]
Sodium, mmol/L	138.5±2.9	139.2±2.8	0.135*	139.1±3.0	139.5±3.6	0.577*	0.287[a]	0.289[c]
Potassium, mmol/L	4.6±0.5	4.4±0.4	<0.001*	4.7±0.4	4.5±0.4	0.026*	0.265[a]	0.548[c]
eGFR, mL/dk/1.73 m^2	87.2±14.7	86.9±15.6	0.904*	86.8±15.8	86.6±19.8	0.958*	0.890[a]	0.561[c]

Data are mean±standard deviation, median (IQR), or number (%). [a] Student T test, [c] Mann-Whitney U test, [e] repeated measures for ANOVA test, * Paired T test, † Wilcoxon Sign Test, p[1], baseline laboratory findings in SGLT-2i (-) *vs.* SGLT-2i (+); Δp, change of laboratory findings in SGLT-2i (-) *vs.* SGLT-2i (+).

Abbreviations: WBC, white blood count, FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ALT, alanin aminotransferaz; AST, aspartate aminotransferase.

Table 5. Adverse events

Adverse Effects	All patients receiving SGLT-2i n=118	Empagliflozin group n=75	Dapagliflozin group n=43	p
Dysuria, n (%)	18 (15.3)	12 (16.0)	6 (14.0)	0.999[c]
Urinary tract infection, n (%)	9 (7,6)	6 (8.0)	3 (7.0)	0.999[c]
Dyspepsia, n (%)	5 (4.2)	3 (4.0)	2 (4.7)	0.999[c]
Total adverse effects, n (%)	29 (24.6)	19 (25.3)	10 (23.3)	0.999[c]

Data are number (%). [c] Mann-Whitney U test

values were obtained with a Hitachi modular autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA), enzymatic colorimetry was applied for total cholesterol, triglyceride and HDL values. LDL values were calculated with the standard Friedewald formula (13).

Statistical Analysis

IBM SPSS Statistics for Windows 20.0 (IBM Corp., USA) was used in the analysis of all data obtained in this study. In light of the results of the Kolmogorov-Smirnov test, numerical data with normal distribution were identified and presented as mean ± standard deviation, while data found to have non-normal distribution were presented as median values with interquartile ranges. The Mann-Whitney U test and Student t-test were applied when comparing two groups of data with normal distribution. Categorical variables were assessed with numbers and percentages, and Fisher exact and Chi-square tests were used in drawing comparisons between these groups of data. At the 12-week follow-up, changes in laboratory findings were evaluated with the Paired-Sample T test or Wilcoxon Sign Test. Changes in laboratory findings between the control group and the SGLT-2i group were tested by repeated measures for ANOVA analysis. Values of $p < 0.05$ were accepted as statistically significant.

RESULTS

The mean age of NDHT patients with T2DM was 56.2±6.4 years and 60.2% of them were male. It was determined that the majority of patients who were started on SGLT-2i treatment were given empagliflozin (63.6%). Baseline characteristics (Table 1) and baseline laboratory parameters (Table 2) did not differ significantly between the SGLT-2i treatment groups and control group.

At 12-week follow-up, the reduction in FBG and HbA1c levels were higher in the SGLT-2i group compared to the control group. A greater improvement in lipid levels was detected in the SGLT-2i group. Change in urea, creatinine and calcium values were higher in the SGLT-2i group, while these parameters did not change in the control group. Changes in other laboratory findings did not differ significantly between the groups (Table 2).

Demographic characteristics and distributions of discharge antihypertensive drugs did not differ in the empagliflozin and dapagliflozin groups (Table 3). Median baseline total cholesterol (248 vs. 202 mg/dL, p = 0.037), median baseline triglyceride (248 vs. 209 mg/dL, p = 0.040) and mean baseline LDL (144.3±33.4 vs. 132.0±30.2 mg/dL, p = 0.042) levels were higher in the dapagliflozin group than empagliflozin group, while mean baseline HDL level was lower (37.7±11.8 vs. 41.8±9.6 mg/dL, p = 0.028). Other baseline laboratory findings did not differ significantly between the empagliflozin and dapagliflozin groups (Table 4). At the 12-week follow-up, reduction in FBG and HbA1c levels was similar between the empagliflozin and dapagliflozin groups. Change in lipid levels were higher in the dapagliflozin group. While creatinine and phosphorus values increased in the empagliflozin group after 12 weeks of follow-up, these parameters did not change in the dapagliflozin group (Table 4).

Adverse events were dysuria in 15.3% of the patients, urinary tract infection (UTI) in 7.6% and dyspepsia in 4.2%. The rate of adverse events was 24.6% (n = 29). The rate of adverse event were similar in the empagliflozin and dapagliflozin groups (Table 5).

DISCUSSION

This study evaluated the short-term effects of SGLT-2i on lipid levels among patients with NDHT and T2DM with inadequate glycemic control. Among the NDHT patients who received SGLT-2i, there were greater decreases in FBG and HbA1c levels with greater improvement in lipid profiles. This improvement in lipid profiles was more pronounced among patients receiving dapagliflozin.

Hypertension is an essential risk factor for the development of chronic macrovascular and microvascular complications, which are widespread in patients with DM (14). The Prevalence of Diabetes, Hypertension, Obesity and Endocrine Diseases in Turkey (TURDEP-II) study reported hypertension rates among diabetic patients of 67.8% for female and 57.7% for male (15), while the Turkish Nationwide Survey of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD) study reported the prevalence of hypertension among T2DM patients as 67.5% (16).

Lifestyle changes play important roles in the management of both diabetes and hypertension (17). However, this may not be sufficient for glycemic control and blood pressure. In spite of lifestyle changes, diabetes and hypertension may not be controlled in a significant proportion of patients receiving traditional first-line oral antidiabetic drugs and antihypertensive therapy. Therefore, combination therapies

are needed (18). SGLT-2i agents may have significant effects on glycemic control without presenting serious side effects (3). The incidence of adverse events in approximately 25% of SGLT-2i users was within the range of incidence reported in previous studies (12-34%) (19, 20). Failure to achieve glycemic control based on elevated HbA1c levels in T2DM patients may lead to an increased risk of cardiovascular events (21). In NDHT patients with T2DM who received SGLT-2i had greater decreases in FBG and HbA1c levels. However, the efficacy of empagliflozin and dapagliflozin was similar in reducing blood glucose and HbA1c. Previous studies have reported that empagliflozin reduced levels of blood glucose and HbA1c and the incidence of UTI more markedly than dapagliflozin (22, 23). Empagliflozin and dapagliflozin treatments, which have similar mechanisms in glycemic control, may have similar effects in the short term. On the other hand, SGLT-2i-induced glycosuria may create a positive milieu for bacterial growth in the urinary tract (24). A meta-analysis study reported that the association between dapagliflozin and the development of UTI was dose-dependent (25). This may explain the similar rates of UTI observed here in the empagliflozin and dapagliflozin users.

Beyond glycemic control, SGLT-2i may offer significant effects in lowering blood pressure and reducing cardiovascular risk (4). An impaired lipid metabolism can accelerate atherosclerosis and increase the risk of cardiovascular disease (26). Diabetes and antidiabetic drugs may cause functional impairment as a result of their negative effects on lipid metabolism (8-11). To evaluate the effect of SGLT-2i on lipid profiles in NDHT patients with T2DM, a control group matched with potential risk parameters, including baseline antihypertensive drug use and lipid profile, was established. The results of the comparative analysis between groups showed that patients using SGLT-2i had a higher trend of improvement in the lipid profile. Previous studies have shown that SGLT-2i caused small increases in LDL and HDL levels (27, 28). However, those studies included only diabetic patients. Based on the effects of antihypertensive drugs prescribed for NDHT patients in the current study, the improvements in lipid profiles may be higher. This may be related to several mechanisms. It has been suggested that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may modulate peroxisome proliferator-activated receptor (PPAR) gamma (PPAR-γ), which plays a role in regulating glucose and lipid metabolism (29, 30). Besides, zinc-alpha-2-glycoprotein (ZAG), which plays a role in insulin resistance and lipid modulation, can be suppressed by PPAR-γ (31). A previous study showed that patients with T2DM had lower circulating ZAG expression, and dapagliflozin treatment for 12 weeks resulted in increased circulating ZAG expression (32).

On the other hand, there may be a mechanism that SGLT-2i may affect lipid metabolism by modulating serum electrolyte levels (33-35). Experimental and population-based studies indicated that serum electrolyte levels are associated with lipid metabolism and metabolic syndrome (36, 37). SGLT2i can modulate serum calcium, potassium and phosphorus levels, but have no significant effect on sodium levels (33). This was consistent with the findings in the current study. However, changes in serum calcium and potassium levels were similar in dapagliflozin and empagliflozin users, while phosphorus levels increased significantly only in empagliflozin users. Empagliflozin is claimed to modulate the hepatic metabolome (35). An experimental study in a high phosphorus diet rats showed that hepatic arachidonic acid and eicosapentaenoic acid concentrations were increased and that they activated PPAR-alpha (34). Overall, these findings support that SGLT-2i plays a role in lipid metabolism via PPAR regulation. However, different SGLT-2i agents may cause different efficacies for lipid metabolism.

Although basal lipid profiles of patients receiving dapagliflozin were worse than those of patients receiving empagliflozin, greater improvement in lipid profiles was observed at 12 weeks of follow-up. In addition, there was no significant improvement in LDL levels in patients receiving empagliflozin. Previous studies have shown that dapagliflozin is associated with a significant increase in HDL levels, whereas empagliflozin is associated with increased LDL levels (10, 38). Differences in pharmacokinetic properties and the SGLT2/SGLT1 receptor selectivity of SGLT-2i agents may explain their different roles in lipid metabolism. The effects of dapagliflozin on osmotic diuresis, including sodium excretion, may be more prolonged (39). Opposite this, the SGLT2:SGLT1 receptor selectivity ratio is half as compared with empagliflozin (40) The high selectivity of SGLT1 receptors, mostly found in the bowel, can better regulate blood sugar changes and reduce cardiovascular risk (41).

The major limitations of this study were its retrospective design and small sample size. Another important limitation is that long-term effects of SGLT-2i agents may differ. Finally, there may be a need for experimental studies evaluating the interactions between antihypertensive drugs and SGLT-2i.

CONCLUSIONS

In NDHT patients with T2DM, the addition of SGLT-2i to treatment management in cases where glycemic control is not achieved is associated with more improvement of the lipid profile without significant side effects. However, the effects of various SGLT-2i agents on this improvement

may be different. Patients using dapagliflozin showed significantly greater improvement in lipid profiles.

Acknowledgments:
Ethics Committee Approval: The study was approved by the local ethics committee (Decision Date/No: 11.2022/E2-22-3007).

Informed Consent: Retrospective study

Authorship Contributions:
Idea/Concept: BD, Design: BD, Supervision: BD, OOC, Data Collection or Processing: BD, OOC, Analysis or Interpretation: BD, OOC, Literature Search: BD, OOC, Writing: BD, Critical Review: OOC, References And Fundings: -, Materials: -.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

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