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Laboratory changes in older patients using SGLT2 inhibitors

Yaşlı hastalarda SGLT2 inhibitörü kullanımı: laboratuvar değerlendirilmesi

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ABSTRACT

Aim: In this study, we aimed to investigate the results of laboratory parameters related to the use of sodium glucose cotransporter 2 (SGLT2) inhibitors in individuals over 65 years of age who were using empagliflozin or dapagliflozin for the treatment of type 2 diabetes mellitus (T2DM).

Material and Method: A total of 140 patients over 65 years of age who had empagliflozin (10 mg once daily) or dapagliflozin (10 mg once daily) added to their current treatment for T2DM were divided into two groups. Laboratory results at the beginning of treatment and at the 24th week of treatment and drug-related adverse events were noted. The study was retrospectively designed.

Results: Significant decreases in fasting blood glucose and HbA1c were observed in both groups. There was a significant decrease in lipid parameters in the dapagliflozin group. Phosphorus values were elevated in the empagliflozin group. In both groups, there was a significant increase in hemoglobin and calcium values. There was no significant difference in terms of adverse events.

Conclusion: We think that SGLT2 inhibitors, which have many positive effects other than blood sugar regulation with new mechanisms of action that continue to be discovered, can be administered as the primary treatment for appropriate patient groups.

Keywords: SGLT2 inhibitors, older patients, empagliflozin, dapagliflozin, diabetes mellitus

ÖZ

Amaç: Bu çalışmada Tip-2 Diabetes mellitus (T2DM) ile takipli, empagliflozin veya dapagliflozin kullanan 65 yaş üzeri bireylerde sodyum glukoz kotrasporter 2 (SGLT2) inhibitörü kullanımına bağlı laboratuar parametrelerinde ortaya çıkan sonuçları incelemeyi amaçladık.

Gereç ve Yöntem: 65 yaş üzeri T2DM ile takipli mevcut tedavisine empagliflozin (günde bir kez 10 mg) veya dapagliflozin (günde bir kez 10 mg) eklenmiş 140 hasta iki gruba ayrıldı. Tedavi başlangıcında ve tedavinin 24. haftasındaki laboratuar sonuçları, ilaca bağlı yan etkiler kaydedildi. Çalışma retrospektif olarak tasarlandı.

Bulgular: Her iki grupta da anlamlı açlık kan şekeri ve HbA1c düşüşleri gözlendi. Dapagliflozin grubunda lipid parametrelerinde anlamlı düşüş görüldü. Empagliflozin grubunda fosfor değerlerinde yükselme saptandı. Her iki grupta ise hemoglobin ve kalsiyum değerlerinde anlamlı artış meydana geldi. Toplam yan etkiler açısından anlamlı farklılık saptanmadı..

Sonuç: Kan şekeri regülasyonu dışında birçok olumlu etkileri olan ve yeni etki mekanizmaları keşfedilmeye devam edilen SGLT2 inhibitörleri uygun hasta gruplarında öncelikle tercih edilebilecek preperatlar olduğunu düşünüyoruz.

Anahtar Kelimeler: SGLT2 inhibitörleri, yaşlı hastalar, empagliflozin, dapagliflozin, diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease with increasing prevalence around the world, causing significant mortality and morbidity, especially in the elderly population (1).

It is very important to slow down the vascular complications accompanying T2DM, especially in older patient groups. However, treatment success may be limited due to drug side effects with fragility, multiple drug use, treatment incompatibility, and hypoglycemia in the elderly population (2-4).

SGLT2 inhibitors, which have been frequently used in recent years, are oral antidiabetic drugs that act by inhibiting glucose and sodium reabsorption in proximal tubules (**Table 1**) (5). Thanks to their natriuretic and glucosuric effects, they have a renoprotective effect and contribute to cardiovascular protection (6-8).

In older patients followed with T2DM, hypoglycemia and glycemic fluctuations are undesirable side effects. The risk of hypoglycemia is very low due to the fact that the decrease in glucose levels with SGLT2 inhibitor use is independent of insulin (9). In addition, reduced glucotoxicity improves beta cell function (10).

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In this study, we examine laboratory parameters before and after treatment in individuals over 65 years of age using SGLT2 inhibitors. In doing so, we hope to highlight the effects of these drugs other than blood sugar regulation, such as anti-inflammatory and vasculoprotective effects, to enrich the literature.

MATERIAL AND METHOD

This study was planned as a single-center retrospective study in June and July 2022. The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 22.06.2022, Decision No: E2-22-2035). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study included 147 patients over 65 years of age who were being followed with uncontrolled T2DM despite the maximum tolerable dose of metformin, sulfonylurea, dipeptidyl peptidase 4 inhibitor (DPP4), pioglitazone, glinide, or insulin. Laboratory data were recorded after 24 weeks for patients who had SGLT2 inhibitors added to their treatment regimens.

Patients under 65 years of age, with a history of gestational diabetes or type 1 diabetes, with a cancer or currently receiving anticancer treatment, with chronic pancreatitis, with a previous history of SGLT2 inhibitor use, with glomerular filtration rate of <45 mL/min, and with genitourinary tract infection or acute renal failure were excluded from the study.

Study Protocol

Clinical, demographic, and laboratory findings of the patients were recorded from the automation system of the hospital. Patients who received empagliflozin (10 mg once daily) or dapagliflozin (10 mg once daily) in addition to their current treatment constituted the study's two subgroups. Laboratory data were recorded at the start of treatment and after 24 weeks.

Laboratory Parameters

In the morning, fasting blood samples were drawn for the evaluation of biochemical parameters and other laboratory parameters. After the blood samples were centrifuged at 2500 × g for 10 minutes, plasma and serum samples were separated. All parameters were evaluated in the same laboratory. Serum glucose, serum electrolytes, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase were measured with a Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA) by the enzymatic ultraviolet hexokinase method. HbA1c was measured by cation-exchange high-performance liquid chromatography method using the ARKRAY ADAMS A1c HA8180 automated glycohemoglobin analyzer (ARKRAY Global Business Inc., Kyoto, Japan). Albumin was measured by the bromocresol green method. Total cholesterol was measured by enzymatic colorimetric method and high-density lipoprotein cholesterol was measured by enzymatic colorimetric method with a Hitachi modular autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Low-density lipoprotein cholesterol level was calculated with the Friedewald formula for patients with triglyceride levels of <400 mg/dL (14). Patients with triglyceride of >400 mg/dL were evaluated by enzymatic colorimetric method with the second-generation LDL-C Plus Kit and the Hitachi Modular P800 (Roche Diagnostic Corp., Indianapolis, IN, USA).

Statistical Analysis

The STATA program (StataCorp LLC, College Station, TX, USA) was used for data analysis. Normality testing was performed with the Shapiro–Wilk test. Normal distributions were shown as mean ± standard deviation and non-normal distributions as median (interquartile range: 25th-75th percentile). Categorical variables were expressed as numbers and percentages. The Student t-test or Mann–Whitney U test was used to compare numerical variables between the SGLT2 inhibitor therapy groups. Chi-square, Yates correction, and Fisher exact chi-square tests were used for comparisons of categorical data. Changes of laboratory parameters at 24 weeks compared to baseline were evaluated by repeated measures for analysis of variance (ANOVA). Values of $p<0.05$ (*) were considered significant in statistical analysis.

RESULTS

The mean age of the study population was 69.0±3.6 years and the majority of patients were male (61.2%). Analysis of the SGLT2 inhibitor distribution revealed that 68.7% (n: 101) of the patients received empagliflozin and 31.3% (n: 46) received dapagliflozin. The male ratio was higher in the empagliflozin group compared to the dapagliflozin group (67.3% vs. 47.8%; p=0.029). Other demographic characteristics showed no significant differences between the SGLT2 inhibitor therapy groups (**Table 1**).

Table 1. Common SGLT2 inhibitors

	Empagliflozin	Dapagliflozin	Canagliflozin
Preparation	10 mg/25 mg	5 mg/10 mg	100 mg/300 mg
Dosage	10 mg daily, 25 mg max	5 mg daily, 10 mg max	100 mg daily, 300 mg max
Half-life	12.4 h	12.9 h	100 mg: 10.6 h 300 mg: 13.6 h
Time to reach peak plasma concentration	1.5 h	2 h	1-2 h
Oral bioavailability	70-90%	78%	65%
Excretion	54.4% urine, 41.2% feces	75% urine, 21% feces	51.7% feces, 33% urine

Source: Le Liu, Yu-Qing Ni, Jun-Kun Zhan, You-Shuo Liu. The Role of SGLT2 Inhibitors in Vascular Aging. Aging and Disease, Volume 12, Number 5; 1323-1336, August 2021. http://dx.doi.org/10.14336/AD.2020.1229.

At baseline, the mean uric acid level (5.5±1.4 vs. 4.7±1.1; p=0.014) was higher in the empagliflozin group compared to the dapagliflozin group, while the mean albumin (44.2±4.0 vs. 45.7±2.5; p=0.037) and mean phosphorus (3.6±0.5 vs. 3.9±0.7; p=0.007) levels were lower. Other baseline laboratory findings showed no significant differences between SGLT2 inhibitor therapy groups (**Table 2**).

The changes in short-term laboratory findings in patients receiving SGLT2 inhibitor therapy at 24 weeks of follow-up are shown in detail in Table 2. In both SGLT2 inhibitor therapy groups, mean urea levels and mean calcium levels were higher at 24 weeks compared to baseline, and mean fasting blood glucose, mean potassium, and mean HbA1c were lower (p<0.05). These changes were similar between the two SGLT2 inhibitor therapy groups (p>0.05).

In the dapagliflozin group, mean total cholesterol level (191.6±46.8 vs. 179.4±39.7; p<0.001) was lower at 24 weeks compared to baseline, while no significant difference was seen for other laboratory findings. In the empagliflozin group, mean creatinine level (0.9±0.2 vs. 1.0±0.3; p=0.007), mean phosphorus level (3.6±0.5 vs. 3.8±0.6; p<0.001), mean platelet count (242.0±63.8 vs. 252.4±68.6; p=0.019), and mean hemoglobin level (13.8±1.6 vs. 14.1±1.7; p=0.005) were higher at 24 weeks compared to baseline, while no significant difference was seen for other laboratory findings. In addition, the changes in creatinine, phosphorus, platelet count, and hemoglobin were higher in the empagliflozin group compared to the dapagliflozin group (**Table 2**).

The total incidence of adverse events, including urinary tract infection (8.8%) and dysuria (2.7%), was 10.2% (n: 15). Adverse events and their subtypes did not differ significantly between the SGLT2 inhibitor therapy groups (**Table 3**).

Table 2. Demographic characteristics of patients with type 2 diabetes mellitus

Variables	Whole population n=147	Empagliflozin n=101	Dapagliflozin n=46	p
Age, years	69.0±3.6	68.9±3.6	69.2±3.7	0.618
Gender, n (%)				
Female	57 (38.8)	33 (32.7)	24 (52.2)	0.029*
Male	90 (61.2)	68 (67.3)	22 (47.8)	
BMI, kg/m2	26.7±2.0	26.7±2.6	26.7±1.3	0.988
Comorbidity, n (%)				
Hypertension	110 (74.8)	76 (75.2)	34 (73.9)	0.841
CAD	97 (66.0)	68 (67.3)	29 (63.0)	0.708
Hyperlipidemia	116 (78.9)	80 (79.2)	36 (78.3)	0.999
Antihypertensive drugs, n (%)				
ACEI	48 (32.7)	38 (37.6)	10 (21.7)	0.061
ARB	48 (32.7)	33 (32.7)	15 (32.6)	0.999
CCB	48 (32.7)	36 (35.6)	12 (26.1)	0.343
Statin, n (%)	87 (59.2)	60 (59.4)	27 (58.7)	0.999
Oral antidiabetic drugs, n (%)				
Metformin	133 (90.5)	88 (87.1)	45 (97.8)	0.081
Sulfonylurea	36 (24.5)	23 (22.8)	13 (28.3)	0.536
DPP4	74 (50.3)	52 (51.5)	22 (47.8)	0.724
Glitazone	9 (6.1)	6 (5.9)	3 (6.5)	0.999
Glinide	3 (2.0)	1 (1.0)	2 (4.3)	0.480
Insulin	55 (37.4)	35 (34.7)	20 (43.5)	0.359

Data are mean±standard deviation, median (IQR), or number (%).
*: Considered statistically significant (p<0.05).
Abbreviations: BMI, body mass index; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase-4 inhibitor.

Table 3. Changes in short-term laboratory findings in patients receiving SGLT2 inhibitor therapy

Variables	Empagliflozin			Dapagliflozin		
	Baseline	24 weeks	p	Baseline	24 weeks	p
FBG, mg/dL	174.2±56.7	156±56.5	0.012*	172.8±43.1	145±51.4	0.002*
Urea, mg/dL	38.5±10.4	41.8±14.3	0.012*	36.9±10.5	43.4±13.8	0.043*
Creatinine, mg/dL	0.9±0.2	1.0±0.3	0.007*	0.9±0.2	0.9±0.3	0.266
Uric acid, mg/dL	5.5±1.4	5.7±1.8	0.173	4.7±1.1	5.3±1.5	0.653
Albumin, g/dL	44.2±4.0	45.4±4.6	0.089	45.7±2.5	45.3±3.8	0.804
AST, U/L	19 (16-24)	19 (15-23)	0.380	19 (15-28)	17 (15-22.5)	0.238
ALT, U/L	24 (18-31)	22 (18-29)	0.181	21 (18-29)	21 (17-27)	0.822
ALP, U/L	80 (69-100)	83 (71-94)	0.913	83 (64-99)	86 (71-101.5)	0.723
Total cholesterol, mg/dL	176.4±56.0	180.0±56.3	0.208	191.6±46.8	179.4±39.7	0.044*
HDL, mg/dL	42.5±10.4	42.5±9.4	0.985	46.0±11.4	46.7±10.6	0.463
LDL, mg/dL	98.3±39.7	101.2±40.8	0.323	111.1±37.7	101.2±30.1	0.060
Triglyceride, mg/dL	152 (110-198.5)	146.5 (106-232.5)	0.431	161 (108-242)	159 (105-190)	0.159
Calcium, mg/dL	9.4±0.5	9.7±0.5	0.005*	9.5±0.8	9.7±0.5	0.048*
Magnesium, mg/dL	1.8±0.2	1.9±0.2	0.109	1.8±0.3	1.9±0.3	0.535
Phosphorus, mg/dL	3.6±0.5	3.8±0.6	<0.001*	3.9±0.7	3.9±0.6	0.635
Sodium, mmol/L	139.1±2.7	139.4±2.9	0.175	139.3±2.7	139.7±3.7	0.490
Potassium, mmol/L	4.6±0.5	4.5±0.4	0.026*	4.7±0.4	4.6±0.4	0.049*
eGFR, mL/min/1.73 m2	76.8±15.5	74.6±16.0	0.091	78.3±13.9	75.0±18.7	0.252
HbA1c, %	8.7±1.6	8.0±1.4	<0.001*	8.8±1.2	7.8±1.1	<0.001*
TİT (+)	21 (20.8)	14 (13.9)	0.144	9 (19.6)	6 (13.0)	0.366
WBC, $\times 10^3$/mL	8.1±2.3	8.1±2.1	0.712	8.1±2.2	8.1±2.1	0.870
Neutrophils, $\times 10^3$/mL	4.7 (3.5-6.2)	4.8 (3.8-5.8)	0.999	4.4 (3.7-5.7)	4.6 (3.60-5.8)	0.856
Lymphocytes, $\times 10^3$/mL	2.2 (1.7-2.6)	2.2 (1.8-2.5)	0.149	2.2 (1.6-2.8)	2.0 (1.6-2.9)	0.429
Platelets, $\times 10^3$/mL	242.0±63.8	252.4±68.6	0.019*	263.1±68.1	251.7±66.8	0.060
NLR	2.2 (1.6-3.0)	2.2 (1.7-2.9)	0.268	2.1 (1.7-2.9)	2.1 (1.8-3.0)	0.646
Hemoglobin, g/dL	13.8±1.6	14.1±1.7	0.005*	13.2±1.6	13.5±1.7	0.158
RDW	14.4±1.5	14.6±1.4	0.139	14.6±1.3	14.8±1.6	0.195
MPV	8.7±1.0	8.7±1.8	0.965	8.5±1.0	8.6±1.1	0.131

Data are mean±standard deviation, median (IQR), or number (%). *: Considered statistically significant (p<0.05). Abbreviations: WBC, white blood cell count, FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NLR, neutrophil/lymphocyte ratio; MPV, medium platelet volume; RDW, red cell distribution width.

Table 4. Adverse events in patients with type 2 diabetes mellitus receiving SGLT2 inhibitor therapy

Adverse events	Whole population n=310	Empagliflozin n=170	Dapagliflozin n=140	p
Dysuria, n (%)	4 (2.7)	2 (2.0)	2 (4.3)	0.786
Urinary tract infection, n (%)	13 (8.8)	9 (8.9)	4 (8.7)	0.999
Total adverse effects, n (%)	15 (10.2)	10 (9.9)	5 (10.9)	0.999

Data are number (%).

DISCUSSION

SGLT2 inhibitors are frequently used by many clinicians in fields including cardiology, endocrinology, nephrology, and internal medicine. However, as of 2021, data on the use of these drugs among elderly individuals, who constitute 9.8% of the world's population, were still very limited (11).

SGLT2 inhibitors have begun to appear in clinical guidelines for many diseases. In recent studies, the glucose-lowering, cardioprotective, and renoprotective effects of SGLT2 inhibitors were described. In addition, many positive effects such as delayed vascular aging have begun to be shown to occur with different mechanisms. Empagliflozin and dapagliflozin have been shown to increase nitric oxide bioavailability and reduce the formation of reactive oxygen radicals induced by tumor necrosis alpha (12). In this way, it is thought that it may exert its protective effect against vascular aging by reducing endothelial inflammation.

Studies have also shown that SGLT2 inhibitors increase hemoglobin and hematocrit values (13,14). Dapagliflozin has been shown to exert this effect by increasing hepcidin levels (15), while empagliflozin has been shown to increase erythropoiesis and increase hemoglobin and hematocrit values (16). Although this result is evaluated positively in some studies because it may increase myocardial oxygenation, patients should be closely monitored for thrombosis and stroke risk (17). In this study, similar to the literature, an increase in hemoglobin values was observed in older patients. It is thought that SGLT2 inhibitors may contribute positively to delayed vascular aging by increasing tissue perfusion, but further studies are needed on the different mechanisms of this increase.

Chronic inflammation has been shown to increase endothelial dysfunction, which causes age-related disorders, and to exacerbate atherosclerosis (18). There are studies showing that SGLT2 inhibitors have vasculoprotective efficacy in animal models of T2DM (19). We saw that, while there was a decrease in lipid parameters in the dapagliflozin group, the same effect was not achieved in the empagliflozin group. In an experimental study, it was determined that empagliflozin was associated with an increase in LDL-C levels via the reduction of catabolism (20). One possible explanation for this may be differences in pharmacokinetic properties and SGLT2/SGLT1 receptor selectivity.

In our study, we observed that serum calcium increased in both groups. There are studies showing that empagliflozin strongly reduces calcium calmodulin-dependent kinase (CaMKII) activity in ventricular myocytes in animal models. This results in reduced calcium release from the sarcoplasmic reticulum and improved myocardial contractility (21).

In our results, especially after the use of empagliflozin, there was an increase in phosphorus values. This increase can contribute to increased delivery of oxygen to tissues by shifting the oxygen-dissociation curve to the right. In this way, it can make a positive contribution to tissue perfusion in older patient groups. However, SGLT2 inhibition may cause secondary hyperparathyroidism as a result of increased phosphate uptake (22). As a result of SGLT2 inhibitors increasing renal tubular phosphate reuptake, the level of 1,25-dihydroxyvitamin D decreases, and it is reported that the risk of bone fractures may increase with reduced calcium absorption from the intestines (23). This is an undesirable effect, especially for older patients with higher risks of falls and fractures. According to a meta-analysis, however, there was no increase in the risk of bone fractures in patients taking SGLT2 inhibitors (24). There are also studies showing that empagliflozin binds to SGLT2 with more than 2500-fold affinity compared to SGLT1, while dapagliflozin binds with 1200-fold affinity (25). The high selectivity of SGLT2 may explain the differing results for empagliflozin.

There are studies suggesting that the mechanism underlying the arterial stiffness prevention effect of empagliflozin is independent of its antihypertensive activity and endothelial function. It can be assumed that it acts with the direct activation of specific receptor signaling pathways (26).

In our study, it was seen that despite the other maximum tolerable doses of treatment used by the patients, there was a significant decrease in HbA1c and fasting blood glucose. SGLT2 inhibitors appear to be important drugs that increase the treatment options of clinicians in appropriate patient groups of all ages. In addition, there were no side effects due to the SGLT2 inhibitors that would necessitate drug withdrawal. However, it is possible that some individuals in this older patient population were not able to describe their symptoms.

Lack of information about patients' blood pressure and weight changes can be considered as one of the limitations of our study. Especially in the population over 65 years of age, weight and muscle loss, sarcopenia, and frailty are important factors that can increase the risk of falling. The fact that the findings cannot be compared with those of the population under 65 years of age and the number of patients being low can be counted as other deficiencies of this study.

CONCLUSION

SGLT2 inhibitors have promising effects in improving vascular function together with their blood sugar-lowering effects. With natriuretic and glucosuric effects, they can reduce arterial hypertension, atherosclerosis, and arterial stiffness. It is thought that SGLT2 inhibitors may have many other potential effects that have not yet been fully demonstrated. Therefore, more prospective basic and clinical research on these drugs is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 22.06.2022, Decision No: E2-22-2035).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. American Diabetes Association, older adults: Standards of Medical Care in Diabetes. Diabetes Care 2019; 42: 139–47.
2. Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. Diabetes Care 2012; 35: 2650–64.
3. ItoH, OmotoT, Abe M, et al. Relationships between the duration of illness and the current status of diabetes in elderly patients with type 2 diabetes mellitus. Geriatr Gerontol Int 2017; 17: 24–30.
4. Öten E, Çapraz M. The effect of body mass index on osteoporosis and fracture risk in patients with type 2 diabetes mellitus. J Health Sci Med 2021; 4: 882-5.
5. Pradhan A, Vohra S, Vishwakarma P, Sethi R. Review on sodium-glucose cotransporter 2 inhibitor in diabetes mellitus and heart failure. J Family Med Prim Care 2019; 8: 1855-62.
6. Brown AJM, Lang C, McCrimmon R, Struthers A. Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo controlled study. BMC Cardiovasc Disorders 2017; 17: 229.
7. Mordi NA, Mordi IR, Singh JS, et al. Renal and Cardiovascular Effects of sodium-glucose cotransporter 2 (SGLT2) inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure (RECEDE-CHF): protocol for a randomised controlled double-blind cross-over trial. BMJ Open 2017; 7: e018097.
8. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation 2017; 136: 1643-58.
9. Hasan FM, Alsahli M, Gerich JE. SGLT2 inhibitors in the treatment of type 2 diabetes. Diabetes Res Clin Pract 2014; 104: 297-322
10. Brunton, S.A. The potential role of sodium glucose co-transporter 2 inhibitors in the early treatment of type 2 diabetes mellitus. Int J Clin Pract 2015; 69: 1071-87.
11. United States Census Bureau, International Database.
12. Uthman L, Homayr A, Juni RP, et al. Empagliflozin and dapagliflozin reduce ROS generation and restore NO bioavailability in tumor necrosis factor αstimulated human coronary arterial endothelial cells. Cell Physiol Biochem. 2019; 53: 865-86.
13. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373: 2117–28.
14. Taşkaldıran I, Kuşkonmaz Ş, Çulha C. Use of sodium glucose co-transporter 2 inhibitor (SGLT2i) in geriatric population. Turk J Diab Obes 2021; 2: 158-64.
15. Ghanim H, Abuaysheh S, Hejna J, et al. Dapagliflozin suppresses hepcidin and increases erythropoiesis. J Clin Endocrinol Metab 2020 Feb11. pii: dgaa057.
16. Mazer CD, Hare GMT, Connelly PW, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation 2020; 141: 704-7.
17. Imprialos KP, Boutari C, Stavropoulos K, et al. Stroke paradox with SGLT-2 inhibitors: a play of chanceor a viscosity-mediated reality? J Neurol Neurosurg Psychiatry 2017; 88: 249-53.
18. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. Circ Res 2018; 123: 825- 48.
19. Steven S, Oelze M, Hanf A, et al. The SGLT2 inhibitor empagliflozin improves the primary diabetic complications in ZDF rats. Redox Biol 2017; 13: 370-85.
20. Briand F, Mayoux E, Brousseau E, et al. Empagliflozin, via switching metabolism toward lipid utilization, moderately increases LDL cholesterol levels through reduced LDL catabolism. Diabetes 2016; 65: 2032-8.
21. Mustroph J, Wagemann O, Lücht CM, et al. Empagliflozin reduces Ca/calmodulin-dependent kinase II activity in isolated ventricular cardiomyocytes. ESC Heart Fail 2018; 5: 642-8.
22. Taylor SI, Blau JE, Rother KI. Possible adverse effects of SGLT2 inhibitors on bone. Lancet Diabetes Endocrinol 2015; 3: 8-10.
23. Oren Steen, Ronald M Goldenberg, The role of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Can J Diabetes 2017; 41: 517-23.
24. Ruanpeng D, Ungprasert P, Sangtian J, Harindhanavudhi T. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and fracture risk in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Metab Res Rev 2017; 33: 10.1002/dmrr.2903.
25. Anker SD, Butler J. Empagliflozin, calcium, and SGLT1/2 receptor affinity: another piece of the puzzle. ESC Heart Fail 2018; 5: 549–51.
26. Lunder M, Janić M, Japelj M, Juretič A, Janež A, Šabovič M. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. Cardiovasc Diabetol 2018; 17: 153.