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EFFICACY OF SGLT-2 INHIBITORS IN THE TREATMENT OF TYPE 2 DIABETES: SINGLE CENTRE EXPERIENCE

TİP 2 DİYABET TEDAVİSİNDE SGLT-2 İNHİBİTÖRLERİNİN ETKİNLİĞİ: TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Sodium-glucose transporter-2 (SGLT-2) inhibitors lower blood glucose levels by reducing renal glucose reabsorption without affecting insulin secretion. The aim of our study was to evaluate the effect of SGLT-2 inhibitor treatment on glycemic control and the possible superiority of the drugs by comparing clinical parameters and laboratory findings in Type 2 diabetes mellitus (T2DM) patients.

Material and Methods: Two hundred and nineteen T2DM patients who received SGLT-2 inhibitor therapy [empagliflozin (EMPA) (n=146) or dapagliflozin (DAPA) (n=73)/10 mg] were enrolled retrospectively. The patients' demographic characteristics, detailed medical history, comorbidities, physical examination findings, complications, weight and systolic-diastolic blood pressure follow-up, laboratory findings (at baseline, 3rd, and 12th month), and overall follow-up outcomes were evaluated.

Result: The mean values of HbA1c and fasting blood glucose (FBG) decreased significantly compared with the baseline values after the treatment. The mean body weight and uric acid values were significantly reduced in the 3rd month of the treatment. Similarly, the values of the liver function tests decreased substantially after treatment.

Conclusion: The beneficial effects of SGLT-2 inhibitors on glycemic control and liver functions in patients with T2DM have been demonstrated. In addition, there was no major difference in terms of clinical parameters, laboratory findings, and drug safety in patients between EMPA and DAPA.

Keywords: Type 2 diabetes mellitus, sodium-glucose cotransporters, empagliflozin, dapagliflozin

ÖZET

Amaç: Sodyum-glukoz taşıyıcı-2 (SGLT-2) inhibitörleri, insülin sekresyonunu etkilemeden renal glukoz reabsorpsiyonunu azaltarak kan glukozunu düşürür. Çalışmamızın amacı, Tip 2 diabetes mellituslu (T2DM) hastalarda SGLT-2 inhibitör tedavisinin glisemik kontrol üzerindeki etkisini ve ilaçların olası üstünlüklerini klinik parametreler ve laboratuvar bulguları ile karşılaştırarak değerlendirmektir.

Gereç ve Yöntem: SGLT-2 inhibitörü tedavisi [empagliflozin (EMPA) (n=146) veya dapagliflozin (DAPA) (n=73)/10 mg] alan 219 T2DM hastalarının verileri geriye dönük olarak kaydedildi. Demografik özellikler, detaylı tıbbi öykü, komorbiditeler, komplikasyonlar, vücut ağırlığı ve kan basıncı takibi, laboratuvar bulguları (başlangıçta, 3. ve 12. aylarda) incelendi.

Bulgular: Bu çalışmamızda SGLT-2 tedavisinden sonra ortalama HbA1c ve açlık plazma glukoz değerleri başlangıç değerlerine göre anlamlı oranda azaldı. Ortalama vücut ağırlığı ve ürik asit değerleri tedavinin 3. ayında anlamlı oranda azaldı. Benzer şekilde karaciğer fonksiyon testleri değerlerinde de tedavi sonrası iyileşmeler görüldü.

Sonuç: SGLT-2 inhibitörlerinin T2DM hastalarında glisemik kontrol ve karaciğer fonksiyonu üzerindeki olumlu etkileri açıkça gösterilmiştir. Ayrıca klinik parametreler, laboratuvar bulguları ve ilaç güvenliği açısından EMPA ve DAPA arasında önemli bir fark saptanmamıştır.

Anahtar Kelimeler: Tip 2 diabetes mellitüs, sodyum glukoz kotransporterlar, empagliflozin, dapagliflozin

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic multi-systemic disease characterised by insulin resistance, insulin deficiency, and hyperglycaemia. T2DM carries a high risk of morbidity and mortality frequently related to renal failure, cardiovascular diseases (CVD), and micro/macrovascular complications (1, 2).

The primary target for treating T2DM is to achieve optimal glycemic control starting with lifestyle changes like diet and exercise as the first-line treatment. Oral antidiabetics (OADs) are used in the second-line treatment of T2DM (3). Conventional OADs act either by directly increasing the insulin secretion from pancreatic β-cells or by indirectly suppressing tissue insulin resistance, glucose production, and absorption in the liver and intestine, respectively (4). In recent years, studies have focused on new antidiabetic treatment modalities whose functions are independent of insulin secretion.

Sodium-glucose transporter-2 (SGLT-2) receptors expressed in the proximal renal tubules are responsible for glucose reabsorption from the glomerular filtrate independent of insulin. Furthermore, SGLT-2 receptor expression is reported to be increased in T2DM and is one of the mechanisms responsible for severe hyperglycaemia in T2DM (5). SGLT-2 inhibitors increase glycosuria by inhibiting the renal tubular reabsorption of glucose and sodium; therefore, they lower blood glucose levels without directly affecting insulin secretion or its sensitivity (5, 6). Unlike several OADs, SGLT-2 inhibitors have been frequently reported to provide glycemic control without causing side effects such as hypoglycaemia or weight gain (7). Moreover, SGLT-2 inhibitors are reported to be associated with effective blood pressure control, favourable cardiovascular risk profile, and reduced risk of cardiovascular death in the literature (8, 9).

In this study, we aimed to evaluate the effect of SGLT-2 inhibitor treatments (dapagliflozin [DAPA] and empagliflozin [EMPA]) on glycemic control and clinical and laboratory parameters in our tertiary referral centre.

MATERIALS AND METHODS

Sample

This study was conducted between January 1st 2018 to November 30th 2019 with the approval of the İstanbul Faculty of Medicine, Clinical Research Ethics Committee (Date: 06.12.2019, No; 20). Two hundred and nineteen patients with the diagnosis of T2DM aged over 18 years who received SGLT-2 inhibitor therapy (EMPA 10 mg or DAPA 10 mg) were evaluated retrospectively. The exclusion criteria were defined as; age <18 years, Type 1 Diabetes Mellitus, pregnancy, end-stage renal failure or patients on dialysis, or advanced stage (Child B or C) liver failure. All patients received appropriate antidiabetics in addition to SGLT-2 inhibitors as an add-on therapy, and prior treatment continued unless a severe side effect. Chronic renal failure (CRF) was defined as an estimated glomerular filtration rate (e-GFR)<60 ml/min/1.73 m^2 and microalbuminuria was defined as urinary albumin-to-creatinine ratio >20 mg/g (10). Patients' demographic characteristics, detailed medical history, presence of comorbidities, physical examination findings, complications of diabetes, data of weight, and systolic-diastolic blood pressure follow-up, laboratory findings (at baseline-3rd month-12th month), antidiabetic drugs other than SGLT-2 inhibitor used by patients and follow-up outcomes at 12th-month treatment were evaluated using the recorded medical data of patients.

Laboratory

Complete blood count analysis was performed from the patients' venous blood samples. Haematological parameters were analysed using a haematology analyser (CellDyne 3700, Abbott, Abbott Park, IL, USA). Biochemical analyses were performed from the serum samples by using an electro-chemiluminescence immunoassay analyser (Beckman Coulter Unicel DXI 800, Brea, CA, USA). The analysis of serum hormone levels was performed via an immunodiagnostic system (Siemens, Advia Centaur xp, Germany). HbA1c level analysis was performed in Beckman Coulter Au480 model automated HbA1c analyser using the turbidimetric immunoinhibiting method.

Statistical analysis

In our study, the 21.0 version (IBM, Armonk, NY, USA) of the SPSS (Statistical Package for the Social Sciences) programme was used for the statistical analysis of data. In descriptive statistics, discrete and continuous numerical variables were expressed as mean, ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were expressed as the number of cases and (%). In the univariable analysis, cross-table statistics were used to compare categorical variables (Chi-Square, Fisher exact test) abnormally distributed parametric data were compared with Student's t-test and Paired t-test; non-parametric data that did not meet the normal distribution were compared with Mann–Whitney U and Kruskal–Wallis tests. P<0.05 value was considered statistically significant.

RESULTS

In this study, 219 T2DM patients were included, including 89 females (40.6%) and 130 males (59.4%). The mean age was 59.2±8.6 years (range; 21-79); there was no statistically significant difference between male (59.7±8.4 years) and female (58.5±8.8 years) patients in terms of mean age (p=0.4). The mean diabetes duration was 15.9±7.6 years. While the most common comorbidity was hypertension (70.8%), coronary heart disease was seen in

42.5%, CRF in 6.4% (no patient had stage 4 or 5 chronic kidney disease), microalbuminuria in 36.5%, congestive heart failure (CHF) (1.4%) and peripheral artery disease (1.4%). While the most used oral antidiabetic drug was metformin (94%), basal insulin was used in 38.8%, and the basal-bolus regimen in 26%. Additionally, 62.6% of the patients received angiotensin-converting enzyme (ACE) inhibitor/Angiotensin receptor blockers (ARB), and 10.5% of the patients used diuretics (loop and thiazides) (Table 1). Of the study patients, 66.7% (n=146) were treated with EMPA and 33.3% (n=73) with DAPA. Among background OAD treatment, only sulfonylurea treatment was lower in EMPA-receiving patients (22% vs 37%; p=0.02, Odds ratio [OR]:5.6), and basal insulin treatment tended to be higher in EMPA-receiving patients than in those receiving DAPA (43.2% vs 30.1%; p=0.06). Other background medications did not differ between the two treatment groups (p=0.8 for metformin, p=0.6 for thiazolidinediones, p=1 for GLP-1 agonists, p=0.7 for basal-bolus regimen).

The mean values of HbA1c and fasting blood glucose (FBG) were significantly reduced compared with the baseline values in all patients after treatment (Table 2 and Figure 1). Although the microalbuminuria levels decreased numerically, they did not reach statistical significance. Similarly, the mean values of body weight and uric acid levels decreased significantly during 3rd month of treatment. In addition, it was determined that the mean values of liver function tests (ALT, GGT, AST; at the end of the 12th month; ALP at the end of the 3rd month) reduced significantly after the treatment. Moreover, the mean serum HDL value increased significantly at the end of the 12th month of treatment. On the other hand, although a slight decline was observed in GFR values at the beginning, there was no statistically significant difference in e-GFR and systolic and diastolic blood pressure values during the follow-up period (Table 2).

Table 1: Clinical features of the study participants

Variables	Results
Age, years, mean±SD (range)	59.2±8.6 (21-79)
Gender, female, n (%)	89 (40.6)
Duration of diabetes, years, mean±SD	15.9±7.6
Smoking history (ever), n (%)	111/216 (41.3)
Hypertension, n (%)	155 (70.8)
Hyperlipidaemia, n (%)	142 (64.8)
Chronic kidney failure, n (%)	14 (6.4)
Heart failure, n (%)	3 (1.4)
Microalbuminuria, n (%)	61/167 (36.5)
Coronary heart disease, n (%)	93 (42.5)
Cerebrovascular accident, n (%)	7 (3.2)
Peripheral artery disease, n (%)	3 (1.4)
Diabetic foot, n (%)	9 (4.1)
Treatment history, n (%)	
Metformin	206 (94)
Sulphonylureas	59 (27)
Meglitinids	48 (22)
DPP-4 inhibitors	63 (28.8)
Tiazolidinediones	7 (3.2)
GLP-1 analogues	6 (2.7)
Basal insulin	85 (38.8)
Basal-bolus regimen	57 (26)
Statins	142 (64.8)
Fenofibrates	21 (9.6)
ACE-I/ARB	137 (62.6)
Diuretics	23 (10.5)

SD: Standard deviation, DPP-4: Dipeptidyl peptidase-4, GLP-1: Glucagon-like peptide-1, ACE-I: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers

While the pre-treatment hypoglycaemia rate was 15.5% in all cases; it was determined to be 15.4% in 3rd month and 14.5% in the 12th month of treatment (p>0.05 for each). Besides, SGLT inhibitor treatment was discontinued in 14 patients (6.4%). All patients who discontinued the treatment had diabetes for more than 7 years, most of them were female (57.1%) and EMPA users (85.7%). Discontinuation of treatment was due to hypoglycaemia in four patients, urogenital infection in six patients, impaired renal function in one patient, and other reasons in three patients. The treatment was discontinued in 10 patients (4.6%) at 3rd month. due to genital infection in one patient, hypovolemia/dehydration in two patients, and due to other reasons in seven patients.

In our study, in patients who received EMPA therapy; mean values of HbA1c, FBG, and microalbuminuria decreased significantly at the 3rd and 12th month compared with the baseline values. The mean serum uric acid value was also reduced in the 3rd month compared with the baseline. Additionally, liver function tests (ALP, ALT, GGT) decreased significantly at the end of the 3rd month (Table 3). In the group receiving DAPA, it was determined that the mean HbA1c value during the entire follow-up period and FBG, microalbuminuria at the 3rd month decreased significantly compared to the baseline values. In addition, it was observed that there was a significant reduction in body weight during the follow-up period. The values of the liver function tests were also decreased significantly (Table 4). However, there was no statistically significant difference between the hypoglycaemia rates (DAPA 16.7% vs. EMPA 11.0%) at the end of the 3rd month in both groups (p=0.166). No statistically significant difference was found when comparing the effects of EMPA vs. DAPA on the clinical parameters during the follow-up period.

Table 2: Clinical characteristics and laboratory values of all patients at baseline and 3rd and 12th month of treatment

Variables (mean±SD)	Baseline	3rd month	12th month	p-value[1]	p-value[2]	p-value[3]
Body weight (kg)	83.4±14.5	83.1±14.2	83.92±14.5	**0.001**	**0.052**	**0.008**
HbA1c (%)	9.24±1.6	8.010±1.5	7.64±1.4	**<0.001**	**<0.001**	**<0.001**
Fasting plasma glucose (mg/dL)	195.0±72.9	162.4±54.3	172.8±68.2	**<0.001**	0.833	**0.022**
Urea (mg/dL)	33.59±10.6	35.41±10.4	38.44±14.2	0.096	**0.046**	**0.001**
Creatinine (mg/dL)	0.86±0.2	1.14±3.5	0.89±0.2	0.504	0.665	0.063
Uric acid (mg/dL)	5.04±2.0	4.82±1.1	5.11±1.2	**0.001**	0.490	0.845
Sodium (mmol/L)	139.9±2.4	140.2±2.3	140.6±2.4	0.744	0.582	0.259
ALP (U/L)	80.02±27.1	74.39±24.1	78.59±24.3	**0.002**	0.275	0.609
AST (U/L)	20.51±7.9	19.66±6.7	19.00±6.1	0.118	0.601	**0.039**
ALT (U/L)	25.01±13.4	22.75±11.9	23.05±11.9	**<0.001**	0.762	**0.005**
GGT (IU/L)	25.90±17.0	23.87±20.1	23.67±11.7	**<0.001**	0.256	**0.015**
Triglyceride (mg/dL), median (IQR)	157 (111)	152 (109)	181.6 (154)	**0.8**	0.7	0.9
HDL-C (mg/dL)	44.07±12.3	44.64±12.1	44.67±12.1	0.4	0.6	0.6
LDL-C (mg/dL)	115.0±50.5	108.4±32.8	106.4±29.9	0.535	0.549	0.629
Total-C (mg/dL)	189.1±43.1	185.2±38.5	181.0±36.6	0.598	0.622	0.918
Microalbumin/creatinine (mg/g), Median (IQR)	11.4 (37)	10 (29)	4.4 (18)	0.1	0.9	0.3
e-GFR (ml/min)	87.6±18	86.06±16.6	84.1±20	0.6	0.06	0.04
Systolic BP (mmHg)	130.7±19.4	133.7±17.5	137.0±19.6	0.290	0.797	0.944
Diastolic BP (mmHg)	78.65±10.5	81.78±9.3	80.60±10.6	0.089	0.138	0.573
Red Blood Cell (10^6/uL)	4.86±0.48	5.03±0.4	5.07±0.5	**<0.001**	0.929	**<0.001**
Haemoglobin (g/L)	13.72±1.4	14.05±1.5	14.30±1.5	**<0.001**	0.067	**<0.001**
Haematocrit (%)	41.08±3.9	42.45±4.2	43.21±4.3	**<0.001**	**0.042**	**<0.001**

[1]: Baseline 3rd month [2]: 3rd month-12th month [3]: Baseline-12th month
Bold values are statistically significant
SD: Standard deviation, IQR: Interquartile range, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Total-C: Total cholesterol, e-GFR: Estimated glomerular filtration rate, BP: Blood pressure

DISCUSSION

SGLT-2 inhibitors have additional beneficial effects other than their glucose-lowering effects. SGLT2 inhibitor therapy also provides weight loss due to the burning of fatty acids induced by glycosuria and blood pressure control due to osmotic diuresis (11). SGLT-2 inhibitor therapy has been associated significantly with a decrease in systolic (3-6 mmHg) and diastolic (1-2 mmHg) blood pressure in patients with T2DM (12). Berhan A. and Barker A. reported that there was a significant reduction in HbA1c and FBG levels with SGLT-2 inhibitors compared to placebo in their studies (13). However, we did not observe a significant change in blood pressure with the SGLT-2 inhibitor, possibly due to the measurement difference. In addition, due to the retrospective characteristics of our study, the blood pressure values may have been recorded incompletely, which may be the cause of the inconsistency of the blood pressure results in contrast to the literature. In a meta-analysis in which the outcomes of 27 published studies were reviewed and involving a total of 7363 T2DM patients; Toyama et al. reported that SGLT-2 inhibitors were highly effective and reliable agents in lowering HbA1c level (0.29%; 95% CI, −0.39 to 0.19). Additionally, the researchers noted that these drugs effectively reduced FBG, systolic-diastolic blood pressure, and body weight (14). In another study, Liakos et al. reported a significant reduction in body weight and blood pressure values by EMPA treatment (15). Similarly, in our study, it was determined that the mean values of HbA1c and FBG decreased significantly in comparison to the baseline values in all patients after treatment. In addition, the mean body weight values were also significantly reduced in the 3rd month of treatment compared with the baseline values. It was also observed that there was a significant reduction in body weight during the follow-up period in patients treated with DAPA. However, there were no statistically significant differences in the systolic and diastolic blood pressure values after DAPA-EMPA treatment during the follow-up period. In our consideration, the findings that were inconsistent with the published data about the body weight observed in the 12th month of treatment may be due to the higher frequency of insulin treatment with EMPA.

The elevated uric acid concentration has been closely associated with cardiovascular disease, hypertension, and

Table 3: Clinical and biochemical parameters in patients treated with empagliflozin

Variables (mean±SD)	Baseline	3rd month	12th month	p-value[1]	p-value[2]	p-value[3]
Body weight (kg)	83.24±13.9	83.77±14.2	85.25±13.3	**<0.001**	0.185	0.065
HbA1c (%)	9.29±1.6	8.10±1.6	7.68±1.4	**<0.001**	**0.002**	**<0.001**
Fasting Plasma Glucose (mg/dL)	199.1±80.2	160.8±57.8	168.3±70.3	**<0.001**	0.775	**0.010**
Urea (mg/dL)	33.64±10.7	34.69±9.7	40.49±16.6	**0.045**	0.167	**0.001**
Creatinine (mg/dL)	0.88±0.2	0.89±0.2	0.95±0.2	0.554	0.466	**0.019**
Uric acid (mg/dL)	5.19±2.3	4.85±1.1	5.28±1.3	**0.015**	0.239	0.485
Sodium (mmol/L)	140.1±2.4	140.3±2.3	140.6±2.3	0.4	0.3	0.3
ALP (U/L)	82.4±26.3	73.6±21.8	76.9±22.5	0.001	0.3	0.5
AST (U/L)	25.16±14.4	22.86±11.0	24.89±13.3	**0.007**	0.585	0.130
ALT (U/L)	26.45±18.5	24.34±21.8	24.56±12.3	**<0.001**	0.351	0.095
GGT (IU/L)	26.5±18.6	24.2±21	24.6±12	0.6	0.6	0.08
Triglyceride (mg/dL), median (IQR)	147 (98)	140 (98)	168 (154)	0.853	0.419	0.734
HDL-C (mg/dL)	44.69±12.4	45.32±11.6	45.26±11.6	0.335	0.112	**0.031**
LDL-C (mg/dL)	106.0±374.8	33.69±92.2	72.86±153.4	**0.016**	0.433	**0.006**
Total-C (mg/dL)	186.8±44.7	183.2±37.5	177.0±33.3	0.608	0.681	0.820
Microalbumin/creatinine (mg/g), Median (IQR)	11 (40)	9. 8 (25)	5.3 (15)	0.1	0.6	0.1
e-GFR (ml/min)	86.3±19	84.3±17	80.3±21	0.4	0.15	0.049
Systolic BP (mmHg)	131.2±18.8	133.8±16.2	134.0±18.3	0.2	0.5	0.5
Diastolic BP (mmHg)	78.5±10.3	82.5±9.3	78.7±11	**0.005**	0.14	**0.35**
Red Blood Cell (10^6/uL)	4.9±0.5	5.04±0.5	5.1±0.5	**<0.001**	0.001	0.9
Haemoglobin (g/L)	13.75±1.3	14.07±1.4	14.29±1.4	**<0.001**	0.943	**0.037**
Haematocrit (%)	41.20±3.6	42.55±3.9	43.29±4.0	**<0.001**	0.933	**0.011**

[1]: Baseline 3rd month, [2]: 3rd month-12th month, [3]: Baseline-12th month
Bold values are statistically significant
SD: Standard deviation, IQR: Interquartile range, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Total-C: Total cholesterol, e-GFR: Estimated glomerular filtration rate, BP: Blood pressure

CRF. It has been demonstrated that after SGLT-2 inhibitor therapy, due to the increase in uric acid excretion, uric acid levels, and renal functions improved, which reduces the risk of cardiovascular disease (16). In a meta-analysis in which 62 studies were reviewed and 34,941 T2DM patients were included, Zhao et al. reported that SGLT-2 inhibitors significantly reduced serum uric acid levels (17). In our study, the mean uric acid value was significantly decreased at the 3rd month of treatment compared with the baseline values in all patients.

It has been reported that post-treatment improvement of hepatic dysfunction with SGLT-2 inhibitors was achieved possibly due to the improvement in hyperglycaemia and insulin resistance independent of reduction in body weight. In a study consisting of 115 T2DM patients treated with DAPA (n=69) and EMPA (n=46), Lee et al. reported that ALT levels statistically decreased in all cases [40.3±28.0 vs. 29.0±14.1 U/L (p<0.001)] at the end of 6th month of SGLT-2 inhibitor treatment (18). Similarly, Gunhan et al. documented a significant reduction in ALT and AST levels (p=0.001 and 0.007, respectively) in 119 T2DM patients receiving DAPA (41.2%) and EMPA (58.8%) after 6 months of treatment (19). In accordance with these data, we detected that the post-treatment liver function tests' values (ALT, GGT, AST; at the end of the 12th month; ALP at the end of the 3rd month) significantly decreased in our study.

In diabetic patients, SGLT-2 inhibition is considered to reduce albuminuria by improving glomerular filtration in the early stages of diabetic nephropathy (20). However, Liu et al. concluded that SGLT-2 inhibitors had no significant effect on e-GFR levels in their meta-analysis (21). In another meta-analysis, Xu et al. noted that SGLT-2 inhibitor therapy was not significantly associated with e-GFR change in 22,843 T2DM cases (22). Although a slight decline was observed with SGLT-2 inhibitor treatment, no statistically significant difference was found in the mean values of creatinine, glomerular filtration rate, and sodium after SGLT-2 inhibitor therapy in our study.

Table 4: Clinical and biochemical parameters in patients treated with dapagliflozin

Variables (mean±SD)	Baseline	3rd month	12th month	p-value[1]	p-value[2]	p-value[3]
Body weight (kg)	83.75±15.4	81.71±14.1	81.80±16.2	**0.012**	**0.034**	**0.021**
HbA1c (%)	9.13±1.4	7.82±1.1	7.57±1.5	**<0.001**	**0.036**	**<0.001**
Fasting Plasma Glucose (mg/dL)	186.9±55.2	165.6±47.0	179.0±66.3	**0.007**	0.466	0.764
Urea (mg/dL)	33.47±10.5	36.83±11.6	35.71±9.9	0.818	0.158	0.176
Creatinine (mg/dL)	0.82±0.1	1.61±6.0	0.81±0.2	0.803	0.750	0.820
Uric acid (mg/dL)	4.72±1.2	4.76±1.1	4.87±1.2	**0.029**	0.575	0.262
Sodium (mmol/L)	140±2.4	140.3±2.4	140.6±2.7	0.8	1	1
ALP (U/L)	76.3±27.4	76±28.3	81.1±27.1	0.4	0.2	0.8
AST (U/L)	24.69±11.2	22.52±13.6	20.45±9.2	**0.002**	0.720	**0.008**
ALT (U/L)	24.79±13.4	22.94±16.3	22.43±11.0	**0.020**	0.513	0.088
GGT (IU/L)	24.8±13.5	22.95±16.3	22.4±11	0.6	0.5	0.1
Triglyceride (mg/dL), median (IQR)	190.5 (130)	174.5 (148)	206 (160)	0.220	0.935	0.205
HDL-C (mg/dL)	42.83±12.3	43.31±13.2	43.87±13.0	0.520	0.389	0.106
LDL-C (mg/dL)	116.6±35	110±36	110.5±36	0.16	0.9	0.3
Total-C (mg/dL)	193.9±39.3	189.2±40.4	186.3±40.8	0.165	0.765	0.896
Microalbumin/creatinine (mg/g), median (IQR)	12.9 (36)	11.6 (40)	3.45 (17)	0.8	0.7	1
e-GFR (ml/min)	90.29±16.3	89.49±15.3	91.78±25.8	0.468	0.964	0.639
Systolic BP (mmHg)	129.7±20.4	133.6±20.1	139.7±21.1	0.610	0.832	0.608
Diastolic BP (mmHg)	78.93±11.0	80.50±9.5	82.38±10.2	0.685	0.476	0.959
Red Blood Cell (10^6/uL)	4.82±0.5	5.02±0.5	5.06±0.5	**<0.001**	0.194	**0.003**
Haemoglobin (g/L)	13.67±1.5	14.02±1.6	14.30±1.7	**<0.001**	**0.009**	**<0.001**
Haematocrit (%)	40.85±4.3	42.27±4.6	43.11±4.7	**<0.001**	**0.011**	**<0.001**

[1]: Baseline 3rd month, [2]: 3rd month-12th month, [3]: Baseline-12th month
Bold values are statistically significant
SD: Standard deviation, IQR: Interquartile range, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, HDL-C: high-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Total-C: Total cholesterol, e-GFR: Estimated glomerular filtration rate, BP: Blood pressure

The inhibition of glucose and sodium reabsorption in the proximal renal tubules by SGLT-2 inhibitors triggers osmotic/natriuretic diuresis and reduction of plasma, interstitial, and extravascular volume. The reduction of plasma volume increases haematocrit (HCT) and haemoglobin (HGB) levels (23). In addition, recently, SGLT2 inhibitors have been associated with elevations in serum erythropoietin secretion, which results in increased haemoglobin and haematocrit values (24). In a study conducted in 808 patients with the diagnosis of T2DM, Aberle et al. reported significantly increased HCT and RBC values at the 56th week of DAPA treatment (25). In accordance with published data, it has been observed that RBC, HGB, and HCT levels significantly increased after SGLT-2 inhibitor therapy in our study.

Microalbuminuria is strongly associated with cardiovascular and progressive kidney diseases (20). In a meta-analysis including 7363 T2DM cases, Toyama et al. highlighted that SGLT-2 inhibitors effectively reduced the microalbuminuria values (14). Similarly, in another study consisting of 119 patients treated with DAPA (41.2%) and EMPA

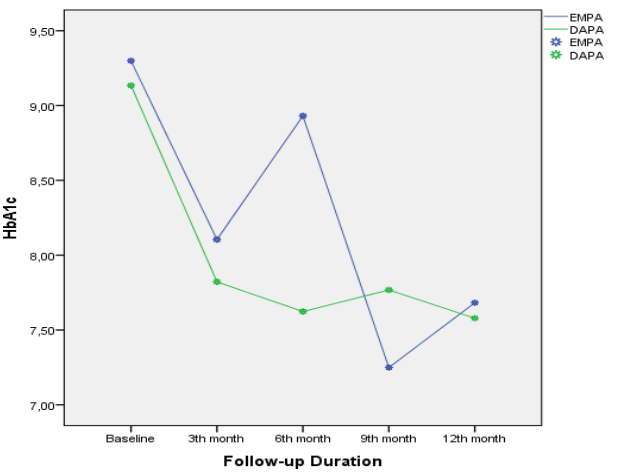

Figure 1: Comparison of change in HbA1c levels during the treatment in patients treated with EMPA and DAPA (p<0.001)
EMPA: Empagliflozin, DAPA: Dapagliflozin

(58.8%), Gunhan et al. concluded that SGLT-2 inhibitors had a beneficial effect in reducing microalbuminuria (189. In addition, Dekkers et al. reported that the microalbuminuria values decreased by 43.9% with DAPA treatment (26). Although microalbuminuria levels decreased numerically with SGLT-2 inhibitor treatment, they did not reach the statistical significance possible due to the small sample number in our study (Type 2 error).

An important clinical advantage of SGLT-2 inhibitors over other antidiabetic drugs is that they are not associated with the risk of hypoglycaemia (27). In a study including 350 T2DM patients, Ku et al. stated that there was no significant difference in the post-treatment Hypoglycemia rates between DAPA and EMPA (28). In our study, the hypoglycaemia rates did not show significant differences between patients receiving DAPA and EMPA treatments (16.7% vs. 11.0%, respectively) at the end of the 3rd month.

Our study has some limitations. First, the retrospective design of the study was the main limitation. Having missing data was an important limitation. On the other hand, this is one of the largest real-world data in terms of the efficacy and safety of SGLT-2 inhibitor treatment in Turkey.

CONCLUSION

In conclusion, the beneficial effects of SGLT-2 inhibitors (EMPA and DAPA) on glycemic control and liver functions in patients with T2DM were demonstrated in this study. Moreover, the protective effects of both agents on cardiovascular and renal diseases have been highlighted in association with a decrease in serum uric acid concentration and microalbuminuria. In addition, there was no major superiority of one of the two SGLT-2 inhibitors (EMPA, DAPA) over the other in terms of clinical parameters, laboratory findings, and patient drug safety.

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