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Efficacy and Side Effect Profile of Empagliflozin and Dapagliflozin in Combination Therapy: A Real-World Experience

Empagliflozin ve Dapagliflozinin Kombinasyon Tedavisindeki Etkinliği ve Yan Etki Profilinin Değerlendirilmesi: Gerçek Yaşam Deneyimi

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Abstract

Objective: Sodium-glucose co-transporter inhibitors (SGLT2i) offer significant cardiovascular benefits, although several adverse events have also been reported with their use. The present study aimed to determine how the preference of SGLT2i is influenced by the adverse effects and the cardiovascular and renal benefits they demonstrate in clinical practice. In addition, the effectiveness of different SGLT2i in combination therapy was revealed. **Material and Methods:** The patients in their third to the eighth month of SGLT2i treatment, who were admitted to our out-patient clinic for the follow-up evaluation of fasting plasma glucose (FPG) level, hemoglobin A1c (HbA1c) level, and body weight, were included in the present study. The follow-up evaluations were defined as those conducted at the sixth month and the final month of follow-up visits. The final-month evaluation was defined as the one conducted upon the patients' last admission to the out-patient clinic between 10 and 14 months of the SGLT2i treatment. **Results:** A total of 244 patients received the SGLT2i treatment. Among the patients who fulfilled the inclusion criteria, 52 patients were in the empagliflozin group and 37 patients were in the dapagliflozin group. The FPG and HbA1c levels declined significantly in both empagliflozin ($p=0.004$ and $p=0.002$) and dapagliflozin ($p=0.04$, $p<0.001$) groups. In the combination therapy involving both the SGLT2i, the FPG and HbA1c levels decreased considerably ($p<0.001$). Urinary tract infection was observed as the most common complication in both empagliflozin and dapagliflozin groups. **Conclusion:** In Turkey, SGLT2i preference in Type 2 diabetes mellitus (T2DM) is closely associated with the data reported in the related literature. Empagliflozin and dapagliflozin, in all combinations, are, therefore, considered effective treatment options for T2DM. It is recommended to select a targeted patient population when considering the adverse effect profile as there is a trend of inconsistent follow-up in Turkey.

Keywords: Sodium-glucose transporter 2 inhibitors; diabetes mellitus, Type 2; hemoglobin A1c; combination therapy; adverse events

Özet

Amaç: Sodyum glukoz birlikte-taşıyıcı inhibitörleri [Sodium-glucose co-transporter inhibitors (SGLT2i)], önemli kardiyovasküler faydalarının yanında, birçok yan etkisi tanımlanmıştır. Bu çalışmada, klinik uygulamada SGLT2i tercihinin, SGLT2i'nin tanımlanmış yan etkileriyle kardiyovasküler ve renal olumlu etkilerden nasıl etkilendiğini belirlemek ve SGLT2i'nin kombinasyon tedavisindeki etkinliğini ortaya çıkarmaktır. **Gereç ve Yöntemler:** Çalışmaya, SGLT2i başlanması sonrası 3. ila 8. aylar arasında ayaktan poliklinik kontrolüne gelerek açlık kan şekeri (AKŞ), hemoglobin A1c (HbA1c) ve vücut ağırlığı ölçümleri yapılmış olan hastalar dâhil edildi. Takipler, 6. ay ölçümü ve son ölçüm olarak değerlendirildi. Son değerlendirme, hastaların 10-14. aylar arasında son poliklinik başvuruları olarak tanımlandı. **Bulgular:** Toplamda 244 hasta SGLT2i tedavisi almıştır. Çalışmaya dâhil edilme ölçütlerini karşılayan hastalardan empagliflozin grubunda 52 hasta, dapagliflozin grubunda 37 hasta bulunmaktadır. Empaglifozin ve dapagliflozin grubunda hem AKŞ hem de HbA1c değerlerinde istatistiksel olarak anlamlı düşüş saptanmıştır (sırasıyla $p=0,004$, $p=0,002$ ve $p=0,04$, $p<0,001$). Her 2 SGLT2i ile kombinasyon tedavisinde hem AKŞ hem de HbA1c değerleri anlamlı olarak düşmüştür ($p<0,001$). Her 2 grupta en sık görülen yan etki, idrar yolu enfeksiyonudur. **Sonuç:** Ülkemizde, Tip 2 diabetes mellitus (T2DM) tedavisinde SGLT2i tercihi literatürle yakın ilişkilidir. Tüm kombinasyon seçeneklerinde dapagliflozin ve empagliflozin T2DM için etkin bir tedavi seçeneğidir. Yan etki profili göz önüne alındığında, ülkemizde takip sıklığının yeterli olmaması nedeniyle tedavi verilecek hastalar dikkatle seçilmelidir.

Anahtar kelimeler: Sodyum-glukoz transporter 2 ınhibitörleri; diabetes mellitus, Tip 2; hemoglobin A1c; kombinasyon tedavisi; advers olay

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease involving insulin resistance (1). Various oral anti-diabetic (OAD) combination therapies and injection treatments have already been developed for the treatment of T2DM patients. However, with the emergence of novel pieces of evidence, the preference for a particular combination therapy and treatment approach differs among physicians.

Sodium-glucose co-transporter inhibitors (SGLT2i) are the new-generation OADs that regulate blood glucose levels by lowering the renal uptake of sodium and glucose. With the validation of the renal and cardiovascular benefits of SGLT2i over the years, these have been included in the first line of treatment in T2DM (2). In Turkey, first dapagliflozin, and then a year later empagliflozin became popular for T2DM treatment. Both dapagliflozin and empagliflozin have demonstrated effectiveness in terms of weight loss and lowering of blood glucose levels in long-term randomized controlled trials (3,4). In cardiovascular safety studies, empagliflozin significantly decreased the cardiovascular mortality rate and total mortality rate (5). Canagliflozin, another SGLT2i, also resulted in a significant decrease in 3-point major adverse cardiovascular events (3-P MACE), although it could not demonstrate a considerable decrease in the cardiovascular mortality rate (6). Dapagliflozin decreased cardiovascular death or hospitalizations for heart failure in the DECLARE-IMI 58 study, while not demonstrating any decline in cardiovascular deaths (7). SGLT2i offer significant cardiovascular benefits, although with several incidences of adverse events, such as bone fractures, amputation, urinary bladder carcinoma, and genital and urinary tract infections (5-8). Therefore, it is imperative to conduct a detailed evaluation to select the appropriate patients for SGLT2i prescription. Accumulating evidence over the years is expected to alter the SGLT2i preference in clinical practice as well as the patient profile for SGLT2i prescription. In this context, the present study aimed to determine how the preference of SGLT2i is influenced by the adverse effects and the renal and cardiovascular benefits they demonstrate in clinical practice, in addition to exploring the efficiency of SGLT2i in combination therapies.

Material and Methods

Study Design

The present study was designed as a retrospective study. The patients who were diagnosed with T2DM at the Department of Endocrinology and Metabolism, Karadeniz Technical University, between January 2017 and July 2019, were included in the study. The study procedures were approved by the local ethics committee of Karadeniz Technical University (Approval Date: 31 May 2019; Approval No: 24237859-442). The study was conducted in accordance with the principles established by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) along with following the guidelines for Good Pharmacoepidemiology Practice and the local regulations, including local data protection regulations, by the International Society for Pharmacoepidemiology.

The criteria for the inclusion of patients were as follows:

1. Aged >18 years,
2. A minimum of 12 months of documented diagnosis of T2DM,
3. Ongoing OAD and/or injection therapy,
4. Empagliflozin or dapagliflozin treatment added between January 2017 and July 2019,
5. Admitted to the out-patient clinic for the evaluation of fasting plasma glucose (FPG) level, hemoglobin A1c (HbA1c) level, and body weight between the third and the eighth month after the initiation of SGLT2i treatment,
6. Glomerular filtration rate (GFR) ≥60 mL/min.

The exclusion criteria were as follows:

1. Presence of acute coronary syndrome, acute cerebrovascular event, chronic liver disease, pregnancy or cancer,
2. Use of medications, such as steroids, capable of elevating blood glucose levels,
3. A history of alcohol or drug abuse,
4. Previous diagnosis of T1DM or latent autoimmune diabetes in adults,
5. Poor compliance with the treatment pro cess or not taking insulin injections regularly,

Treatment Plan

Each patient was prescribed a diabetic diet plan appropriate to their body mass index (BMI) by the dieticians in our hospital. The insulin regimens and doses administered were recorded for each patient throughout the treatment period. The target FPG level and the postprandial glucose level were defined as 80-130 mg/dL and <180 mg/dL, respectively.

Data Collection

Clinical data of the patients were retrieved from the hospital's electronic records. The evaluations of the FPG level, HbA1c level, and body weight performed between 4 and 8 months and those performed between 10 and 14 months were considered the 6-month evaluations and final evaluations, respectively. The final evaluation was defined as the one conducted upon the patients' last admission to the out-patient clinic between 10 and 14 months. In the case of patients with more than one FPG record over three months, the average of the measurement values was used in the analysis. The basal and bolus insulin doses were recorded for each patient.

Since the present study was designed as a retrospective study, the initial HbA1c and FPG levels between the groups were expected to be significantly different. Therefore, it was considered that a comparison of the percentage changes in the variables would be more appropriate. This comparison was realized using the following formulas: ΔFPG=(baseline FPG-final FPG)/baseline FPG; ΔHbA1c=(baseline HbA1c-final HbA 1c)/baseline HbA1c.

Biochemical Analysis

The biochemical parameters of patients' plasma were analyzed. The plasma glucose levels had been measured using the enzymatic reference method involving hexokinase (Beckman Coulter AU5800). Beckman Coulter, AU5800, California. The plasma HbA1c levels had been estimated using high-performance liquid chromatography and mass spectroscopy (Premier HB9210) Trinity Biotech, ABD. Low-density lipoprotein in plasma had been measured using an enzyme-based colorimetric assay (Beckman Coulter AU5800). Plasma creatinine had been assessed using the kinetic Jaffé method (Beckman Coulter AU5800). Urine protein level had been measured using the "protein error of indicator" method (IQ 200/iChem velocity). Beckman Coulter, California.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences version 23.0 (IBM Corp. Armonk, NY, USA). The categorical variables were expressed as frequency (n) and percentage (%). The continuous variables in the present study, which did not have a normal distribution and were analyzed using the Shapiro-Wilk test, were expressed as median (minimum-maximum) values. When comparing two variables, the independent variables were compared using the Mann-Whitney U test, and the dependent variables were compared using Wilcoxon signed-rank test. Comparisons among three or more variables were conducted using the Friedman test. Dependent categorical variables were compared using McNemar's test. A p value of less than 0.05 was considered significant.

Results

A total of 244 patients who had received treatment with empagliflozin (n=136) and dapagliflozin (n=108) between January 2017 and July 2019 were included in the present study. Among these 244 patients, 155 patients who were not admitted to the out-patient clinic were excluded from the study. The remaining patients, 52 patients in the empagliflozin group and 37 patients in the dapagliflozin group, who fulfilled all inclusion criteria, were finally included in the study. The demographic and clinical characteristics of these patients are presented in Table 1. The mean duration of follow-up for these patients was 12±2 months. The patients in the empagliflozin group were older, while the patients in the dapagliflozin group had higher body weight and BMI ($p<0.05$). The duration of DM was similar between the two groups. While significantly higher values of median HbA1c level ($p=0.001$) and insulin dose ($p=0.049$) were observed in the dapagliflozin group, the median FPG levels did not differ significantly between the groups. The rate of empagliflozin preference was observed to be significantly

Table 1. Demographic and baseline clinical characteristics of patients included in the present study.

Variable		Groups Empagliflozin (n=52)	Dapagliflozin (n=37)	p value
Age (year)¥		57 [34-73]	53 [19-70]	0.022**
Sex‡				
Male		19 (36.5)	10 (27.0)	0.475***
Female		33 (63.5)	27 (73.0)	
Weight (kg)†		85.8±15.2	98.4±18.3	0.001*
BMI (kg/m²)¥		31.6 [22.0-61.5]	35.5 [27.1-51.1]	0.009**
Duration of diabetes (years)¥		9 [1-35]	8 [1-40]	0.812**
Hypertension‡	Yes	48 (92.3)	29 (78.4)	0.068****
	No	4 (7.7)	8 (21.6)	
Heart failure‡		9 (17.3)	3 (8.1)	0.346****
Macrovascular complications‡		35 (67.3)	8 (21.6)	<0.00***
Microvascular complications‡	Retinopathy	15 (28.8)	8 (21.6)	0.602***
	Neuropathy	26 (50.0)	12 (32.4)	0.152***
	Nephropathy	18 (34.6)	12 (32.4)	1.000***
Previous hypoglycemia events‡		7 (13.5)	4 (10.8)	0.757****
Fasting plasma glucose (mg/dL)¥		136.5 [84-254]	172 [78-408]	0.115**
HbA1c (%)¥		7.8 [5.3-12.5]	8.9 [6.4-13.4]	0.001**
Previous insulin dose (unit)¥		35 [10-228]	79 [12-230]	0.049**
Duration of follow-up (month)¥		10.2 [3-25.3]	15.2 [4-24.3]	0.005**
Total number of out-patient visits (n)¥		5 [2-14]	4 [2-18]	0.677**
Ratio of duration of follow-up to total number of out-patient visits¥		2.2 [0.7-9.6]	3.0 [0.8-12.1]	0.022**

¥Median (minimum-maximum); ‡n (%); †Mean±standard deviation; *Independent samples t-test; **Mann-Whitney U test; ***Chi-square test; ****Fisher's exact test; BMI: Body mass index; HbA1c: Hemoglobin A1c.

higher in patients with macrovascular complications (67.3%; p<0.001). The duration of follow-up was considerably higher in the dapagliflozin group compared to the empagliflozin group (p=0.005). On the contrary, the rate of admission to the out-patient clinic was higher in the empagliflozin group compared to the dapagliflozin group (p=0.022).

A higher preference for empagliflozin compared to that for dapagliflozin was observed ever since the two have been introduced in clinical practice. This difference in preference was particularly evident between January 2019 and July 2019 (Table 2). Metformin was revealed as the most commonly used OAD agent in both groups (94.4%), with 47 (90.4%) patients in the empagliflozin group and all patients in the dapagliflozin group being prescribed metformin.

The other OAD agents prescribed to patients most commonly, after metformin, were dipeptidyl peptidase-4 inhibitors (DPP4i) and sulfonylurea, respectively. A total of 58 (65.2%) patients in the study population were administered insulin treatment. The distribution of OAD usage was similar in the 2 groups (Table 3). The changes in the OAD regimens following the initiation of SGLT2i treatment are presented in Table 4.

Table 2. Initiation of empagliflozin-dapagliflozin.

Variable	Groups Empagliflozin (n=52)‡	Dapagliflozin (n=37)‡
Jan 17-July 17	------	16 (43.2%)
July 17-Jan 17	------	6 (16.2%)
Jan 18-July 18	10 (19.2%)	6 (16.2%)
July 18-Jan 19	17 (32.7%)	9 (24.3%)
Jan 19-July 19	25 (48.1%)	------

‡n (%).

Table 3. Details of the baseline treatment and pre-study treatment regimens for all patients.

		Groups	
	Overall‡	**Empagliflozin (n=52)‡**	**Dapagliflozin (n=37)‡**
Metformin, *yes*	84 (94.4)	47 (90.4)	37 (100.0)
Sulfonylurea, *yes*	16 (18.0)	8 (15.4)	8 (21.6)
DPP4i, *yes*	23 (25.8)	16 (30.8)	7 (18.9)
Pioglitazon, *yes*	4 (4.5)	3 (5.8)	1 (2.7)
GLP-1 receptor agonists, yes	4 (4.5)	1 (1.9)	3 (8.1)
Basal insulin ±bolus insulin	44 (52.2)	22 (42.3)	22 (59.5)
Mixed insulin	14 (15.7)	10 (19.2)	4 (10.8)
Treatment regimen			
Metformin only	48 (53.9)	25 (48.1)	23 (62.2)
Metformin+DPP-4i	17 (19.1)	13 (25.0)	4 (10.8)
Metformin+sulfonlyurea	8 (9.0)	4 (7.7)	4 (10.8)
Metformin+pioglitazon	2 (2.2)	2 (3.8)	0 (0.0)
Metformin+eksenatide	3 (3.4)	1 (1.9)	2 (5.4)
Metformin+ ≥2 OADs	6 (6.7)	2 (3.8)	4 (10.8)
Other OADs	5 (5.6)	5 (9.6)	0 (0.0)
Basal±bolus insulin+metformin ±other OADs	41 (46.1)	19 (36.5)	22 (59.5)
Basal ±bolus insulin ±other OADs	3 (3.4)	3 (5.8)	0 (0.0)
Mixed insulin+metformin ±other OADs	14 (15.7)	10 (19.2)	4 (10.8)
Mixed insulin ±other OADs	0 (0.0)	0 (0.0)	0 (0.0)
Insulin ±other OADs	58 (65.2)	32 (61.5)	26 (70.3)

‡n (%); DPP4i: Dipeptidyl peptidase-4 inhibitors; GLP-1: Glucagon-like peptide 1; OAD: Oral anti-diabetic.

Table 4. Requirement of oral anti-diabetics during empagliflozin and dapagliflozin treatments.

	Groups		
	Empagliflozin (n=52)	**Dapagliflozin (n=37)**	**p value**
Metformin‡			
Baseline	47 (90.4)	37 (100.0)	0.073****
After SGLT2i	47 (90.4)	37 (100.0)	0.073****
Secretagogues‡			
Baseline	8 (15.4)	8 (21.6)	0.635***
After SGLT2i	5 (9.6)	7 (18.9)	0.225****
DPP-4i‡			
Baseline	16 (30.8)	7 (18.9)	0.311***
After SGLT2i	13 (25.0)	6 (16.2)	0.463***
Pioglitazone‡			
Baseline	3 (5.8)	1 (2.7)	0.638****
After SGLT2i	0 (0.0)	0 (0.0)	1.000****
GLP-1‡			
Baseline	1 (1.9)	3 (8.1)	0.303****
After SGLT2i	1 (1.9)	2 (5.4)	0.568****

‡n (%); ***Chi-square; ****Fisher's exact test; SGLT2i: Sodium-glucose co-transporter inhibitors; DPP-4i: Dipeptidly peptidose-4 inhibitors; GLP-1: Glucagon-like peptide 1.

The mean systolic blood pressure decreased significantly in both groups during the follow-up period ($p<0.05$). The units of the total dose of injected insulin were considerably higher in the dapagliflozin group compared to the empagliflozin group ($p=0.049$). Empagliflozin was the preferred agent in patients with lower GFR levels ($p=0.007$). The GFR levels decreased significantly in both groups ($p<0.05$ for all). The basal low density lipoprotein (LDL) value was relatively higher in the dapagliflozin group ($p=0.001$). However, at the end of the study, the LDL values of the two groups were not significantly different ($p>0.05$ for all). The other laboratory measurement values are presented in Table 5.

Regular data from the follow-ups at 6 and 12 months were retrieved for 25 patients in the empagliflozin group and 19 patients in the dapagliflozin group. The basal, 6-month, and 12-month FPG values in the empagliflozin group were 136 mg/dL, 128 mg/dL, and 122 mg/dL, respectively ($p=0.048$); the corresponding values in the dapagliflozin group were 177 mg/dL, 127 mg/dL, and 142 mg/dL, respectively ($p=0.114$) (Figure 1). The basal HbA1c value in the empagliflozin group was 7.9%, while the HbA1c values at 6 and 12 months, respectively ($p=0.002$). The corresponding HbA1c values in the dapagliflozin group were 9.1%, 7.4%, and 7.8%, respectively ($p=0.002$) (Figure 2). When compared to empagliflozin there was a higher preference for dapagliflozin in patients with higher blood glucose levels and those who were overweight (Table 6). When the baseline and final values of FPG and HbA1c were analyzed, a statistically significant decrease was observed in the empagliflozin group ($p=0.004$ and $p=0.002$, respectively). Similarly, a significant decline was observed in the corresponding values in the dapagliflozin group ($p=0.04$ and $p<0.001$, respectively) (Table 6). When the two groups were compared, ΔFPG and ΔHbA1c did not differ significantly ($p=0.721$ and $p=0.07$, respectively). While the decrease in body weight observed in the empagliflozin group was significant ($p=0.002$), the decrease observed in the dapagliflozin group was not ($p>0.05$). Moreover, both SGLT2i were observed to be effective in combination therapy (Table 7), as evidenced by the significant decrease in the FPG and HbA1c levels in the patients who were administered insulin and OAD as well as in the patients who received only OAD. The addition of SGLT2i to the treatment for patients who were already on metformin and DPP4i (±other OADs ±insulin) and those who were on metformin+sulfonylurea (±other OADs ±insulin) significantly decreased both FPG ($p=0.048$ and $p=0.028$) and HbA1c levels ($p=0.036$ and $p=0.005$).

Urinary tract infection was observed as the most common adverse effect in both groups (Table 8). No statistically significant difference existed between the groups in terms of adverse effects ($p<0.05$). However, the rate of discontinuation of medication due to adverse effects was relatively higher in the empagliflozin group. Urinary bladder malignancy was detected in one patient in the dapagliflozin group 2 years after the discontinuation of SGLT2i.

Discussion

The present study revealed that treatment with SGLT2i in combination therapy is highly effective, although there are occurrences of adverse events. Among the 244 patients that had been prescribed SGLT2i during the 30 months considered in the present study, 155 (63.5%) patients were not admitted to the out-patient clinic within the first 8 months. The established guidelines recommend that patients with T2DM be admitted to the out-patient clinic between three and 6 months, referring to which it could be observed in the present study that the number patients not complying with follow-up visits was rather high. Finally, 89 patients who were prescribed SGLT2i and were admitted to the out-patient clinic for follow-up visits within the first 8 months were included in the present study.

According to the TEMD study conducted previously in Turkey, almost half of the patients with T2DM admitted to a third-level healthcare facility were administered insulin (9).

In our hospital, which is also a third-level healthcare facility, dapagliflozin is prescribed to patients who are on insulin treatment, and despite that, the target HbA1c level has not been achieved (Table 1). Similarly, Gün-

Table 5. Comparative analysis of the changes in the clinical and laboratory parameters between empagliflozin and dapagliflozin groups.

	Groups		
	Empagliflozin (n=52)	**Dapagliflozin (n=37)**	**p value**
Systolic blood pressure (mmHg)¥			
Baseline	130 [90-200]	135 [110-200]	0.673**
Final	120 [100-170]	125 [110-190]	0.429**
p value€	0.033	0.023	
Diastolic blood pressure (mmHg)¥			
Baseline	80 [50-110]	80 [70-100]	0.430**
Final	80 [50-100]	80 [60-100]	0.502**
p value€	0.097	0.084	
Total dose of injected insulin (unit)¥			
Beginning	35 [10-228]	79 [12-230]	0.049**
Final	32 [0-190]	57 [12-234]	0.088**
p value€	0.293	0.445	
Ratio of the total dose of injected insulin to weight (unit/kg/day)¥			
Beginning	0.4 [0.1-2.1]	0.7 [0.1-1.7]	0.125**
Final	0.4 [0.0-1.7]	0.6 [0.1-1.9]	0.148**
p value€	0.614	0.475	
Alanine aminotransferase (IU/L)¥			
Baseline	21 [3-93]	26 [8-68]	0.192**
Final	19 [6-55]	24 [7-112]	0.224**
p value€	0.090	0.206	
Low density lipoprotein (mg/dL)¥			
Baseline	80.5 [34-177]	116 [33-164]	0.001**
Final	90.5 [28-200]	113 [16-191]	0.080**
p value€	0.077	0.656	
Creatinine (mg/dL)¥			
Baseline	0.8 [0.5-1.2]	0.7 [0.4-1.1]	0.027**
Final	0.8 [0.5-1.4]	0.7 [0.4-1.3]	0.046**
p value€	0.150	0.195	
Glomerular filtration rate (mL/min)¥			
Baseline	95.5 [60-124]	101 [64-141]	0.007**
Final	94 [46-122]	101 [44-133]	0.003**
p value€	0.010	0.022	
Proteinuria (mg/mL)¥			
Baseline	0 [0-100]	0 [0-100]	0.480**
Final	0 [0-300]	0 [0-100]	0.764**
p value€	0.485	0.930	

¥Median (minimum-maximum); **Mann-Whitney U test; €Wilcoxon test.

han et al. (10) conducted a study immediately after the release of SGLT2i into the market and demonstrated that 60% of the patients who were initiated with SGLT2i were already on insulin treatment. Considering that the blood-glucose-lowering effect of SGLT2i is independent of insulin, the reason for this could be explained largely by the fact that SGLT2i would be preferred for those patients for whom the target FPG level has not been achieved despite insulin treatment. Another reason could be related to the lower

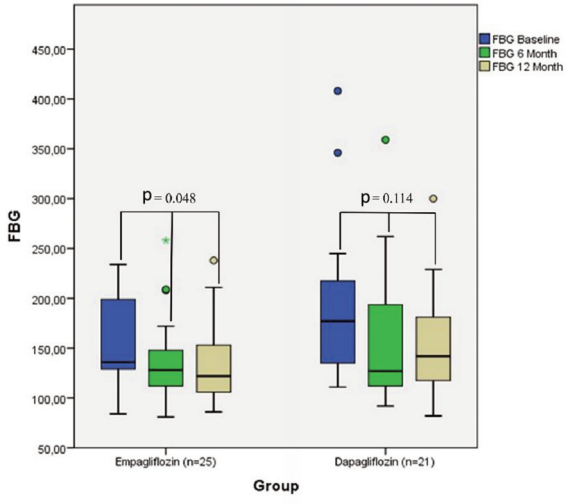

Figure 1. Changes in the fasting plasma glucose level in the patients admitted regularly to out-patient clinic at 6-month and 12-month follow-up visits following the sodium-glucose co-transporter inhibitors addition.
FPG: Fasting plasma glucose.

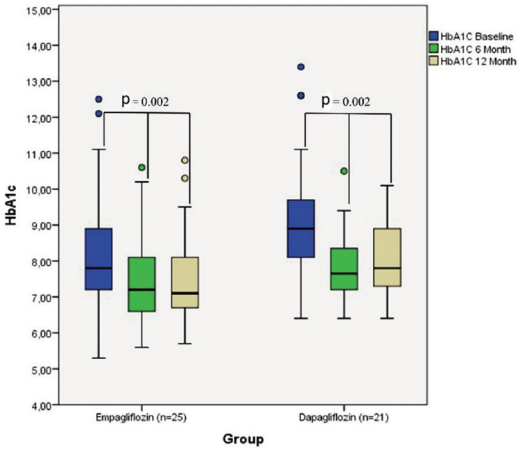

Figure 2. Changes in the hemoglobin A1c in patients regularly admitted to the out-patient clinic at 6-month and 12-month follow-up visits following the sodium-glucose co-transporter inhibitors addition.
HbA1c: Hemoglobin A1c.

Table 6. Inter-group comparison of the impact of treatment on body weight, fasting blood glucose level, and hemoglobin A1c level.

	Groups		
	Empagliflozin (n=52)	**Dapagliflozin (n=37)**	**p value**
Weight (kg)†			
Baseline	85.8±15.2	98.4±18.3	0.001*
Final	84.3±16.1	97.9±18.6	<0.001*
p value***	0.002	0.555	
Fasting plasma glucose (mg/dL)¥			
Baseline	136.5 [84-254]	172 [78-408]	0.115**
Final	125 [86-383]	157 [76-300]	0.017**
p value****	0.004	0.040	
ΔFPG	0,09	0,11	0.721*
HbA1c (%)¥			
Baseline	7.8 [5.3-12.5]	8.9 [6.4-13.4]	0.001**
Final	7.3 [5.7-10.6]	7.8 [6.1-10.10]	0.094**
p value****	0.002	<0.001	
ΔHbA1c	0,07 [-0,22-0,47]	0,1 [-0,16-0,92]	0.070**

†Mean±standard deviation; ¥Median (minimum-maximum); *Student t-test; **Mann-Whitney U test; ***Paired t-test; ****Wilcoxon test; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c.

risk of developing normoglycemic ketosis. The cardiovascular safety data was unavailable for dapagliflozin when it was introduced in Turkey. However, the cardiovascular benefits of empagliflozin had already been established when it was introduced, because of which it was initiated at a higher rate (67.3%) in the patients with concomitant macrovascular complications. In addition, considering the cardiovascular benefits, empagliflozin was preferred even in patients with lower HbA1c levels. Furthermore, the

Table 7. Efficiency of SGLT2i-overall and in different combinations.

	Fasting plasma glucose (mg/dL) Beginning	Fasting blood glucose (mg/dL) Final	p value**	HbA1c (%) Beginning	HbA1c (%) Final	p value**
Insulin, yes (n)	145.5 [84- 408]	139.5 [76-383]	0.038	8.9 [5.3-13.4]	7.9 [5.7 – 10.8]	<0.001
Insulin, no (n)	158 [108-236]	125.5 [93 – 211]	<0.001	7.9 [6.7 – 9.9]	7.2 [6.2 – 9.2]	<0.001
p value*	0.978	0.689		0.021	0.027	
Metformin only	145.5 [87 – 408]	139.5 [77- 383]	0.034	8.5 [5.3 – 13.4]	7.8 [5.7 – 10.8]	<0.001
Combination, yes	146 [84-311]	125 [76 – 211]	0.002	8.4 [6.0 – 12.6]	7.6 [5.7 – 10.3]	<0.001
p value*	0.872	0.249		0.605	0.401	
Metformin+DPP4i ±other OADs±insulin	142 [84 – 236]	123 [76 – 205]	0.048	7.9 [6.0 – 11.1]	7.6 [5.7 – 10.3]	0.036
Metformin+sulfonylurea ±other OADs±insulin	181.5 [108 – 234]	157 [93 – 211]	0.028	8.9 [6.7 – 9.9]	7.5 [6.2 – 9.2]	0.005

Note that the patients who were given or discontinued OAD after the addition of SGLT2i were excluded.
*Mann-Whitney U test; **Wilcoxon test; DPP4i: Dipeptidly peptidase-4 inhibitors; OADs: Oral anti-diabetics.

Table 8. Summary of adverse events.

	Groups		p value
Variables	Empagliflozin (n=52)‡	Dapagliflozin (n=37)‡	
Urinary tract infection	5 (9.6)	4 (10.8)	1.000****
Genital infection	3 (5.8)	1 (2.8)	0.642****
Urinary bladder carcinoma	0 (0.0)	1 (2.7)	0.416****
Patients count who discontinued treatment due to low GFR	1 (1.9)	2 (5.4)	0.568****
Patients count who discontinued treatment due to adverse effect	8 (15.4)	2 (5.4)	0.185****

‡n (%); ****Fisher's exact test; GFR: Glomerular filtration rate.

frequency of out-patient clinic visits was higher in patients with high cardiovascular risk who were administered empagliflozin (Table 1). As presented in Table 2, empagliflozin was the preferred SGLT2i during the last 12 months. These findings indicate that the EMPAREG study (5) has greatly influenced SGLT2i preference among physicians. The data provided in the present study demonstrate that both the preferred SGLT2i molecule and the preferred patient group for SGLT2i have changed over time. While initially, SGLT2i was preferred for patients with high HbA1c levels who were receiving insulin, now they appear to be preferred for patients with lower HbA1c levels during the last 12 months of treatment without the occurrence of cardiovascular disease or renal damage. The existing data indicate that endocrinologists refer to the literature closely and accordingly update and alter their criteria for patient selection and molecule preferences. Since this process is dynamic, it is expected that the upcoming studies would continue to influence and alter these preferences.

In the beginning, 39 patients received combination therapy, and four patients were on pioglitazone treatment. The complete pioglitazone treatment regimen was discontinued after the addition of SGLT2i. The reason for this could be the reported association of pioglitazone with urinary bladder carcinoma (11). The same concern could be associated with SGLT2i (12). Interestingly, no additional OAD agent was required for patients who were under follow-up. Except for pioglitazone, there was discontinuation of the

DPP4i treatment in three (6%) patients and the sulfonylurea treatment in three (6%) other patients in the empagliflozin group. As the target HbA1c level was achieved in these patients, it was observed that despite the high risk for hypoglycemia, there were an aim to take advantage of the cardiovascular benefits of SGLT2i. Although there was a decreasing trend without a significant decline in the diastolic blood pressure, which was consistent with the literature, a considerable decrease in the systemic blood pressure was achieved with the use of both the SGLT2i (Table 5) (5-7).

It was remarkable that only a few patients were admitted regularly in the out-patient clinic at the 6-month and 12-month visits, with only 25 (18.3%) patients in the empagliflozin group and 19 (17.6%) patients in the dapagliflozin group. In the 12-month visits, a considerable decrease in the HbA1c levels had been achieved in both groups (Figure 2). On the other hand, the FPG levels were higher in the dapagliflozin group compared to the empagliflozin group, as the initial FPG levels in the former group were also higher.

On the basis of the 6-month follow-up evaluations of FPG and HbA1c levels, a decrease in efficiency was observed in the dapagliflozin group in the 12-month evaluations (Figure 1 and Figure 2). The insulin doses did not change significantly in the 14 (73.3%) patients of the dapagliflozin group who were admitted regularly to the out-patient clinic at 6-and 12-month follow-up visits. When the baseline and final evaluations of the patients were compared, a considerable decline in the FPG and HbA1c levels was observed with the use of both the SGLT2i. Previously, Calapkulu et al. (13) reported a 0.79% decrease in the HbA1c level after six months of dapagliflozin treatment. Gunhan et al. (10) reported a baseline HbA1c percentage of 8.4±1.54 in the dapagliflozin group, which was observed to decrease to 7.76±1.45 after 3 months and 7.62±1.41 after 6 months ($p<0.001$ and $p=0.002$, respectively); while for the empagliflozin group, it decreased from 8.17±1.40 to 7.41±1.29 after 3 months and 7.31±1.10 after 6 months ($p<0.001$ and $p<0.001$, respectively). Taken together, these findings indicate that both the SGLT2i are effective treatment options for the Turkish population. Ku et al. (14) conducted a prospective study in which they added 25 mg empagliflozin or 10 mg dapagliflozin to the treatment regimens of patients whose blood glucose level could not be regulated using metformin and sulfonylurea. At the end of the 52nd week of the follow-up period, a comparison of the efficiency of different SGLT2i revealed that empagliflozin was superior to dapagliflozin in terms of regulating the blood glucose level (14). In the present study, ΔFPG and ΔHbA1c were not significant between the two groups, and the greater decrease in the FPG and HbA1c levels in the dapagliflozin group was strongly associated with the higher initial FPG and HbA1c levels in this group. The present study demonstrated that both empagliflozin and dapagliflozin were quite effective in a variety of combination therapies. The effectiveness of empagliflozin and dapagliflozin in different combinations is presented in Table 7.

In the study reported by Calapkulu et al. (13), a significant decrease in body weight was observed with dapagliflozin at 3-month and 6-month follow-up evaluations. Moreover, in the report by Günhan et al. (10), the baseline body weight (95.62±21.30 kg) of the patients who received dapagliflozin decreased to 91.99±19.79 kg at the 6-month follow up evaluation ($p<0.001$), while the baseline body weight (93.47±23.85 kg) of the patients receiving empagliflozin increased to 94.48±23.55 kg ($p=0.004$). That is, at the 6-month follow-up, while the patients in the dapagliflozin group lost weight, the patients receiving empagliflozin gained weight despite the decreasing dose of insulin. On the contrary, in the present study, although patients in both empagliflozin and dapagliflozin groups lost weight, this decrease was significant only in the empagliflozin group ($p=0.002$). Contrary to the findings of Günhan et al. (10), in the present study, dapagliflozin led to a decrease in body weight, and this decrease was not statistically significant. This situation could be explained by the fact that 70% of the patients in the dapagliflozin group were already under insulin treatment, and there was no change in the ratio of the total dose of injected insulin to weight. Furthermore, in comparison to the 12-month follow-up, there was an insignifi-

cant loss of efficiency of dapagliflozin in terms of the estimated FPG and HbA1c values at the 6-month follow-up (Figure 1 and Figure 2). This loss of efficiency of dapagliflozin could not be associated with the lowering of insulin dosages and could be explained largely by the patient-related factors, including that in comparison to the empagliflozin group, the dapagliflozin group had longer intervals of admissions to the out-patient clinic and no significant weight loss. Lee et al. (15) reported a considerable decrease in the alanine transaminase levels at the 6-month follow-up in the patients treated with empagliflozin as well as those treated with dapagliflozin. A similar finding was reported by Gunhan et al. (10). In the present study, although a decrease was observed in the alanine transaminase levels, this decrease was not statistically significant. The limited decline in body weight could explain this insignificant decrease in the alanine transaminase levels.

The discontinuation of the treatment in 15.4% (n=8) of the patients in the empagliflozin group was remarkable. The reasons for the discontinuation were as follows: low GFR level (<45 mL/min) in 1 (1.9%) patient and genital or urinary tract infection in the others. In the dapagliflozin group, the treatment was discontinued in only 2 (5.4%) patients due to a low GFR (<45 mL/min) level. Although the baseline blood glucose levels were better in the empagliflozin group, the higher rate of treatment discontinuation indicated a suspicion that the drug-related adverse effects were related to, besides the blood glucose level, the high rate of occurrence of co-morbid conditions. Although urinary tract and genital infections are easily controllable using antibiotic therapy, it was observed in the present study that the temporarily discontinued treatment was not initiated again due to patients' anxiety. After six months of dapagliflozin treatment, treatment was discontinued in one patient upon the patient's request. Eighteen months later, the patient was diagnosed with low-grade urinary bladder carcinoma. It was inferred that the development of urinary bladder carcinoma secondary to dapagliflozin treatment in this patient occurred due to the comparatively shorter duration of treatment.

Study Limitations

As with all research, there were certain limitations of the present study as well. The first limitation was that the study was designed as a retrospective one. The second limitation was that not all patients visited the out-patient clinic regularly at the 6-month and 12-month follow-ups.

Conclusion

SGLT2i preference in T2DM is closely associated with the data reported in the related literature. The SGLT2i are effective in all treatment combinations. In consideration of the trend of low rate of out-patient visits in Turkey and the adverse effect profile of SGLT2i, the process of patient selection becomes an important area warranting attention.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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