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ORIGINAL ARTICLE

Comparative evaluation of clinical outcomes of dapagliflozin and empagliflozin in type-2 diabetes mellitus

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Abstract

Background Sodium-glucose transporter 2 (SGLT-2) inhibitors provide additional benefits besides glycemic control.

Aim This study aims to compare the clinical outcomes of dapagliflozin and empagliflozin.

Methods This retrospective study evaluated data retrieved from medical records of patients who were under follow-up with the diagnosis of type 2 diabetes mellitus (T2DM) and were started on dapagliflozin or empagliflozin treatment between January 1, 2017, and June 1, 2020. Demographic features, comorbidities, clinical features, duration of diabetes, baseline, and follow-up laboratory test results were recorded. The significance level was set at $p < 0.05$.

Results This study comprised 342 patients who are on the treatment with dapagliflozin ($n = 228$) or empagliflozin ($n = 114$). The glycosylated hemoglobin a1c (HBA1C) level was significantly decreased in both the dapagliflozin (8.18–7.59, $p < 0.001$) and empagliflozin (8.35–7.58, $p < 0.001$) groups. The urine albumin-to-creatinine ratio (ACR) was also decreased in both groups. A decrease in urine ACR was observed independent of using a renin–angiotensin–aldosterone system (RAAS) blocker both in the whole group and in patients with diabetic nephropathy. The time to addition of a new anti-diabetic agent to the treatment was shorter in the dapagliflozin group (14.4 months vs 17.7 months, $p = 0.041$, respectively).

Conclusion Dapagliflozin and empagliflozin are the drugs to choose for renoprotection in diabetics independent of the use of a RAAS blocker. Even the time to addition of a new anti-diabetic agent is longer in the empagliflozin group, head-to-head comparative trials are needed to asess the potential differences in this regard.

Keywords Dapagliflozin · Diabetes mellitus · Diabetic nephropathy · Empagliflozin · Renoprotection · Sodium-glucose transporter 2

Introduction

Diabetes mellitus (DM) is a global health problem with increasing prevalence gradually. There are approximately 451 million DM patients worldwide, with that number expected to rise to 693 million by 2045 [1]. More than 90% of cases are type 2 DM (T2DM) [2]. Drugs that act in different pathophysiological pathways have begun to be used for the treatments of diabetics as the understanding of different pathophysiological mechanisms that play a role in the development of DM has improved over the years [3]. The main goals of patient-centered management of DM are optimizing the quality of life and preventing complications [4]. Cardiovascular disease (CVD) and kidney disease are two of the most common among diabetics that reduce their quality of life and shorten their life span [5, 6].

Pharmacological therapeutic approaches in DM have been evolving. Some glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose transporter 2 (SGLT-2) inhibitors have shown in recent years' cardiovascular safety studies that they provide additional benefits besides glycemic control [7, 8]. In clinical studies, it has been shown that empagliflozin and canagliflozin reduce cardiovascular morbidity and mortality in patients with T2DM with CVD [9, 10]. In patients with heart failure (HF) and patients with diabetic nephropathy (DN), SGLT-2 inhibitors have also been proven to provide significant additional clinical benefits [8]. Furthermore, dapagliflozin has been approved by the US Food and Drug Administration (FDA) for use in patients

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with low ejection fraction (EF) HF and patients with chronic kidney disease (CKD) without DM [11, 12]. Besides, the FDA has recently approved empagliflozin for the treatment of patients with HF with preserved EF [13].

Today, metformin is still the first-choice drug for pharmacological treatment in patients with T2DM. Furthermore, SGLT-2 inhibitors, together with GLP-1 analogs, are the drugs to choose in patients with T2DM and CVD, or those at high risk of CVD, and/or in patients with DN, independent of glycosylated hemoglobin a1c (HbA1C) level [14].

The two SGLT-2 inhibitor drugs that are available in Turkey are dapagliflozin and empagliflozin. In this retrospective study, we aimed to compare the clinical outcomes of dapagliflozin and empagliflozin in patients with T2DM, as a single-center experience.

Materıals and methods

All patients who were under follow-up with the diagnosis of T2DM in the Endocrinology and Metabolism clinic and started on dapagliflozin or empagliflozin treatment between January 1, 2017, and June 1, 2020, were included. Patients under the age of 18 were excluded. The patient's sex, age, duration of diabetes in years, concomitant medications, presence of comorbidities (hypertension (HT), hyperlipidemia (HPL) and HF), and presence of chronic complications of DM (microvascular complications and macrovascular complications) were recorded. Patients with albumin-to-creatinine ratio (ACR) of 30 and/or estimated glomerular filtration rate (eGFR) of < 60 mL/dk/1.73 m^2 in two or more occasions were considered as DN. eGFR was calculated based on serum creatinine level, by using the CKD epidemiology collaboration formula (CKD-EPI) formula [15]. Patients with retinopathy were defined as those who have diabetic retinopathy findings during an examination by ophthalmologists. Creatinine level, eGFR, ACR, alanine transaminase level (ALT), glycosylated hemoglobin A1C (HBA1C) percentage, and cholesterol levels were recorded. The number of needs to hospitalization, whether or not they had an urogenital system infection and whether or not they had a major adverse cardiovascular event (MACE), was also recorded. MACE was defined as non-fatal stroke, non-fatal myocardial infarction, or cardiovascular death [16].

Statistical analysis

Statistical analysis was performed by using the IBM SPSS software (Version 23; IBM Corp., Armonk, NY, USA). All variables were subjected to descriptive analyses. Categorical variables were presented as number (n) and percentage (%). Continuous variables were presented as median (minimum–maximum) or mean (± standard deviation) based on distribution. Chi-square test was performed to compare categorical data. Depending on the distribution of variables, the means of continuous variables were compared by using independent samples t-test or Wilcoxon-Mann–Whitney test. Paired-samples t-test was performed to compare the mean of the same variable at various time points if the variable has a normal distribution and the Wilcoxon signed-ranks test if it did not. Comparison of the variation of HBA1C and ACR over time between groups was performed using the general linear model ANOVA procedure. $P < 0.05$ was set as the significance level.

Results

A total of 342 patients who are on the treatment with dapagliflozin ($n = 228$) and empagliflozin ($n = 114$) were included in this study. Demographic and clinical characteristics are summarized in Table 1. There were significant differences in sex distribution, age, follow-up duration, basal creatinine level, eGFR, HDL level, the prevalence of coronary artery disease, DN, HT, HF, and smoking status between groups (Table 1). The duration of diabetes, HBA1C, basal urine ACR, level of LDL, and triglyceride did not differ significantly between groups. The most frequently used anti-diabetic agent was metformin apart from SGLT2 inhibitors. The concomitant medical treatment of patients is summarized in Table 2.

The HBA1C level was significantly decreased in both the dapagliflozin (8.18–7.59, $p < 0.001$) and empagliflozin (8.35–7.58, $p < 0.001$) groups during the follow-up period (Table 3). There was no difference between groups in terms of quantity of decrease in the HBA1C level ($p = 0.486$).

A slight but statistically significant increase in eGFR was found in both dapagliflozin and empagliflozin groups (from 89 to 93, $p < 0.001$; from 83 to 88, $p < 0.001$, respectively). In both groups, the urine ACR was also decreased during follow-up. There was no difference in terms of reduction in the urine ACR between groups ($p = 0.25$ (for all patients), $p = 0.712$ (for patients with DN)). The comparison of HBA1C and renal outcomes is summarized in Table 3.

The need for hospitalization for any reason, MACE, urinary infections, and genital infections were all comon between groups. The time it took to add a new anti-diabetic agent to the treatment was shorter in the dapagliflozin group than in the empagliflozin group (14.4 months, 17.7, $p = 0.041$, respectively) (Table 4).

A statistically significant decrease in urine ACR was observed independent of the use of a renin–angiotensin–aldosterone system (RAAS) blocker (angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)) both in the whole group and in patients with DN (Table 5). The decreases in

Table 1 Demographic and clinical characteristics of groups

	Total ($n=342$)	Dapagliflozin group ($n=228$)	Empagliflozin group ($n=114$)	p value
Female/male[a]	180 (52.6)/162 (47.4)	132 (57.9)/96 (42.1)	48 (42.1)/66 (57.9)	0.08
Age[b] (y)	59.5 ((±9.5)	58.5 (±9)	61.4 ((±10.2)	0.01
Disease duration[b] (y)	11.1 (±6.4)	11.08 (±6.3)	11.16 (±6.5)	0.90
Follow-up duration[b] (month)	24.5 (±3.7)	24.9 (±3.6)	23.7 (±3.7)	0.004
Basal creatinine[b] (mg/dL)	0.83 (±0.20)	0.80 (±0.19)	0.90 (±0.19)	<0.001
eGFR[b] (mL/dk/1.73 m^b)	87.3 (±15.6)	89.8 (±14.5)	82.8 (±16.5)	<0.001
ALT[b] (U/L)	29.3 (±20.4)	29.8 (±22)	28.4 (±17)	0.54
Basal urine ACR[c] (mg/g)	15.5 (0.4–1193)	17.6 (0.4–979)	13.7 (1–1193)	0.233
HBA1C[b] (%)	8.27 (±1.3)	8.21 (±1.13)	8.36 (±1.61)	0.32
LDL[b] (mg/dL)	113(±38)	114 (±37.7)	112 (±38.8)	0.72
HDL[b] (mg/dL)	44.5 (±11.9)	45.6 (±11.8)	42.4 (±11.9)	0.03
Triglyceride[b] (mg/dL)	181 (±133)	181 (±110)	181 (±168)	0.95
CAD[a]				
Yes	107 (31.3)	51 (22.4)	56 (49.1)	<0.001
No	235 (68.7)	177 (77.6)	58 (50.9)	
CVD[a]				
Yes	11 (3.2)	9 (3.9)	2 (1.8)	0.34
No	331 (96.8)	219 (96.1)	112 (98.2)	
PAD[a]				
Yes	9 (2.6)	5 (2.2)	4 (3.5)	0.10
No	333 (97.4)	223 (97.8)	110 (96.5)	
Retinopathy[a]				
Yes	61 (17.8)	38 (16.7)	23 (20.2)	0.45
No	281 (82.2)	190 (83.3)	91 (79.8)	
Nephropathy[a]				
Yes	74 (21.6)	58 (25.4)	16 (14)	0.018
No	268 (78.4)	170 (74.6)	98 (86)	
Neuropathy[a]				
Yes	100 (29.2)	67 (29.4)	33 (28.9)	1.00
No	242 (70.8)	161 (70.6)	81 (71.1)	
Hypertension[a]				
Yes	229 (67)	144 (63.2)	85 (74.6)	0.038
No	113 (33)	84 (36.8)	29 (25.4)	
Hyperlipidemia[a]				
Yes	277 (81)	183 (80.3)	94 (82.5)	0.66
No	65 (19)	45 (19.7)	20 (17.5)	
Smoking[a]				
Yes	117 (34.2)	62 (27.2)	55 (48.2)	<0.001
No	225 (65.8)	166 (72.8)	59 (51.8)	
Heart failure[a]				
Yes	23 (6.7)	9 (3.9)	14 (12.3)	0.006
No	319 (93.3)	219 (96.1)	100 (87.7)	

Y year, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *ACR* albumin-to-creatinine ratio, *HBA1C* glycosylated hemoglobin A1c, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *PAD* peripheral artery disease

[a]Data are presented as numbers and percentages

[b]Data are presented as mean ± standard deviation

[c]Data are presented as median (minimum–maximum)

Table 2 Comparison of concomitant treatment

	Total ($n=342$)	Dapagliflozin group ($n=228$)	Empagliflozin group ($n=114$)	p value
Metformin[a]	324 (94.7)	221 (96.9)	103 (90.4)	0.018
Sulphanilurea[a]	136 (39.8)	103 (45.2)	33 (28.9)	0.005
Pioglitazon[a]	23 (6.7)	19 (8.3)	4 (3.5)	0.111
DPP-4 inh[a]	146 (42.7)	107 (46.9)	39 (34.2)	0.028
GLP-1 RA[a]	24 (7)	18 (7.9)	6 (5.3)	0.501
Acarbose[a]	24 (7)	20 (8.8)	4 (3.5)	0.077
Basal insulin[a]	94 (27.5)	61 (26.8)	33 (28.9)	0.701
Pre-meal insulin[a]	42 (12.3)	23 (10.1)	19 (16.7)	0.115
Mix insülin[a]	12 (3.5)	8 (3.5)	4 (3.5)	1.000
RAAS blocker[a]	114 (33.3)	66 (28.9)	48 (42.1)	0.021
Tiazid[a]	63 (18.4)	46 (20.2)	17 (14.9)	0.300
CCB[a]	71 (20.8)	40 (17.5)	31 (27.2)	0.047
Loop diuretic[a]	22 (6.4)	8 (3.5)	14 (12.3)	0.004
MRA[a]	12 (3.5)	4 (1.8)	8 (7)	0.024
Statin[a]	263 (76.9)	175 (76.8)	88 (77.2)	1.000
Fenofibrate[a]	37 (10.8)	26 (11.4)	11 (9.6)	0.714
Anti-agregan[a]	134 (39.2)	82 (36)	52 (45.6)	0.100

DPP-4 dipeptidyl peptidase-4, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *RAAS* renin–angiotensin–aldosterone system, *MRA* mineralocorticoid receptor antagonist

[a]Data are presented as numbers and percentages

[b]Data are presented as mean ± standard deviation

the urine ACR were found to be higher in patients taking RAAS blockers together with SGLT2 inhibitors compared with those who did not (median 8.3 vs 4.35, respectively, $p=0.004$). The analysis was performed in patients with DN, and the decreases in the urine ACR were found to be similar between patients who used RAAS blocker and who did not (median 40.8 vs 38.02, respectively, $p=0.642$).

Discussion

This retrospective study was conducted to compare glycemic efficacy and clinical outcomes of dapagliflozin and empagliflozin in patients with T2DM. Both drugs were found to cause a statistically significant reduction in the HBA1C level with no difference between each other. ACR and eGFR

Table 3 Comparison of glycemic and renal outcomes

	Dapagliflozin group ($n=228$)			Empagliflozin group ($n=114$)			Total ($n=342$)		
	Before	After	P value	Before	After	p value	Before	After	p value
HBA1C[a] (%)	8.18 (±1.13)	7.59 (±1.07)	<0.001	8.35 (±1.64)	7.58 (±1.04)	<0.001	8.24 (±1.34)	7.58 (±1.06)	<0.001
Creatinine[a] (mg/dL)	0.80 (±0.19)	0.75 (±0.17)	<0.001	0.89 (±0.19)	0.81 (±0.20)	<0.001	0.83 (±0.20)	0.77 (±0.18)	<0.001
eGFR[a](mL/dk/1.73 m^2)	89 (±14)	93 (±14)	<0.001	83 (±15.9)	88 (±16.1)	<0.001	87 (±15.2)	91 (±14.9)	<0.001
Urine ACR[b] (all patients) (mg/g)	17.6 (0.4–979)	9.3 (0.15–1925)	<0.001	13.7 (1–1193)	7.1 (0.60–797)	<0.001	16.2 (0.4–1193)	8.1 (0.15–1925)	<0.001
Urine ACR[b] (with DN)[c] (mg/g)	71.1 (30.5–979)	35.3 (0.15–1925)	0.001	86.7 (30.8–1193)	28.7 (2.3–797)	<0.001	75 (30.5–1193)	32.1 (0.15–1925)	<0.001

HbA1c glycosylated hemoglobin A1c, *eGFR* estimated glomerular filtration rate, *ACR* albumin-to-creatinine ratio, *DN* diabetic nephropathy

[a]Data are presented as mean ± standard deviation

[b]Data are presented as median (minimum–maximum)

[c]Patients have urine alb/cre ratio higher than 30

Table 4 Comparision of clinical outcomes

	Total ($n=342$)	Dapagliflozin group ($n=228$)	Empagliflozin group ($n=114$)	p value
Hospitalization for any reason[a]	30 (8.8)	20 (8.8)	10 (8.8)	1.00
MACE[a]	11 (3.2)	8 (3.5)	3 (2.6)	0.75
Time to add new ADA[b] (month)	15.3 (±8.7)	14.4 (±8.8)	17.7 (±8)	0.041
Urinary infection[a] (all)	63 (18.4)	41 (18)	22 (19)	0.769
Female	56 (31.1)	39 (29.5)	17 (35.4)	0.47
Male	7 (4.3)	2 (2.1)	5 (7.6)	
Genital infection[a]	6 (1.8)	4 (1.8)	2 (1.8)	1.00
Female	6 (3.3)	4 (3)	2 (4.2)	0.65
Male	-	-	-	-

MACE major adverse cardiovascular event, *ADA* anti-diabetic agent

[a]Data are presented as numbers and percentages

[b]Data are presented as mean ± standard deviation

were improved in a mean of 23.7 months with the use of the SGLT-2 inhibitor, in addition to glycemic efficacy.

SGLT-2 inhibitors are oral anti-diabetic agents that have relatively low efficacy in the reduction of HBA1C levels ranging between 0.5 and 1.0% [17–19]. In randomized clinical trials of dapagliflozin and empagliflozin, the mean reductions in HBA1C level compared with placebo were 0.43% and 0.30%, respectively [9, 20]. In a prospective observational study in patients with T2DM, who were already on triple oral anti-diabetic agent combinations, dapagliflozin and empagliflozin were compared as an add-on therapeutic option. It was found that adding empagliflozin or dapagliflozin to the treatment regimen in this population provides a reduction in the HBA1C level, with slightly more reduction in the empagliflozin group [21]. After a 3-year observational period, both drugs showed a durable effect on glycemic control. It has been observed that empagliflozin performed better in that study [22]. Baruah and Kalra compared dapagliflozin, canagliflozin, and empagliflozin retrospectively and reported significant glycemic efficacy of SGLT-2 inhibitors without intergroup differences [23]. During a mean follow-up of 24.5 months, we determined a significant reduction in the HBA1C level with the use of SGLT-2 inhibitor, in this study. There was no difference between dapagliflozin and empagliflozin in the reduction HBA1C level. However, the time to addition of a new anti-diabetic agent was longer in the empagliflozin group.

The number of trials evaluating renal outcomes in patients under treatment with SGLT2 inhibitors is increasing. Empagliflozin was associated with a significant relative risk reduction of incident or worsening nephropathy in T2DM when added to the standard treatment [24]. Dapagliflozin was also associated with a relative risk reduction of renal composite outcomes [20]. Besides data coming from randomized clinical trials, in a large multicentric real-world observational cohort study, it was demonstrated that initiation of SGLT-2 inhibitors is associated with a lower rate of adverse renal outcomes compared to initiation of other anti-diabetic agents [25]. There has not been a randomized clinical trial that compared dapagliflozin and empagliflozin head-to-head. In a prospective observational study, however, there was no difference in renal outcomes [22]. There was a significant decrease in the urine ACR both in the whole group and in the group with DN, with no difference between dapagliflozin and empagliflozin. In

Table 5 Relation of ACR and use of renin–angiotensin–aldosterone-system blocker

	Before	After	*P*
Urine ACR (a*ll patients)* (mg/g)			
With RAAS blocker[a]	24.5 (1.7–1193)	12 (0.6–1172)	<0.001
Without RAAS blocker[a]	12.2 (0.4–979)	7.5 (0.15–1925)	<0.001
Urine ACR (with DN)[b] (mg/g)			
With RAAS blocker[a]	109 (30.6–1193)	45 (2.1–1172)	0.001
Without RAAS blocker[a]	59.8 (30.5–979)	25 (0.15–1925)	0.001

ACR albumin-to-creatinine ratio, *RAAS* renin–angiotensin–aldosterone system, *DN* diabetic nephropathy

[a]Data are presented as median (minimum–maximum)

[b]Patients have urine ACR higher than 30

addition, we also demonstrated a slight but statistically significant increase in eGFR with the use of an SGLT-2 inhibitor. To our knowledge, such a result has not yet been reported in the literature so far.

SGLT-2 inhibitors reduce the risk of DN progression in patients who are under treatment with RAAS blocker [26]. More than 80% of patients both in the EMPA-REG trial and the DECLARE-TIMI 58 trial were under treatment with RAAS blocker [9, 20]. In a real-world multicentric observational study, the frequency of using ACE inhibitor or ARB in the SGLT-2 inhibitor arm was 37.6% and 31.7%, respectively [25]. The overall frequency of RAAS blocker use was 33.3% in this study. We observed a decrease in the urine ACR in both the whole group and among the patients with nephropathy independent of the use of a RAAS blocker. These findings are consistent with those of a meta-analysis that concluded the renoprotective properties of using SGLT-2 inhibitors are present regardless of albuminuria status and use of RAAS blocker [27]. Moreover, the similar reduction in urinary ACR in individuals with DN using SGLT2 inhibitors with and without RAAS blockers is another finding that highlights the importance of SGLT2 inhibitors in renoprotection.

In clinical trials, SGLT-2 inhibitors are associated with an increased rate of genitourinary tract infections with no difference between dapagliflozin and empagliflozin [22, 28, 29]. In the following years, it was reported that the use of SGLT2 inhibitors did not increase the risk of urinary tract infection [30]. The frequency of urinary tract infection was 18.4% (31.1% among females) with no difference among groups, in this study. In the literatüre, the association between SGLT-2 use and genital infections is more consistent than the SGLT-2 use and urinary tract infections [29, 31]. In fact, in 2018, the FDA issued a warning about the risk of serious infection (like Fournier gangrene) in the genital area with the use of SGLT2 inhibitors [32]. In this study, the frequency of genital infections was 3.3% among female patients with no difference between groups. All were in the form of vulvovaginal mycotic infections. No serious genital tract infection, such as Fourniers gangrene, was observed.

In the EMPA-REG trial, empagliflozin was associated with decreased risk of death from cardiovascular causes, death from any cause, and hospitalization for HF [9]. Conversely, dapagliflozin was found to be similar to placebo in terms of MACE, in the DECLARE-TIMI 58 study [20]. In a large international real-life study, it was demonstrated that initiation of an SGLT2 inhibitor, as compared with other anti-diabetic agents, is associated with a lower risk of cardiovascular events [33]. In this study, the frequencies of MACE and hospitalization for any reason were similar between the dapagliflozin and empagliflozin groups.

The race and genetic characteristics, lifestyle of patients, and adherence to treatment were unknown. Along with these conditions, the fact that the study is single-centered and retrospective is among the limitations.

Conclusıon

Regardless of whether or not diabetics are using RAAS blocker, dapagliflozin and empagliflozin are the drugs to use for renoprotection. Even if the time to add a new anti-diabetic agent is longer in the empagliflozin group, head-to-head comparative trials are needed to assess the potential differences in this regard.

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Author contribution All authors solely contributed to this article.

Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval On July, 2020, the Ethics Committee of Akdeniz University reviewed and approved this study (decision number: KAEK-565).

Competing ınterests The authors declare no competing interests.

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