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Efficacy and Safety of Dapagliflozin 10 mg as Add-on to Metformin *versus* Metformin with or without Other Hypoglycemic Agents in Type 2 Diabetes Mellitus Patients, Retrospective Observational Study

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ABSTRACT

Objective: *To assess 10 mg dapagliflozin effectiveness and safety in a real-world setting as add-on therapy and compare it with metformin with or without other hypoglycemic agents (HGA) in type 2 diabetes mellitus (T2DM) patients.* ***Methods:*** *Retrospective chart review observational study at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. Patients were divided into two groups. Dapagliflozin group who had a prescription of dapagliflozin added to metformin (Met) ± 1 or more HGA. The control group was patients using Met ± 1 or more HGA and who didn't have any sodium glucose co-transporter 2 inhibitor (SGLT2i) prescription. The primary outcome is the change of HbA1c during follow-up period from baseline.* ***Results:*** *114 patients had at least one prescription for dapagliflozin. For control group 78 patients were included. The decrease in the mean change of HbA1c for dapagliflozin group was significantly higher compared to control group between baseline and during 12-months follow-up period (-1.22% vs. -0.12%; p<0.001), respectively. The change in body weight and body mass index (BMI) were significantly decreased during follow-up from baseline with dapagliflozin group, while increased with control group (-1.74 kg, vs. +0.27 kg; p<0.001) and (-0.70 kg/m^2, vs. 0.10 kg/m^2; p<0.001), respectively. There was significant difference in urinary tract infection (UTI) with dapagliflozin group [10 (12.8%)], compared to control group [2 (2.6%)] (p=0.032).* ***Conclusion:*** *Dapagliflozin showed extra HbA1c reduction when added to metformin with or without a broad range of HGA in comparison to other HGA in patients with T2DM.*

Keywords: Type 2 diabetes mellitus, Hypoglycemic agents, Saudi Arabia

INTRODUCTION

Diabetes is a chronic disease characterized by hyperglycemia that resulting from resistance to insulin, decreased or absent secretion of insulin, or both [1]. The progressive nature of type 2 diabetes mellitus (T2DM) usually requires combination therapy with multiple antihyperglycemic agents (AHAs) for achieving and maintaining glycemic control [2].

Dapagliflozin is a novel oral antidiabetic agent belonging to the class of sodium glucose co-transporter 2 inhibitor (SGLT2i) that has been approved in the United State and Europe for use in patients with T2DM. Dapagliflozin reduces plasma glucose by selectively and reversibly blocking the SGLT2 receptor and encourages the filtration of glucose into the urine through the kidneys and remove it from the body [3-5]. In randomized clinical trials (RCTs), dapagliflozin demonstrated a significant improvement in glycemic control in relative to placebo when used as monotherapy, or as an adjunct to metformin, sulfonylurea (SU), sitagliptin, or insulin [6]. Moreover, adding dapagliflozin to patients on SU monotherapy gives similar glycemic control of glucagon-like peptide-1 (GLP1) analogues (HbA1c mean difference 0.11%; 95% credible interval (CrI) -0.18 to 0.40) [4]. It was also demonstrated that dapagliflozin reduces body weight and blood pressure [6]. In a study, body weight reduction has been shown in dapagliflozin groups (dual (-3.2 kg) and triple (-3.5 kg), while increased with glimepiride plus metformin group (+1.8 kg) [7]. Moreover, due to osmotic diuresis and natriuresis effect of dapagliflozin associated with urinary glucose excretion, it resulted in reduction in blood

pressure that is similar to the effect of hydrochlorothiazide and was noticed within 12 weeks of treatment initiation [4,8]. Mean fasting lipid levels showed small difference from baseline with dapagliflozin compared to placebo [8].

However, dapagliflozin as adjunct therapy showed higher incidence of urinary tract infection (UTI) and genital infections compared to add-on glimepiride [7]. Moreover, dapagliflozin in add-on dual treatment reported higher incidence of adverse events related to renal impairment (3.8%) compared to add-on triple treatment (dapagliflozin and saxagliptin) (1.9%) and add-on glimepiride (2.2%) [7]. Furthermore, dapagliflozin showed higher risk for volume depletion events in comparison to placebo [4]. Nevertheless, hypoglycemia events were lower with dapagliflozin treatment groups in comparison to glimepiride as adjunct to metformin [7].

Although RCTs are the gold standard to determine drug efficacy and safety, it is important to investigate the effectiveness of a drug in a real-world setting [6]. The purpose of this retrospective analysis is to assess 10 mg dapagliflozin efficacy and safety in a real-world setting as add-on therapy and compare it with metformin with or without other hypoglycemic agents (HGA) in T2DM patients.

MATERIAL AND METHODS

Data Source and Patient Characteristics

Retrospective chart review observational study using data from electronic medical record (EMR) between May 2017 and August 2018 at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia. This hospital is a governmental, teaching, tertiary care hospital. It is a general and subspecialty hospital and is very well-equipped facility. The hospital provides free treatment. Also, it provides primary and secondary care services. In addition, it has a multidisciplinary team trained and expert in the diabetes integral management. This study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of King Saud University (KSU) approved this study before conducting the research. Patient consent was obtained before starting dapagliflozin.

A list of patients with T2DM was provided. Patients aged (20-80) years who diagnosed with T2DM and initiated on dapagliflozin 10 mg once daily as add-on therapy (second, third, or fourth line to oral antidiabetic therapy), switching from one to another, as adjunctive to injectable therapy, or other AHAs, and who completed 12 months follow-up period were included. The exclusion criteria were patients diagnosed with type 1 diabetes mellitus (T1DM), aged <20 years, history of SGLT2i therapy other than dapagliflozin before the baseline, pregnant woman at baseline and during the follow-up period, and patient with chronic kidney disease with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2. Patients who lost to follow-up or those who voluntarily discontinued the treatment were also excluded.

The patient baseline characteristics are age, gender, weight (kg), body mass index (BMI=kg/m2), height (cm), comorbidities, concomitant antihyperglycemic medications (oral or injectable) and other drugs. Moreover, HbA1c level, glucose level, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, serum creatinine (Scr), eGFR (calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation), hematocrit, blood urea nitrogen (BUN), sodium, and potassium were assessed at baseline. Microalbuminuria of >30 mg/L albumin in urine were assessed at baseline and during follow-up.

Adverse events as hypoglycemia, UTI (defined as experiencing signs or symptoms of UTI), and genital infection incidence were all patient self-reported during the clinic visits. Hypoglycemia was categorized into mild, moderate or severe. Mild episodes were blood glucose level of 70 mg/dl or less. Moderate episodes were blood glucose level of less than 54 mg/dl. Severe episodes were events requiring the assistance of another individual. Polyuria was those who experienced frequent urination, while dysuria defined as experiencing discomfort, pain, or burning when urinating, after starting dapagliflozin.

Patients who met the inclusion criteria were divided into two groups. Dapagliflozin group who had a prescription of dapagliflozin (Dapa) added to metformin (Met) ± 1 or more HGA. The control group was patients using Met ± 1 or more HGA and who didn't have any SGLT2i prescription.

Outcomes

The primary outcome is the change of HbA1c during follow-up period from baseline. Secondary outcomes are the change in other parameters (e.g. weight, BMI, SBP, DBP), the safety and tolerability evaluation.

Statistical Analysis

The PASW statistics (SPSS version 20.0) and Microsoft Office Excel (version 1908) were used for all statistical analysis. The statistical tests were two sided and alpha of 0.05 was set for statistical significance. Continuous data were presented as mean ± standard deviation. Frequencies and percentages were used for categorical data. Independent Student's t-test were used for continuous variables and Chi-square test or Fisher's exact test (frequencies of <5 in 2 × 2 table) for categorical variables to assess the difference between the groups. Paired Student's t-test was used to evaluate the change between the baseline mean and follow-up mean of the clinical parameters for each group. For all parameters at least one follow-up reading was obtained. An outcome measure with incomplete data was excluded from the analysis. The potential predictor variables by using linear regression for two groups were (age, gender, nationality, duration of disease, comorbidities, using antiplatelet, and addition of other antihyperglycemic medication at baseline or during follow-up) with the outcome HbA1c. Multivariate and univariate linear model were used to calculate clinical parameters adjusting for predictor variables.

Sub-analysis was conducted to compare the safety and efficacy of Dapa+Met ± 1 or more oral hypoglycemic agents (OHA) vs. Dapa+Met+insulin ± 1 or more OHA.

RESULTS

Study Subjects and Baseline Characteristics

Between May 2017 and August 2018, 114 patients had at least one prescription for dapagliflozin. 78 patients were included while, 8 patients were withdrawn voluntarily, and 28 patients were excluded due to loss of follow-up. For control group 78 patients who met the inclusion criteria were selected randomly from the list provided for patients who have T2DM and included (Figure 1). The baseline patient characteristics for two groups were similar (Table 1). The mean baseline HbA1c was not significantly different between the two groups (p=0.699). The majority of participants were from Saudi nationality 72 (92.3%) for the two groups (p>0.05). The dapagliflozin group was significantly higher for dyslipidemia condition 73 (93.6%) compared to control group 62 (79.5%) (p=0.017). The proportion of patients receiving insulin for both groups were similar 52 (66.7%) (p>0.05).

Effectiveness Outcomes

The decrease in the mean change of HbA1c for dapagliflozin group was significantly higher compared to control group between baseline and during 12-months follow-up period (-1.22% vs. -0.12%; p<0.001), respectively (Table 2). Those with lower HbA1c range at baseline in dapagliflozin group, the reduction of HbA1c was greater (Supplementary Table S1.1). However, an increase in HbA1c after 12-month follow-up has been shown in [7 (9%)] patients who started the dapagliflozin, while [36 (46.2%)] with control group (p<0.001) (Figure 2). Nevertheless, the change in body weight and BMI were significantly decreased during follow-up from baseline with dapagliflozin group, while increased with control group (-1.74 kg, vs. +0.27 kg; p<0.001) and (-0.70 kg/m^2, vs. 0.10 kg/m^2; p<0.001), respectively. The difference in SBP during follow-up period was not statistically significant between the two groups (dapagliflozin group, -3.25 mmHg vs. control group, +0.81 mmHg; p=0.077). There was a slight increase in the change of DBP between the follow-up and baseline with dapagliflozin group (+0.17 mmHg), while decreased with control group (-0.44 mmHg) but was not statistically significant (p=0.651). In addition, the improvement in low-density lipoprotein (LDL), High-density lipoprotein (HDL), and total cholesterol (TC) with dapagliflozin group were not significantly different compared to control group (-0.08 mmol/L, vs. -0.02 mmol/L; p=0.718), (+0.03 mmol/L, vs. 0.00 mmol/L; p=0.278), and (-0.19 mmol/L, vs. +0.02 mmol/L; p=0.161), respectively. On the other hand, the improvement in triglycerides (TG) was significant with dapagliflozin group compared to control group (-0.25 mmol/L, vs. +0.06 mmol/L; p=.016). Furthermore, there was slight improvement in eGFR and decrease in Scr with dapagliflozin group but not statistically significant compared to control group (+0.37 ml/min/1.73m^2, vs. -0.17 ml/min/1.73m^2; p=0.670) (-0.37 mcmol/L, vs. 0.34 mcmol/L; p=0.590) (Table 2).

Sub-group Analysis

There was no statistically significant difference in the mean of clinical parameters between the two dapagliflozin groups (Dapa+Met ± 1 or more OHA vs. Dapa+Met+insulin ± 1 or more OHA) (Supplementary Table S1.2).

Safety and Tolerability Evaluation

Safety and tolerability were evaluated using laboratory tests, and vital signs to collect information on adverse events. Moreover, patients on dapagliflozin were asked at each research visit for signs, symptoms, and suggestive reports of hypoglycemia, UTI, and genital infection. [26 (33.3%)] patients with dapagliflozin group self-reported hypoglycemia during their 12 months follow-up period, mostly with patients on Dapa+Met+insulin ± 1 or more OHA group [21 (26.9%)] but not significantly different from Dapa+Met ± 1 or more OHA group [5 (6.4%)] (p=0.077), while [16 (20.5%)] reported hypoglycemia with control group but not significantly different (p=0.071) (Table 3) (Supplementary Table S1.3). One female patient from dapagliflozin group withdrawn because of hypoglycemia symptoms. [11 (14.1%)] patients from dapagliflozin group experienced (1-2) episodes of hypoglycemia, [9 (11.5%)] experienced (3-4) episodes, and [6 (7.7%)] patients, who were using insulin in their regimen, reported (>4) episodes, while with control group [14 (17.9%)] experienced (1-2) episodes and [2 (2.6%)] had (3-4) episodes (p=0.009). However, the severity for most of hypoglycemic episodes were mild for two groups, and were not significantly different [dapagliflozin group, 25 (32.1%) vs. control group, 16 (20.5%); p=0.102]. Additionally, [2 (2.6%)] patients from dapagliflozin group had moderate hypoglycemia episodes (Table 3). Both were females with one patient used to have frequent hypoglycemia episodes but decreased after starting the dapagliflozin with glucose level reached 43 mg/dl, and the second patient blood glucose level reached 50 mg/dl.

Moreover, there was significant difference in UTI with dapagliflozin group [10 (12.8%)], compared to control group [2 (2.6%)] (p=0.032). In addition, [14 (17.9%)] patients experienced genital infection with dapagliflozin group, while [2 (2.6%)] patients with control group and was significantly different (p=0.003). [8 (10.3%)] patients reported polyuria after starting the dapagliflozin and [1 (1.3%)] patient from control group, and it was significantly different (p=0.032). Additionally, there was significant difference with those who experienced dysuria with dapagliflozin group [10 (12.8%)] compared to control group [1 (1.3%)] (p=0.009). Most of them were female and the severity was mild for the two groups and self-treatable and only one female case had severe UTI and genital infection with dapagliflozin group. However, one male patient in dapagliflozin group withdrawn due to mild dysuria. Furthermore, [9 (11.9%)] patients needed treatment for their UTI and genital infection with dapagliflozin group (Table 3) (Supplementary Table S1.3).

Nevertheless, [7 (9.0%)] cases developed microalbuminuria during the follow-up period with dapagliflozin group [6 (7.7%) were from Dapa+Met+insulin ± 1 or more OHA group, and 1(1.3%) from Dapa+Met ± 1 or more OHA group], while [6 (7.7%)] patients with control group (Table 3) (Supplementary Table S1.3).

Four male patients in dapagliflozin group withdrawn due to adverse events suspected to be related to dapagliflozin drug therapy. One patient suffered from chest tightness that improved after stopping the dapagliflozin, two patients experienced generalized eczema after 2 months of starting dapagliflozin that is resolved after discontinuing the treatment and it was moderate eczema, and one patient developed osteomyelitis and cellulitis with itchy rash all over the body. Moreover, one female patient complained of severe nausea and vomiting after starting the dapagliflozin, and she discontinued the drug.

Table 1 Participants baseline characteristics

Variables	Dapa+Met ± 1 or more HGA	Met ± 1 or more HGA	p-value
Age, years (mean ± SD)	54.94 ± 7.32	54.88 ± 9.43	0.97
Duration of diabetes, years (mean ± SD)	13.26 ± 7.07	14.48 ± 7.71	0.304
Gender, n (%)			
Male	24 (30.8)	24 (30.8)	>0.05
Female	54 (69.2)	54 (69.2)	
HbA1c, % (mean ± SD)	9.45 ± 1.21	9.37 ± 1.46	0.699

HbA1c levels, n (%)			
<7.5	0	0	0.446
7.5-8.4	21 (26.9)	25 (32.1)	
8.5-9.4	25 (32.1)	24 (30.8)	
9.5-10.4	10 (12.8)	13 (16.7)	
10.5-11.4	16 (20.5)	8 (10.3)	
>11.4	6 (7.7)	8 (10.3)	
Hight, cm (mean ± SD)	160.44 ± 9.65	158.97 ± 7.97	0.303
Weight, kg (mean ± SD)	88.18 ± 18.15	81.29 ± 15.80	0.012
BMI, kg/m^2 (mean ± SD)	34.06 ± 5.03	32.22 ± 6.21	0.044
Nationality, n (%)			
Saudi	72 (92.3)	72 (92.3)	>0.05
Non-Saudi	6 (7.7)	6 (7.7)	
Diabetes-related problems, n (%)			
Neuropathy	7 (9.0)	6 (7.7)	0.772
Retinopathy	3 (3.8)	15 (19.2)	0.003
Nephropathy	0	0	
Microalbuminuria	16 (20.5)	10 (12.8)	0.432
Comorbid disease, n (%)			
Hypertension	61 (78.2)	52 (66.7)	0.107
SBP, mm Hg	135.06 ± 14.42	137.19 ± 19.30	0.437
DBP, mm Hg	73.42 ± 8.66	78.60 ± 9.83	0.001
Dyslipidemia, n (%)	73 (93.6)	62 (79.5)	0.017
CV events	8 (10.3)	5 (6.4)	0.077
ACS	7 (9.0)	2 (2.6)	
MI	1 (1.3)	0	
Heart failure	0	3 (3.8)	
Neoplasm	2 (2.6)	2 (2.6)	>0.05
Previous urinary tract infection (UTI), n (%)	3 (3.9)	1 (1.3)	0.567
<3 mon	1 (1.3)	1 (1.3)	
3-6 mon	1 (1.3)	0	
>6 mon	1 (1.3)	0	
Previous genital infection, n (%)	3 (3.9)	0	0.383
<3 mon	1 (1.3)	0	
3-6 mon	1 (1.3)	0	
>6 mon	1 (1.3)	0	
History of amputation, n (%)	1 (1.3)	0	>0.05
History of fracture, n (%)	2 (2.6)	0	0.497
Antihyperglycemic medications, n (%)			
Met ± 1 or more OHA	26 (33.3)	26 (33.3)	>0.05
Met+insulin ± 1 or more OHA	52 (66.7)	52 (66.7)	
Metformin	78 (100)	78 (100)	>0.05
DPP-4I	42 (53.8)	60 (76.9)	0.002
SU	38 (48.7)	55 (70.5)	0.006
Acarbose	3 (3.8)	4 (5.1)	>0.05

Liraglutide	14 (17.9)	6 (7.7)	0.055
Insulin	52 (66.7)	52 (66.7)	>0.05
Antihypertensive medications, n (%)			
Angiotensin converting enzymes	29 (37.2)	21 (26.9)	0.17
Angiotensin receptor blockers	30 (38.5)	27 (34.6)	0.618
Calcium channel blockers	23 (29.5)	14 (17.9)	0.09
B-blockers	12 (15.4)	18 (23.1)	0.223
Thiazide diuretics	16 (20.5)	17 (21.8)	0.845
K^+ sparing diuretics	1 (1.3)	1 (1.3)	>0.05
Dyslipidemia medications, n (%)			
Statin	73 (93.6)	60 (76.9)	0.003
Ezitimibe	13 (16.7)	3 (3.8)	0.008
Fibric acid	1 (1.3)	5 (6.4)	0.096
Using antiplatelet, n (%)	39 (50)	40 (51.3)	0.873
Start other antihyperglycemic medication at baseline per patient, n (%)	6 (7.7)	16 (20.5)	0.021
Medication started at baseline, n (%)	8 (10.2)	16 (20.5)	0.031
Insulin	3 (3.8)	7 (9.0)	
Liraglutide	2 (2.6)	2 (2.6)	
Metformin	3 (3.8)	0	
DPP-4I	0	4 (5.1)	
SU	0	3 (3.8)	
Addition of antihyperglycemic medication during follow-up period per patient, n (%)	22 (28.2)	9 (11.5)	0.009
Medication added during follow-up period, n (%)			
DPP-4I	7 (9.0)	3 (3.8)	0.178
SU	5 (6.4)	1 (1.3)	
Acarbose	1 (1.3)	0	
Liraglutide	4 (5.1)	1 (1.3)	
insulin or another type of insulin	6 (7.7)	4 (5.1)	

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CV: Cardiovascular; ACS: Acute Coronary Syndrome; MI: Myocardial Infarction; UTI: Urinary Tract Infection; mon: month; Dapa: Dapagliflozin; Met: Metformin; OHA: Oral Hypoglycemic Agent; DPP-4I: Dipeptidyl Peptidase-4 Inhibitor; SU: Sulfonylurea

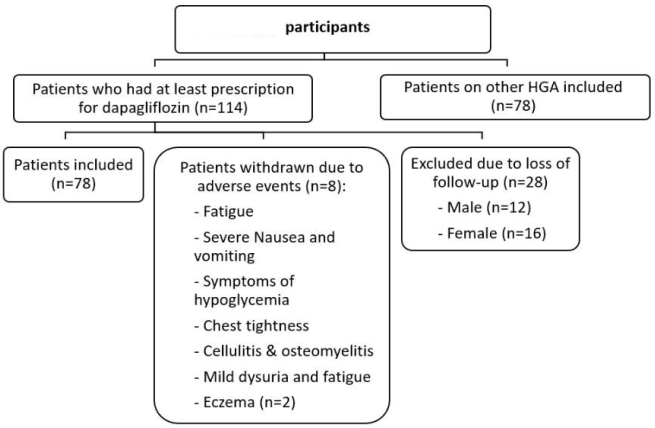

Figure 1 Flowchart of the participants

Table 2 Difference in clinical parameters after 12-month follow-up between dapagliflozin group and control group

Variables	Dapagliflozin group (Dapa+ Met ± 1 or more HGA)		Control group (Met ± 1 or more HGA)		Mean Difference from Control Group	95% Confidence Interval	p-value
	N (n=78)	Mean from Baseline	N (n=78)	Mean from Baseline			
HbA1c, %							
Unadjusted	78	-1.22	78	-0.11	-1.11	[-1.53, -0.68]	<0.001
Adjusted	78	-1.22	78	-0.12	-1.1	[-1.53, -0.68]	<0.001
Weight, kg							
Unadjusted	78	-1.73	78	0.27	-2	[-2.92, -1.09]	<0.001
Adjusted	78	-1.74	78	0.27	-2.02	[-2.93, -1.10]	<0.001
BMI, kg/m²							
Unadjusted	78	-0.7	78	0.1	-0.81	[-1.15, -0.46]	<0.001
Adjusted	78	-0.7	78	0.1	-0.81	[-1.15, -0.46]	<0.001
Glucose, mmol/L							
Unadjusted	66	-2.34	75	0.1	-2.44	[-3.53, -1.36]	<0.001
Adjusted	66	-2	75	-0.19	-1.81	[-2.92, -0.71]	0.001
SBP, mm Hg							
Unadjusted	78	-3.34	78	0.9	-4.24	[-8.72, 0.24]	0.064
Adjusted	78	-3.25	78	0.81	-4.06	[-8.55, 0.44]	0.077
DBP, mm Hg							
Unadjusted	78	0.21	78	-0.49	0.7	[-1.98, 3.38]	0.608
Adjusted	78	0.17	78	-0.44	0.61	[-2.06, 3.28]	0.651
LDL, mmol/L							
Unadjusted	66	-0.11	70	0	-0.11	[-0.34, 0.12]	0.355
Adjusted	66	-0.08	70	-0.03	-0.05	[-0.31, 0.21]	0.718
HDL, mmol/L							
Unadjusted	67	0.03	70	0	0.03	[-0.02, 0.08]	0.248
Adjusted	67	0.03	70	0	0.03	[-0.03, 0.09]	0.278
TG, mmol/L							
Unadjusted	66	-0.24	73	0.05	-0.29	[-0.51, -0.07]	0.011
Adjusted	66	-0.25	73	0.06	-0.3	[-0.55, -0.06]	0.016
TC, mmol/L							
Unadjusted	68	-0.22	74	0.04	-0.26	[-0.52, 0.00]	0.05
Adjusted	68	-0.19	74	0.02	-0.21	[-0.50, 0.08]	0.161
Scr, mcmol/L							
Unadjusted	75	-0.38	75	0.35	-0.74	[-3.31, 1.84]	0.572
Adjusted	75	-0.37	75	0.34	-0.71	[-3.29, 1.88]	0.59
eGFR, ml/min/1.73m²							
Unadjusted	75	0.38	75	-0.18	0.56	[-1.93, 3.04]	0.659
Adjusted	75	0.37	75	-0.17	0.38	[-1.95, 3.02]	0.67
Hct, %							
Unadjusted	25	1.17	43	0.17	1	[-0.33, 3.32]	0.139

Adjusted	25	0.73	43	0.43	0.31	[-1.19, 1.73]	0.67
BUN, mmol/L							
Unadjusted	65	0.47	75	0.02	0.45	[0.09, 0.82]	0.015
Adjusted	65	0.48	75	-0.01	0.47	[0.10, 0.84]	0.014
Na^+, mmol/L							
Unadjusted	65	1.42	75	0.38	1.04	[0.10, 1.98]	0.03
Adjusted	65	1.37	75	0.41	0.96	[-0.01, 1.92]	0.048
K^+, mmol/L							
Unadjusted	65	-0.02	75	0.06	-0.07	[-0.19, 0.04]	0.216
Adjusted	65	-0.02	75	0.06	-0.08	[-0.20, 0.04]	0.181
Microalbuminuria (mg/L)							
Unadjusted	17	-118.69	10	-49	-63.17	[-188.24, 49.07]	0.238
Adjusted	17	-147.24	10	0.56	-146.69	[-337.11, 43.74]	0.121

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; TG: Triglycerides; TC: Total Cholesterol; Scr: Serum Creatinine; eGFR: Estimated Glomerular Filtration Rate; Hct: Hematocrit; BUN: Blood Urea Nitrogen; Na^+: Sodium; K^+: Potassium

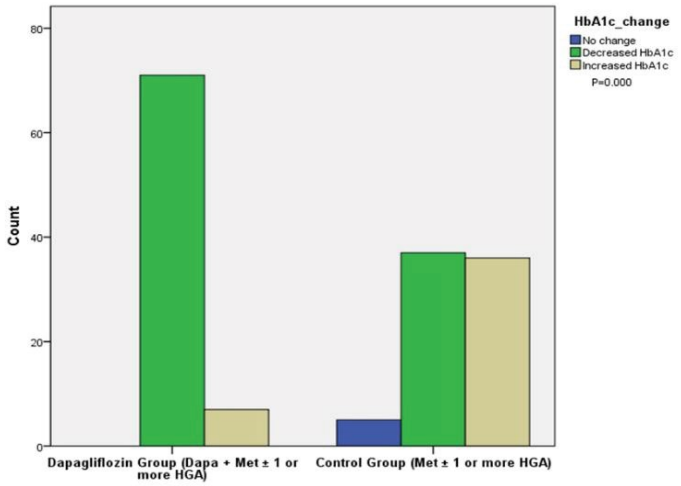

Figure 2 Change in HbA1c between dapagliflozin group and control group. Dapa: Dapagliflozin; Met: Metformin: HGA: Hypogllycemic Agent

Table 3 Adverse events during 12-month follow-up

Variables		Dapagliflozin group (Dapa+ Met ± 1 or more HGA) (n=78)	Control group (Met ± 1 or more HGA) (n=78)	OR [95%CI]	p-value
Hypoglycemia		26 (33.3)	16 (20.5)	1.94 [0.94, 4.00]	0.071
Hypoglycemia no. of episodes	(1-2)	11 (14.1)	14 (17.9)		0.009
	(3-4)	9 (11.5)	2 (2.6)		
	>4	6 (7.7)	0		
Hypoglycemia severity	Mild	25 (32.1)	16 (20.5)		0.102
	Moderate	2 (2.6)	0		0.497
	Severe	0	0		
UTI		10 (12.8)	2 (2.6)	5.58 [1.18, 26.41]	0.032
Genital infection		14 (17.9)	2 (2.6)	8.31 [1.82, 37.95]	0.003

UTI and genital infection severity	Mild	18 (23.1)	2 (2.6)		<0.001
	Moderate	0	0		
	Severe	1 (1.3)	0		
Treatment	yes, needed treatment	9 (11.5)	0		<0.001
	Self-treatable	14 (17.9)	1 (1.3)		0.001
Polyuria		8 (10.2)	1 (1.3)	8.80 [1.07, 72.14]	0.034
Dysuria		10 (12.8)	1 (1.3)	11.32 [1.41, 90.76]	0.009
Microalbuminuria during follow-up		7 (9.0)	6 (7.7)		0.772
Dapa: Dapagliflozin; Met: Metformin; OHA: Oral Hypoglycemic agent; UTI: Urinary Tract Infection					

DISCUSSION

This real-world retrospective study examined the efficacy and safety of dapagliflozin as add-on to different antidiabetic regimens in comparison to other hypoglycemic agents. It showed that HbA1c significantly decreased achieving <7.5% following the addition of dapagliflozin in T2DM patients compared to other HGA confirming the findings of clinical trials in improving glycemic control. The proportion of patients achieved HbA1c of <7.5% with dapagliflozin group are [16 (20.5%)] and [5 (6.5%)] with control group at follow-up period when they were >7.5% at baseline. In addition, those with poor glycemic control of HbA1c >10.4% at baseline, has decreased from [22 (28.2%)] to [2 (2.6%)] at follow-up with dapagliflozin group, whereas [15 (19.2%)] in control group has decreased to [10 (12.8%)] at follow-up. Furthermore, dissimilarly to an observational study which found that the greatest improvement in HbA1c was with the poorest control at baseline [9], this study found that patients who were within the range of 7.5% to 8.4% at baseline had a greater reduction in HbA1c (<7.5%).

In addition, this study showed significant and meaningful changes in the other variables from baseline with dapagliflozin group in comparison to other HGA which is shown in other studies [10,11]. It showed significant reductions in weight, BMI, SBP, and lipid profile [10,11]. Moreover, in contrast to other studies, which showed an increased renal adverse events associated with dapagliflozin [7,12]. this study showed a slight improvement in eGFR and reduction in Scr level with dapagliflozin group but not significant compared to control group.

In patients with T2DM, hypertension and dyslipidemia are prevalent [6]. This study showed reduction in SBP with dapagliflozin group, which is similarly shown in retrospective study [11], but conversely showed a slight increase in DBP. The reason for this difference cannot be determined. With regard to lipid profile, there were no significant decrease in LDL, TC, and increase in HDL cholesterol between the two groups, which in multicenter study found no significant difference in lipid profile [7], while significant reduction in TG has been found in this study with dapagliflozin group. Of note, the dosages for dyslipidemic medications were changed for some patients during follow-up period in this study.

However, no significant difference between the two groups in hypoglycemic events has been found in this study, dissimilar to multicenter study which showed significant decrease in hypoglycemic events with dapagliflozin group [7]. This could be attributed to that dapagliflozin group patients were asked in each visit about hypoglycemia events, unlike control group patients.

An important strength of this study is the evaluation of the overall effectiveness of dapagliflozin in combination with different regimens and compare it with other HGA in patients with wide baseline range of HbA1c and its impact on the glycemic targets in a governmental teaching hospital with an integrative team whose expert on diabetes management in real-world setting. Hence, the results of this study may be more generalizable in clinical practice than results from clinical trials.

Limitations

The retrospective nature of this study inherent it all the limitations including reverse causality risk, data quality concerns, missing information, and heterogeneity of the patients. In addition, the claim for a filled prescription does not

show whether the medication was administered as recommended. It was also not possible to measure adverse events. Future studies are required to investigate the real-world impacts of dapagliflozin on HbA1c and other parameters (e.g. weight, blood pressure, renal function) over longer periods of follow-up and in various populations with larger sample size.

CONCLUSION

In this real-world retrospective study in Saudi Arabia, dapagliflozin showed extra HbA1c reduction when added to metformin and a broad range of HGA, including oral therapies and insulin, in comparison to other HGA in patients with T2DM. Also, it offered additional clinical benefits including weight loss, blood pressure reduction, and lipid profile improvement. The main safety concern was associated with increased incidence of the urinary and genital tract infections.

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Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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