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Role of Dapagliflozin versus Empagliflozin as add-on Therapy on Diabetic Nephropathy

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ABSTRACT: Background: Diabetic nephropathy affect approximately 50% of type 2 diabetics. Early detection of kidney disease is crucial to reduce deterioration of renal function, beside reversing microalbuminuria showed beneficial effects in delaying the onset or even reversing the progression of the disease. Recently, sodium/glucose cotransporter-2 inhibitors have received attention for their anti-inflammatory and reno-cardioprotective effects. **Aim:** This interventional study aimed to evaluate and compare the clinical outcomes of two sodium/glucose cotransporter-2 inhibitors, Dapagliflozin vs. Empagliflozin, as add-on therapy on renal function parameters and other injury markers. **Methodology:** Forty-one of type 2 diabetic nephropathy patients had been divided into two groups randomly. The first group treated with Dapagliflozin 5mg/day and the second group treated with Empagliflozin 10 mg/day, for 16 weeks as add-on. Blood and urine samples were collected at baseline and at week 16 to evaluate the glycemic, weight parameters, renal function (urinary albumin/creatinine ratio, serum urea and creatinine, estimated glomerular filtration rate, and lipid profile. **Results:** After 16 weeks, Dapagliflozin and Empagliflozin significantly reduced HbA1c, body mass index, waist circumference ($p<0.01$). Albuminuria reduced significantly with Empagliflozin and Dapagliflozin ($p<0.05$). A mild elevation in serum creatinine was observed with significant difference between two medications. Empagliflozin showed a mild reduction in glomerular filtration rate compared with Dapagliflozin. Empagliflozin significantly reduced cholesterol while Dapagliflozin significantly reduced LDL-c, TG and VLDL levels ($p<0.05$). No change in HDL-c level in both groups. **Conclusion:** Adding Dapagliflozin or Empagliflozin effectively improved albuminuria, glycemic status and weight parameters. The preference was for Dapagliflozin regarding renal function and lipids.

Keywords: Diabetic Nephropathy, Albuminuria, glomerular filtration rate, Dapagliflozin, Empagliflozin.

Introduction

Diabetic Nephropathy (DN) is one of the frequent, burdensome, long-term complications of diabetes and it represents the leading cause of end-stage renal disease (ESRD) [1]. Diabetic nephropathy characterized by elevated urinary albumin excretion (albuminuria) or reduced glomerular filtration rate (GFR) or both [2,3]. In T1DM, chronic kidney disease (CKD) mostly progresses after ten years; however, in T2DM CKD may already be present at diagnosis. Up to three percent of people with T2DM have albuminuria at the time of diagnosis since the early stages sometimes progress undetected or as prediabetes [4,5,6]. It is well known that early detection of DN, along with aggressive management of its known risk factors are crucial to reduce the deterioration, morbidity and mortality as well as the social and economic burden [7].

The main goal of pharmacological intervention is to prevent the decline in renal function through returning microalbuminuria to the normal, this reduction has beneficial effects in delaying the renal impairment onset or even better reversing the progression of renal damage [8].

Standard treatment options for DN include renin-angiotensin system (RAS) blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), been used for a long time and many trials have demonstrated their safety and efficacy [9–11]. More recently, sodium/glucose cotransporter-2 inhibitors (SGLT2is) and non-steroidal mineral receptor antagonists (MRAs) have received attention for their anti-inflammatory and reno-cardioprotective effects [12]. For every patient with T2DM, the American Diabetes Association advises evaluating albuminuria and estimating GFR once a year [13]. Additionally, the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) also advise diabetic individuals to have their eGFR and albuminuria evaluated annually [14]. Safety and efficacy of Dapagliflozin and Empagliflozin have been evaluated by several clinical trials, mostly the cardio-renal outcomes [15-17].

The effectiveness of Dapagliflozin in diabetic nephropathy was reported with two doses (5,10 mg/day) [18,19], while for Empagliflozin the dose is 10 mg/day [20].

Significance of the present study is to compare the clinical efficacy between Dapagliflozin and Empagliflozin since; to date; no follow-up study regarding these SGLT2is recorded in Iraqi patients with limited data available on Middle Eastern population in general.

Patients and Methods

Study Design

This is an interventional open label randomized clinical trial was conducted from May to December 2022, at the Diabetes Center/ Mustansiriyah University/ Iraq. The ethical committee of the diabetes center and college of pharmacy in Mustansiriyah University gave their approval before the study initiation. All

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patients were fully informed about the study protocol and written consent was obtained from all participants before starting the study. All investigations and procedures carried out in the study involving human participants were in accordance with the 1975 Declaration of Helsinki and its later amendments.

Participants Recruitment

Patients enrolled in the study were with the following criteria: T2DM with nephropathy, age between 18-70 years, on a combination of OADs (sulfonylurea + metformin + gliptin), HbA1c >7%. We excluded any patient taking other medication that may interact with the outcome measures like (ACE inhibitors, ARBs, MRAs). Forty-one patients diagnosed with nephropathy; either by elevated urinary albumin excretion or reduced GFR or both [2,3]; were involved and divided into two groups: DAPA group, treated with Dapagliflozin 5 mg/day (Getz, Pakistan) and EMPA group, treated with Empagliflozin 10 mg/day (Getz, Pakistan). Sulfonylurea was down-titrated; on need; during the treatment period to mitigate the risk of recurrent hypoglycemic events. All the mentioned steps were done under the supervision of specialist physician.

Outcome Measures

The study's outcomes measured the changes at week 0 (baseline) and week 16 (post-treatment) in the following parameters: HbA1c, urinary albumin to creatinine ratio (UACR), serum urea and creatinine, eGFRcr, and lipid profile. Serum urea, creatinine and lipids were measured using enzymatic method with hexokinase [21] on the cobas c311 analyzer system (Roche Diagnostics, Germany). HbA1c was measured using the Tina-quant Hemoglobin A1c Dx Gen.3 assay [22] on the cobas c503 analyzer (Roche Diagnostics, Germany). Urinary ACR was measured using DCA Vantage Analyzer (Siemens diagnostics, Germany) [23]. Estimated GFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine [24].

Statistical Analysis

Statistical analysis was performed using SPSS (version 29) and Microsoft excel (2010). Chi-square Test or Fisher's Exact Test was performed to test the significance of difference between the non-continuous variables. Paired samples T-test was performed for comparison between before and after treatment values. Independent T-test was performed for comparison between patients' groups. A p-value of <0.05 was considered statistically significant.

Results

Demographic and disease characteristics of the patients are shown in table 1. The mean age of the study groups were (51.45 ± 7.99) for DAPA and (54.24 ± 7.75) for EMPA. While mean of body mass index (BMI) were (34.23 ± 4.25) for DAPA and (37.34 ± 4.20) for EMPA.

Table (1): Demographic and disease characteristics of the patients

Characters		DAPA (No=20)	EMPA (No=21)	P-value
Age (years)	≤60	17 (85)	17 (80.95)	0.07 NS
	>60	3 (15)	4 (19.05)	
Sex	Male	7 (35)	11 (52.38)	0.73 NS
	Female	13 (65)	10 (47.62)	
BMI (kg/m²)	25 - 29.9	5 (25)	2 (9.52)	0.07 NS
	30 - 34.9	7 (35)	10 (47.62)	
	35 - 39.9	5 (25)	7 (33.33)	
	≥ 40	3 (15)	2 (9.52)	
WC (cm)	Male ≥ 94	7 (35)	11 (52.38)	0.73 NS
	Female ≥ 80	13 (65)	10 (47.62)	
Smoking	Yes	6 (30)	2 (9.52)	0.36 NS
	No	14 (70)	19 (90.48)	
Educational Level	Illiterate	5 (25)	7 (33.33)	0.06 NS
	Primary	3 (15)	0 (0)	
	Secondary	6 (30)	11 (52.38)	
	College	6 (30)	3 (14.29)	
Duration of DM (years)	<5	2 (10)	1 (4.76)	0.02*
	5-10	6 (30)	4 (19.04)	
	≥10	12 (60)	16 (76.19)	
Family History of DM	Yes	16 (80)	17 (80.95)	0.76 NS
	No	4 (20)	4 (19.05)	
Comorbid disease history	Yes	10 (50)	15 (71.43)	0.11 NS

Data presented as Number and Percentage; Chi Square or Fisher's Exact Test used to assess counts between groups; NS, No significant differences (p≥0.05); *, Significant differences (p<0.05); DAPA, Dapagliflozin; EMPA, Empagliflozin; BMI, Body mass index; WC, Waist circumference; DM, Diabetes Mellitus.

Table 2 displays the impact of Dapagliflozin vs. Empagliflozin on glycemic status, body mass index and waist circumference (WC). Significant reduction in HbA1c, BMI, and WC in both treatment groups (p<0.001).

Table 2: Effect of Dapagliflozin vs. Empagliflozin on glycemic and anthropometric parameters in diabetic nephropathy

Variables		DAPA (No=20)	EMPA (No=21)	P-Value[a]
HbA1c (%)	**Pre-**	10.09 ± 2.09	10.58 ± 1.28	0.56 NS
	Post-	8.80 ± 2.17	8.33 ± 1.00	0.89 NS
% of change		-12.78**	-21.27**	
BMI (kg/m²)	**Pre-**	33.43 ± 4.07	35.91 ± 4.75	0.09 NS
	Post-	32.66 ± 4.34	35.11 ± 4.99	0.11 NS
% of change		-2.30**	-2.23**	
WC (cm)	**Pre-**	113.30 ± 7.57	114.00 ± 8.41	0.80 NS
	Post-	109.50 ± 7.61	112.14 ± 11.17	0.42 NS
% of change		-3.35**	-1.63**	

Data presented as mean ± SD; [a] Independent T-test for comparison between groups; NS, No significant changes (p≥0.05); *, Significant differences (p<0.05); DAPA, Dapagliflozin; EMPA, Empagliflozin; BMI, Body mass index; WC, Waist circumference.

The effects of Dapagliflozin vs. Empagliflozin on renal function show in Table 3. Albuminuria reduced significantly with EMPA (p<0.01) and with DAPA (p<0.05). A mild elevation in serum creatinine level was observed with significant difference between two medications. Cholesterol level was significantly reduced (p<0.05) with EMPA while DAPA significantly reduced LDL-c, TG and VLDL levels (p<0.05). No change in HDL-c level in both groups.

During the study period, three participants complained from mild to moderate UTIs diagnosed by urinalysis and patient' burning sensation. Two cases were in DAPA group and one in EMPA group, all of them were women aged >50 years. No episodes of diabetic ketoacidosis during treatment period. Hypoglycemic events treated by down-titrating sulfonylurea dose.

Table 3: Effect of Dapagliflozin vs. Empagliflozin on renal function and lipid profile in diabetic nephropathy

Variables		DAPA (No=20)	EMPA (No=21)	P-Value[a]
UACR (mg/g)	**Pre-**	133.34 ± 76.48	135.71 ± 74.63	0.92 NS
	Post-	55.17 ± 55.78	78.86 ± 74.11	0.81 NS
% of change		**-58.62***	**-41.89****	
Creatinine (mg/dl)	**Pre-**	0.75 (0.65)	0.80 (0.20)	0.44 NS
	Post-	0.78 (0.61)	1.00 (0.60)	0.03*
% of change		**4.02**	**25.00**	
eGFR (mL/min)	**Pre-**	89.85 ± 30.08	92.91 ± 26.55	0.69 NS
	Post-	92.56 ± 27.86	82.65 ± 29.16	0.39 NS
% of change		**3.0**	**-11.04**	
Urea (mg/dl)	**Pre-**	37.40 ± 21.07	25.26 ± 2.52	0.27 NS
	Post-	31.89 ± 12.41	25.81 ± 4.59	0.50 NS
% of change		**-14.73**	**-5.55**	
TC (mg/dl)	**Pre-**	192.43 ± 66.61	199.21 ± 46.28	0.75 NS
	Post-	175.13 ± 51.15	179.77 ± 52.87	0.84 NS
% of change		**-8.99**	**-9.76***	
LDL-c (mg/dl)	**Pre-**	131.96 ± 47.74	102.07 ± 38.92	0.14 NS
	Post-	103.85 ± 42.48	109.94 ± 46.25	0.76 NS
% of change		**-21.30***	7.71	
HDL-c (mg/dl)	**Pre-**	49.85 ± 20.16	39.03 ± 10.13	0.15 NS
	Post-	48.43 ± 11.99	40.25 ± 9.54	0.11 NS
% of change		-2.85	3.12	
VLDL (mg/dl)	**Pre-**	62.80 ± 30.74	71.35 ± 65.02	0.66 NS
	Post-	40.00 ± 12.87	58.95 ± 20.11	0.002**
% of change		**-36.31***	-17.38	
TG (mg/dl)	**Pre-**	314.15 ± 153.79	368.18 ± 95.06	0.44
	Post-	204.26 ± 64.33	294.78 ± 92.19	0.003**
% of change		**-34.98***	-19.93	

Data presented as mean ± SD or median (interquartile range); [a] Independent T-test used for comparison between groups; NS, No significant changes ($p \geq 0.05$); *, Significant differences ($p < 0.05$); **, High significant differences ($p < 0.01$); DAPA, Dapagliflozin; EMPA, Empagliflozin; UACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate.

Discussion

Consistent with previous studies, adding DAPA or EMPA significantly reduced HbA1c, BMI, and WC [25-27]. Despite no significant differences concerning these parameters between DAPA and EMPA, a greater HbA1c reduction was observed with EMPA that is compatible with the face to face studies showed a greater reduction for HbA1c with EMPA [28,29]. Moreover, Inzucchi et al. found the glycemic reduction effect of EMPA was greater in patients with higher HbA1c values at baseline [30].

The reduction in body weight is a notable feature of SGLT2i in diabetic and non-diabetic as well [31,32] and many studies compared the effects of DAPA or EMPA as add-on therapy [25, 33-35], supporting their efficacy as a fourth OAD. A negative energy balance achieve due to increased urinary glucose excretion result in a reduction in body fat secondary to caloric loss and/or fluid loss [36,37]. Generally, weight reduction effect of SGLT2i consist of two phases, the initial phase (within three months) via osmotic diuresis [38], and the second phase (beyond 3 months) due to loss of fat mass [39].

A Korean studies compared the effect of adding DAPA or EMPA vs. insulin glargine in T2DM, both drugs improved glycemic index with better weight control effect and less hypoglycemic events compared to insulin. These effects make these SGLT2is as attractive treatment option in obese diabetic patients with poor glycemic control, and in those patients unwilling to administer insulin injections [28,36,40].

In present study, both DAPA and EMPA reduced the UACR effectively [41-43]. The EMPA-REG OUTCOME trial confirmed short- and long-term benefits of different doses of EMPA on different stages of albuminuria (normo-, micro-, and macro-albuminuria) [44]. The DAPA-CKD trial also showed a reduction in UACR in both mico- and macro-albuminuria regardless of DM [45]. A recent systematic review clarified that SGLT2is were consistently better in improving UACR compared with GLP-1 and DPP4i and confirmed that SGLT2i decreased the risk for albuminuria onset by 16-20% and for albuminuria progression by 27-48% [46]. The reduction can be a consequence of changes in charge and/or size selectivity of the glomerular filtration barrier, thus a reduction in intraglomerular pressure and improvement in tubular reabsorptive capacity [47].

Glomerular filtration rate found to be mildly decreased with EMPA more than DAPA. This modest decline in the filtration rate (approximately 3-5 mL/min) is commonly attributed to the effect of high sodium level in the proximal tubule activate TGF, leading to reversible intrarenal hemodynamic effects, including afferent vasoconstriction that results in a decrease in intraglomerular pressure providing the proposed renoprotective effect of SGLT2i [48,49].

A significant differences observed between DAPA and EMPA regarding TG and VLDL-c levels while LDL-c level showed a reduction in DAPA vs. an elevation in EMPA. At baseline, LDL-c was higher in DAPA compared with EMPA, this may be the reason for this inversion. A post-hoc analysis of the EMPA-REG OUTCOME trial found that the beneficial effect of EMPA on cardiovascular outcomes was consistent across all categories of LDL-c levels at baseline [50]. Other study with Canagliflozin found that the subgroup with baseline LDL-c levels <120 mg/dL showed an increase of LDL-c whereas the subgroup with baseline LDL-c levels >120 mg/dL had a reduction [51].

Current findings indicates a significant reduction in TG and LDL-c with no significant changes in HDL-c level with DAPA consistent with a systematic review [31] and clinical studies (52–54). On the other hand, the most notable effects of EMPA were decrease in TG with increase in LDL-c and HDL-c but did not reach the significant level as noticed with previous works [55–58]. There is a suggestion that EMPA may increase LDL-c particles without an effect on their size or composition [56].

Although to date there is still no mechanistic explanation for the effect of some SGLT2i inducing increment in plasma LDL-c, one mechanism supposed that EMPA act by switching of energy metabolism from carbohydrate to lipid utilization thus reducing LDL receptor expression and LDL-c catabolism [59]. Other explanation suggested that there's reduction in LDL-c clearance due to increased lipoprotein-lipase activity leading to the increase of LDL-c level [60].

No significant changes in HDL-c level were observed with both drugs are in accordance with a previous studies [33,56,61]. The superiority of DAPA is clear in present study, through a reduction in TG and LDL/HDL ratio vs. a slight reduction in TG with constant LDL/HDL ratio in EMPA. Such effect could be related to the glycosuria induced by SGLT2i may promote a starving-like state, leads to a metabolic improvement through the mobilization and oxidation of fatty acids from the adipose tissue for the production of ketone bodies. This may also fuel hepatic cholesterol synthesis, thus inhibiting atherogenic lipoprotein uptake from the liver [26].

Limitations

The main limitations of this study were inability to identify the effects of these drugs as mono-therapy on nephropathy, single center-study which could potentially limit the generalizability of the results, short follow-up period, and lack of measuring of electrolyte or pancreatic enzymes to evaluate the safety of the studied drugs.

Conclusion

Adding Dapagliflozin or Empagliflozin to the traditional oral antidiabetic drugs in diabetic nephropathy effectively improved albuminuria, glycemic status and weight parameters. The preference was for Dapagliflozin regarding renal function (GFR) and lipids.

Conflict of Interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

The ethical committee of the diabetes center (no. 1340) and college of pharmacy in Mustansiriyah University (no. 69) gave their approval before the study initiation. All patients were fully informed about the study protocol and written consent was obtained from all participants before starting the study.

Consent for publication

Not applicable

Availability of data and materials

Data used for this study will be made available upon request.

Author's contribution

Study conception and design: Abbas Mahdi Rahmah, Hadeel Delman Najim; theoretical calculations and modeling: Mohammed Mahmood Mohammed; data analysis: Hadeel Delman Najim; draft manuscript preparation: Hadeel Delman Najim, Mohammed Mahmood Mohammed. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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