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RESEARCH ARTICLE

IMPACT OF DAPAGLOFLOZIN ADMINISTRATION IN TREATMENT OF PROTEINURIA IN PATIENTS WITH NEPHROTIC SYNDROME

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ABSTRACT

Background and Aims: Nephrotic syndrome addressed as one of the most common causes of inherited chronic kidney disease. Where, protein is excessively filtered into the urine.Sodium-glucose cotransporter 2 (SGLT2) inhibitors in nephrotic patients on immunosuppression are underexplored.This research aimed to investigate the impacts of dapagloflozin in treatment of proteinuria in patients with nephrotic syndrome. ***Material and methods:*** A prospective clinical trial involving fifty-six adult patients, without a diagnosis of diabetes, with persistent proteinuria. Group A; 28 patients received traditional medicines; Group B; 28 patients received dapagloflozin; 10 mg daily. We determine the changes from baseline of urinary protein/creatine (Up/cr) and glomerular filtration rate (based on epi GFR formula). ***Results:*** Both groups exhibited significant reductions in proteinuria posttreatment, with dapagliflozin group achieving a mean UPCR reduction of -94.7%, and Group A -86.7% ($p < 0.001$). Posttreatment, FPG, 2hPG, and HbAlc levels in Group B were significantly lower than thosein Group A ($P<0.05$). Posttreatment, Scr, BUN, UmAlb, UAER, UACR, and 24-hour urine protein quantitative levels inGroup B were significantly lower than those in the control group ($P<0.05$). Posttreatment, hs-CRP, IL-1β, and TNFα levels in Group B were significantly lower than those in Group A ($P<0.05$). The incidence of adverse reactions in Group B significantly lower than Group A ($P<0.05$). ***Conclusion:*** Compared with enalapril maleate alone, the combined application of dapagliflozin in treatment of diabetic kidneydisease has more significant clinical efficacy. It can further controlpatients' blood sugar, reduce their body's inflammatory response,alleviate or eliminate their proteinuria symptoms, promote recovery of their renal function, and enhance safety of theirtreatment to a certain extent that helps to further improve clinical treatment effect.

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INTRODUCTION

Nephrotic syndrome is a disease in which protein is excessively filtered into the urine. This is caused by damage to the clusters of small blood vessels in the kidneys that filter waste and excess water from the blood. The consequences are generalized systemic edema, proteinuria, hypoalbuminemia, and hyperlipidemia (1). Nephrotic syndrome can occur in a variety of diseases. Nephrotic syndrome induced by diseases that specifically target the kidneys are defined as primary nephrotic syndrome, whereas those induced by diseases that involve different parts of the body, such as diabetes, is considered secondary nephrotic syndrome. The treatment for secondary nephrotic syndrome consists of fluid management with diuretics and treatment of the primary disease (2). Chronic kidney diseases represent a global health challenge, with nephrotic syndrome standing out as a complex clinical entity characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia.

Althoughmanagement of nephrotic syndrome has faced uncertainties due to a lack of high-quality randomized trials and systematic reviews (3). In conjunction with sodium-glucose cotransport-2 (SGLT2) inhibitors, known for their renal benefits, have shown efficacy in reducing proteinuria, particularly in diabetic nephropathy (4). In contrast SGLT2 inhibition decreases albuminuria and reduces the risk of kidney disease progression in patients with type II diabetes. These benefits are unlikely to be mediated by improvements in glycemic control alone. Therefore, we aimed to examine the kidney effects of the SGLT2 inhibitor dapagliflozin in patients with proteinuric kidney disease without diabetes (5). Currently, common treatments fordiabetic nephropathy in clinical practice involve blood glucose control, blood pressure control, and kidney protectiontherapy (5). As well, agents are promising and have good availability to be used as inhibitors of DKD progression to newadvanced stages of CKD and ACEI, ARB.

As for monoclonal antibodies that play a role in inhibiting TGF-bethaexpression, they are still not available and expensive. Therefore, DM drugs given orally may have better availability. Theprogression of DKD to advanced stage of CKD is through increased expression of TGF-betha (6).TGF-betha expressionwas found to be higher in patients with persistent proteinuria (7). Recently, an increasing number of studies5,6 have shown that dapagliflozin can not only control blood glucoselevels in diabetic patients, but can also reduce their risk of cardiovascular events and death, and has significant renalprotective effects. However, clinical studies on the treatment of diabetic nephropathy with dapagliflozin are still limited(8). The need of this study developed from the rarity of data in the published articles about the efficacy of dapagliflozin in treating diabetic nephropathy and its impacton patients' proteinuria levels. Thus, the current study aimed to investigate the impacts of dapagloflozin in treatment of proteinuria in patients with nephrotic syndrome.

MATERIALS AND METHODS

Study design: A randomly assigned, double-blind, controlled experiment was performed from July 2023 to March 2024 at the Outpatient Clinic of Shebin El-kom Teaching Hospital, Shebin El-kom City, Menofyia, Egypt. This study complied with the Helsinki Declaration, obtained approval following the ethical approval, participants provided informed consent before enrollment.

Participants: Fifty-six patients with diabetic kidney diseasewere enrolled based on specific inclusion criteria: they included both genders, aged 20 years or older, diagnosed with diabetic nephropathy accordingto relevant diagnostic criteria, with a calculated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 or a 24-hour urine protein excretion rate (24hUP) > 0.3g based on the CKD-EPI formula (9), have not used other hypoglycemic drugs or dapagliflozin, or have stopped using these drugs for at least 4 weeks,have complete clinical data and relevant test data. Patients with severe diseases or tumors of liver, kidney, heart, brain, or other organs;other significant diseases, such as infectious or autoimmune diseases, that may affect the judgment ofstudy results; pregnant or lactating women; who were drug addicted or did not meet complete inclusion criteria were excluded.

Intervention: In this research, all patients were required to complete relevant tests upon enrollment, and their vital signs were closely monitored. Theseverity of the disease was assessed, and appropriate interventions such as hypoglycemic drugs and nutritional supportwere given based on the assessment results. Both groups of patients received a 12-week treatment.

Group A: 28 Patients were treated with oral administration of enalapril maleate (ChangzhouPharmaceutical Factory Co., Ltd., National Drug Approval H10930061), with a dose of 5 mg per administrationtwice a day.

Group B: 28Patients in the observation group received treatment with oral administration of dapagliflozin (Astra Zeneca Pharmaceuticals Co., Ltd., National Drug Approval J20170040), with a dose of 10 mg peradministration, once a day. The efficacy evaluation criteria were as follows: markedly effective: disappearance ofclinical symptoms such as proteinuria in patients, normalization of indicators such as 24-hour proteinuria, 24-hoururinary microalbumin, and blood glucose, and recovery of renal function; effective: basic disappearance of clinicalsymptoms i.e., proteinuria in patients, improvement of indicators such as 24-hour urinary microalbumin and24hours proteinuria by ≥50%, and basic recovery of renal function; ineffective: The clinical symptoms of patient e.g., proteinuria, have not disappeared and may have worsened. The indicators, including microalbuminuria in 24hours urine and 24-hour proteinuria, have not improved. Renal function has not returned to normal.The total effective rate of treatment (number of markedly effective cases + number of effective cases) / total cases × 100%.

Blood glucose indicators were determined prior and posttreatment, 3 mL of fasting and 2-hour postprandial venous blood samples were collected from the patients. The fasting plasma glucose (FPG) and 2hours postprandial glucose (2hPG) levels were measured using the CX8 fully automated biochemical analyzer from Beckman, USA. The patients' glycated hemoglobin (HbA1c) levels were measured using the glycated hemoglobin analyzer from BioRad, USA. Renal function indicators: Before and after treatment, 3 mL of clear empty stomach venous blood was collected from each patient, routinely centrifuged for separation, and the levels of blood creatinine (Scr), blood urea nitrogen (BUN), and urinary microalbumin (UmAlb) were detected using an immunoturbidimetric method. The 24hours urine was collected to determine urine protein quantification using a double reduction urea method, and the 24 hours urine protein excretion rate (UAER) was calculated. The concentration of creatinine (Cr) in the urine was detected using an enzymatic method, and the urine albumin to creatinine ratio (UACR) was calculated.

Inflammatory factor indicators: Before and after treatment, 3 mL of fasting venous blood samples were collected from the patients. The samples were allowed to stand at room temperature for 1 hour and then centrifuged at 3000 rpm for 10–15 minutes to separate the serum, which was stored at −70°C until further use. The levels of highsensitivity C-reactive protein (hs-CRP), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) in the patients' serum were measured using the Boruike ELISA kits (ELISA method) from Changsha Dalfo Bio-Tech Co., Ltd. 5. Adverse reactions: The adverse reactions observed in this study included: diabetic ketoacidosis, hypoglycemia, nausea, vomiting, dizziness, and headache, and the occurrence of the above conditions were recorded by our hospital's related medical staff.

Statistical analysis: A GraphPad Prism 8 was used for graphing and SPSS 23.0 was used for data analysis. For continuous data, the mean andstandard deviation were used to describe the distribution, and t-tests or analysis of variance (ANOVA) were used tocompare differences between two groups. For categorical data, frequency and percentage were used to describe distribution, and chi-square tests or Fisher's exact tests were used to compare differences between two groups. A P-valueless than 0.05 indicated statistical significance.

Multiple logistic regression is used to adjust for the relationship betweenexposure and outcome, thereby reducing the influence of confounding factors.

RESULTS

Participant characteristics: Table 2 shows the participant characteristics for both groups. No significant differences between the groups concerning age, BMI, diabetes, diabetic nephrology, HbA1c, FPG, 2Hpg, Scr, BUN, UmA1b, UAER, UACR, 24h urine protein quantification, or sex distribution ($p > 0.05$).

Effects of dapagliflozin on clinical treatment efficacy between groups: Overall effective rate of treatment in the control group was 79.55%, while that in Group B was 97.73%. Overall effective rate of treatment in Group B was significantly higher than that in Group A ($P<0.05$).

Effects of dapagliflozinon glucose indicators between groups: FPG levels before and after treatment in Group A were (8.65±0.77, 6.78±0.54), and (12.27±2.41, 8.36±0.78) respectively, and HbAlc levels were (7.86±0.88, 6.59±0.67). FPG levels pre- and posttreatment in Group B were (8.54±0.79, 6.02±0.45) and (12.31±2.43, 7.41±0.72) respectively, andHbAlc levels were (7.91±0.85, 6.11±0.54). Pretreatment, there was no significant difference in FPG, 2hPG, andHbAlc levels between both groups ($P>0.05$). Posttreatment, the FPG, 2hPG, and HbAlc levels in Group B were significantly lower than those in Group A ($P<0.05$).

Effects of dapagliflozin on renal function indicators between groups: Pretreatment, Scr levels of Group A were (89.59±5.71, 65.39±5.52), BUNlevels were (17.68±3.26, 14.88±2.25), UmAlb levels were (248.32±5.36, 194.35±5.42), UAER levels were (158.36±12.18, 94.63±8.47), UACR levels were (178.32±12.56, 102.88±8.53), and 24h urine protein quantification levels were(289.94±16.85, 196.27±15.21); Scr levels of Group Bpre- and posttreatment were (89.77±5.54,60.21±5.13), BUN levels were (17.55±3.31, 12.26±2.11), UmAlb levels were (248.35±5.21, 1176.32±5.37), UAERlevels were (158.41±12.24, 85.72±7.53), UACR levels were (178.42±12.45, 83.89±7.09), and 24h urine protein quantification levels were (291.31±16.77, 152.75±12.79). Pretreatment, there was no significant difference in Scr, BUN,UmAlb, UAER, UACR, and 24h urine protein quantification levels between both groups ($P>0.05$); Posttreatment, levels of Scr, BUN, UmAlb, UAER, UACR, and 24h urine protein quantification in Group B weresignificantly lower than those in Group A ($P<0.05$)

Effects of dapagliflozin on inflammatory markers between groups: Pre- and posttreatment, levels of hs-CRP in the control group were (14.78±2.43, 9.53±1.62), IL-1β were (23.74±2.62, 16.42±2.31), and TNF-α were (7.68±0.85, 4.54±0.62), respectively. Levels of hsCRP in Group Bpre- and posttreatment were (14.69±2.51, 6.45±1.23), IL-1β were (23.69±2.65, 13.35±1.74), and TNF-α were (7.59±0.74, 3.25±0.53), respectively. Pretreatment, there was no significant difference in levels of hs-CRP, IL-1β, and TNF-α between both groups ($P>0.05$). Posttreatment, levels of hs-CRP,IL-1β, and TNF-α in Group B were significantly lower than those in Group A ($P<0.05$).

Effects of dapagliflozin on adverse reactions between groups: Incidence of adverse reactions in Group A was 21.59%, while Group B was 5.68%. Incidence of adverse reactions in Group B was significantly lower than that in Group A ($P<0.05$)(Tables 2).

DISCUSSION

Recently, fact alternating life style, and outdoor dietary meal unhealthy contents, incidence of diabetes has beenincreasing year by year. As well, diabetic nephropathy caused by diabetes is increasing along with incidenceof diabetes (11). Kock et al. (12) shows that about 40% of diabetes patients will develop diabetic nephropathy. As a commoncomplication of diabetes, diabetic nephropathy is the second enumerated leading cause of end-stage renal disease, and its harm tohuman health cannot be ignored. The pathogenesis of diabetic nephropathy is complex and mainly related to multiplefactors i.e., hyperglycemia, hypertension, lipid abnormalities, activation of renin-angiotensin-aldosterone system, insulin secretion defects, insulin resistance, and oxidative stress (13). In the early stage of diabetic nephropathy, the mainfeatures are glomerulosclerosis, microvascular damage, and microalbuminuria. At this stage, kidney damage has a certaindegree of reversibility (14). Therefore, providing effective treatment and intervention for early diabetic nephropathy patientsis of great significance in preventing the occurrence of kidney failure. The essential contributor of DKD-related CKD areproteinuria and the expression of TGF-betha. The known agent that has a potential effect in inhibiting CKD progressionare monoclonal antibody. This antidiabetic agent potentially to be developed as a kidney protector.

ACE inhibitors are a class of commonly used antihypertensive drugs in clinical practice. Their main function is toinhibit activity of angiotensin-converting enzyme those reduces generation of angiotensin II, decreases vascularconstriction and tissue cell proliferation, and ultimately lowers blood pressure and reduces burden on the heart (15). Utilized traditional medicine is a commonly used ACE inhibitor that is widely used in treatment of hypertension, heart failure,diabetic nephropathy, and other diseases (16). However, despite various beneficial therapeutic effects of ACE inhibitors,their efficacy in diabetic nephropathy is not perfect and has certain limitations (17). Therefore, recently researchershave started exploring combined use of other drugs to enhance efficacy of ACE inhibitors, in order to furtherimprove patient treatment outcomes and quality of life.SGLT-2 inhibitors are a new type of oral medication for diabetes, which can reduce blood glucose levels by inhibitingthe function of the SGLT-2 protein in renal tubules and reducing the reabsorption of glucose by the kidneys (18). Unliketraditional oral hypoglycemic drugs, SGLT-2 inhibitors not only lower blood glucose levels, but have other effectse.g., weight loss, improving hypertension, and improving insulin resistance (19). Dapagliflozin is an oral SGLT-2inhibitor that has been shown to have some efficacy in treatment of type II diabetes (20). By blocking reabsorptionof glucose by renal tubules, dapagliflozin can lower blood glucose levels and reduce insulin resistance.

Table 1. Comparing the characteristics of participants between both groups

		Group A	Group B	t- value	p-value
Age (years)	Male 12A/15B	42.34 ± 5.46	43.61 ± 5.12	0.61	0.54
	Female16A/13B	38.45 ± 3.46	38.61 ± 6.14		
Diabetes duration		16.85 ± 1.18	16.49 ± 1.04	1.41	0.16
Diabetic Nephropathy		5.24 ± 2.74	4.68 ± 2.68	0.89	0.37
Stage					
II		18	15		
III		10	13		
BMI (kg/m^2)		25.45± 0.89	25.5± 0.51	-0.32	0.75
FPG (mmol/L)		8.42± 0.5	8.26± 0.64	1.19	0.24
2Hpg (mmol/L)		12.39± 0.42	12.37± 0.94	0.14	0.89
HbAlc (%)		7.49± 0.72	7.67± 0.76	0.16	0.24
Scr (μmol/L)		89.69± 5.69	89.36± 5.43	0.24	0.87
BUN (mmol/L)		17.69± 3.64	17.47± 3.34	0.34	0.79
UmAlb (mg/L)		248.32± 5.62	248.37± 5.23	0.37	0.96
UAER (μg/min)		158.26± 11.65	158.42± 12.42	0.23	0.92
UACR (mg/ g)		177.42± 13.42	177.54± 13.52	0.53	0.95
24h Urine Protein Quantification (mg/24h)		289.94± 16.26	291.42± 16.56	0.54	0.65

SD: standard deviation; P-value: probability value.

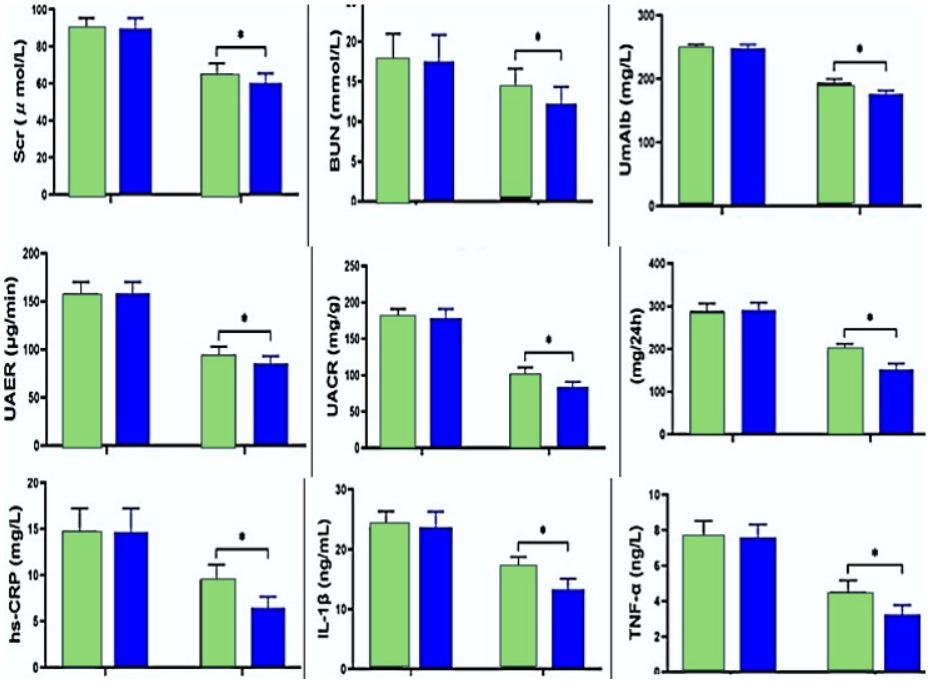

Fig 2. Comparing both groups A;ingreen, B; in blue, Scr, BUN, UmA1b, UAER, UACR, 24hr urine protein quantification, hs-CRP, IL-1β, and TNF-α

Table. 2. Comparing adverse reactions in both groups

Adverse reactions	Group A	Group B	X^2	p-value
Ketoacidosis	2	0	-	-
Hypoglycemia	10	3	-	-
Feel sick	4	2	-	-
Dizziness	2	0	-	-
Total Incidence	64.29%	17.86%	5.134	0.036

As well,dapagliflozin can improve kidney function by reducing proteinuria levels, reducing blood pressure, and improvingvascular function by reducing permeability of glomerular filtration membrane (21).Herrspink et al. (22) have shown that dapagliflozin has potential therapeutic effects in the treatment of diabetic nephropathy (23). Therefore, current clinical trial attempted to add dapagliflozin to the treatment with traditional medicines and explore its clinicaltherapeutic effects of adding dapagliflozin on diabetic nephropathy.

Moreover, posttreatment, levels of Scr, BUN, UmAlb, UAER, UACR, and 24-hourine protein quantification in Group B were significantly lower than those Group A ($P<0.05$). Current study suggests that adding dapagliflozin can promote better recovery of renal function in patients comparedto treatment with only enalapril. The reason for that may be dapagliflozin can have a greater impact on tubuloglomerular feedback and can improve tubular hypertrophy, thereby playing a protective role inkidney function.

Regarding clinical efficacy and blood glucose control, our study revealed that totaleffective rate of Group A was 79.55%, while that Group B was 97.73%, that was significantlyhigher than that of Group A (P<0.05). Posttreatment, levels of FPG, 2hPG, and HbAlc in Group B were significantly lower than Group A (P<0.05). That consistent with Heerspink et al. (24), and Tuttle et al. (25) who confirmed that the use of dapagliflozin can not only stabilize blood glucose levels of diabeticnephropathy patients,unless improve their treatment outcomes. The reason for this may be related to inhibitory effect of dapagliflozin on SGLT-2 in proximal tubules of kidney during application, and it can promote excretion of urinary glucose in patients to some extent. Regarding inflammatory factors and adverse reactions, Posttreatment current study revealed that levels of hs-CRP, IL-1β, and TNF-α in Group B weresignificantly lower than those in Group A (P<0.05), and incidence of adverse reactions in GroupA was 21.59%, while that in Group B was 5.68%, which was significantly lower than that in Group A(P<0.05). These results indicate that addition of dapagliflozin can improve inflammatory response of diabeticnephropathy patients, avoid adverse reactions i.e., hypoglycemia and ketoacidosis, and has a relatively high safetyprofile. Dapagliflozin can inhibit infiltration of inflammatory cells in the body thatcan effectively reduce release of inflammatory factors in the kidneys, and it can improve expression ofoxidative stress markers that plays a crucial role in improving inflammatory response in diabetic nephropathy.

Additionally, dapagliflozin has a unique mechanism for reducing blood glucose levels that can achieve good results incontrolling abnormal blood glucose levels. Moreover, when used in combination with otherhypoglycemic drugs, dapagliflozin can reduce the dosage of hypoglycemic drugs, avoid accumulation of drugs in human body due to highdoses, and thereby reduce likelihood of adverse reactions. There are still several limitations in this study, including that it was a single-center study with a relativelysmall sample size that limit generalizability and representativeness of reported results. As well, lackedanalysis of patient factors e.g., different types of diabetes and complications that may affect efficacy ofDapagliflozin, even lacked long-term follow-up data that makes it impossible to evaluate safetyand effectiveness of Dapagliflozin in long-term use. In addition, the current trial only evaluated role of Dapagliflozin in treatingdiabetic kidney disease and did not study its application in treating other diseases. Therefore, in future research, we willmake further improvements to address these limitations and expand the representativeness of the study to makeresults more generalizable.

CONCLUSION

Compared with traditional medicines or in combination therapy of dapagliflozin for treating diabeticnephropathy reported more significant clinical effects. It can further modulate patients' blood glucose levels, reduce theirsystemic inflammatory response, alleviate or eliminate patients' proteinuria symptoms, promote recovery of theirrenal function. Additionally, combined therapy of dapagliflozin can improve safety of patients' treatmentto some extent, which helps to further improve the clinical treatment effect of patients.

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