Review

Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Non-diabetic Chronic Kidney Disease: A Systematic Review

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Sodium-glucose cotransporter-2 (SGLT2) inhibitors modulate kidney function in diabetic chronic kidney disease trials. Furthermore, recent studies have showed their effect on kidney dysfunction in non-diabetic chronic kidney disease (CKD). Here, we focus on the impact of SGLT2 inhibitors on some renal parameters in non-diabetic CKD by discussing completed and ongoing trials. Different databases and search engines of Web of Science, PubMed, Google Scholar, Scopus, SID, and Magiran were searched until November 2022. We included human studies that evaluated the effect of SGLT2 inhibitors in non-diabetic CKD participants. Two authors independently screened the articles for inclusion, extracted the data, and assessed the quality of the included studies. The primary outcomes were the effect of the SGLT2 inhibitors on proteinuria, GFR and blood pressure. A total of 46 full texts were assessed for eligibility, and further review. After reviewing the full texts, seven eligible articles were entered included in this study.

We suggest that SGLT2 inhibitors provide renal protection by modifying predisposing factors in the development of CKD, specifically albuminuria and GFR decrease. Other beneficial effects of these agents on blood pressure and sympathetic nerve activity might be considered as a possible mechanism for improving renal hemodynamics. We believe SGLT2 inhibitors could be considered as an effective add-on therapy in non-diabetic CKD patients.

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INTRODUCTION

Chronic kidney disease (CKD) is a global health concern with increasing prevalence during the past decade and is expected to be one of the top five causes of death by 2040.[1-3] CKD is defined as "persistently elevated urine albumin excretion, persistently reduced estimated glomerular filtration rate, or both for > 3 months".[4,5] Some of the current treatments for these patients are not optimally effective.[3,6]

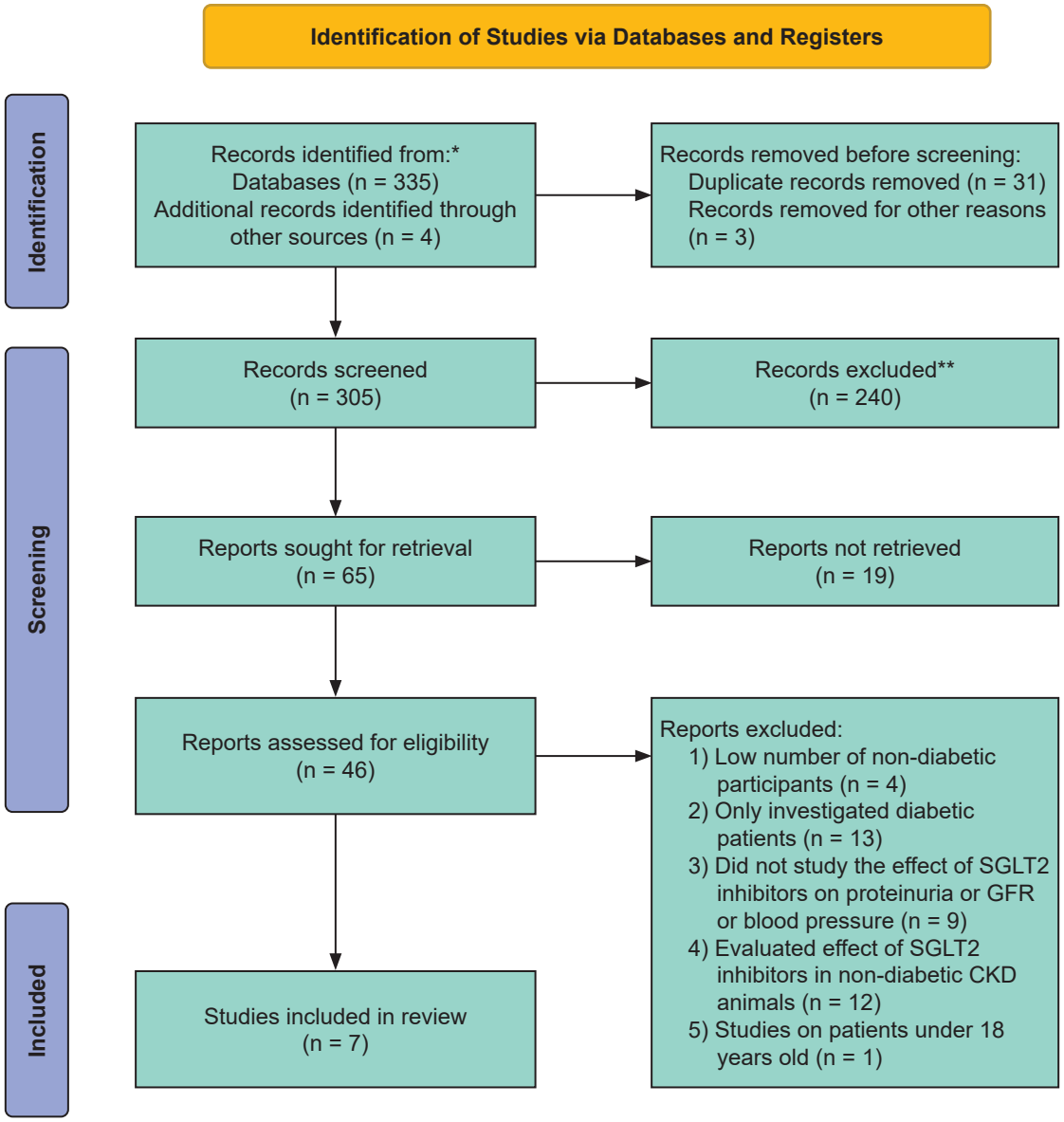
The sodium-glucose cotransporter-2 (SGLT2) inhibitors, including canagliflozin, empagliflozin, and dapagliflozin, are a new class of antihyperglycemic drugs approved for the management of type 2 diabetes mellitus (T2DM) that preserve the kidney and heart function in addition to their blood glucose lowering effect.[7,8] To evaluate the related outcomes of treatment with SGLT2 inhibitors in T2DM, large clinical trials have been conducted in which the study population mostly had glomerular filtration rate (GFR) > 60 mL/min/ m^2. Although these trials have reported improvements in kidney function, the CREDENCE trial was the first to investigate renal outcomes of canagliflozin as the planned aim or the aim planned among patients with diabetic CKD.[9] The trial reported significantly lower risk

of end-stage kidney disease, renal-related death, and kidney dysfunction by SGLT2 inhibition.[10] However, some trials have showed reno-protection in both diabetic and non-diabetic kidney disease by these medications [11] and the data about the efficacy of SGLT2 inhibitors on renal function in the non-diabetic CKD population is limited.

In this systematic review we mainly focused on GFR, blood pressure, proteinuria, and survival as proven factors in CKD progression among the non-diabetic population, to assess the effect of these antidiabetic medications as a possible standard therapy in non-diabetic CKD as in diabetic kidney disease (DKD).

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2015 statement[12] to assess the impact of SGLT2 inhibitors on non-diabetic CKD cases. The primary outcome of this study was the evaluation of the effect of SGLT2 inhibitors on kidney function (Proteinuria / GFR / Blood Pressure / Survival) in non-diabetic CKD participants. The secondary outcome was determination of their associated side effects. Two independent researchers conducted a systematic search in international (Web of Science, PubMed/ Medline, Google Scholar, and Scopus) and national



PRISMA Flow Chart

(SID, Magiran) databases and search engines to detect relevant studies in English and Persian languages, from the beginning up to November 2022 (no time restriction was defined).

Study Selection and Data Extraction

Two researchers independently collected data based on titles. First, titles and abstracts were screened; then, each study was reviewed to exclude unrelated and duplicate studies. Finally, the relevant studies were reviewed, and the references were explored to find more related studies (Figure). Title, name of authors, year of publication, country, study population, sample size, and the study results were extracted before reviewing (Table 1). Any disagreement was resolved through consensus.

Quality Assessment and Risk of Bias

The researchers (the first and second author) independently assessed quality assessment and risk of bias using the Cochrane Risk of Bias Tool (Table 2).[13]

Literature Search and Characteristics of the Included Studies

The inclusion criteria were clinical trials that included adults over 18 years old with CKD and at least one study group without type 2 diabetes and the exclusion criteria were non-human studies, studies in non-CKD patients, studies with participants under 18 years old, and studies on diabetic patients only. Three hundred and thirty-five records were identified via databases and search engines. We also found four records through other sources (references of included studies). After screening, seven full-text articles addressing the effect of SGLT2 inhibitors on human participants were selected (Figure).[14-20] There

Table 1. Characteristics of Included Human Studies

Study	Design/sample/ Duration	Inclusion criteria	Intervention	Outcome
(14) Heerspink HJL, 2020, Multicenter	RCT 4304 cases 2.4 years	- 25<eGFR<75 mL/ min/1.73m^2 - 200<UACR≤5000 mg/g - Adults with CKD, with or without T2DM - Received ACEi or ARB for at least 4 wks before trial if not contraindicated	- Trial: *Dapagliflozin* 10mg/day (n=2152) - Placebo: (n=2152) (On stable optimized dose of ACEi or ARB for the duration of the trial)	- Primary composite outcome: greater significant reduction in trial group - Slope of change in GFR: lesser in trial group - Adverse events (amputation, renal-related adverse event): greater significant reduction in trial group - Major hypoglycemia: greater reduction in trial group - Volume depletion: significant increase in trial group
(15) Heerspink, H. JL, 2021, Multicenter	RCT 4304 cases 2.4 years	- 25<eGFR<75 mL/ min/1.73m^2 - 200<UACR≤5000 mg/g - Adults with CKD, with or without T2DM - Received ACEi or ARB for at least 4 wks before trial if not contraindicated	- Trial: *Dapagliflozin* 10mg/day (n=2152) - Placebo: (n=2152) (On stable optimized dose of ACEi or ARB for the duration of the trial)	- Survival: significantly increased in trial group - All cause mortality rate: significantly decreased in trial group
(16) Cherney, D.Z.I , 2020, Multicenter	RCT 53 cases 6 wks treatment and 6 wks washout period	- Adult with CKD without DM. - 18<age<75 - 500< 24-h urinary protein excretion≤ 3500 mg - eGFR> 25 mL/min/1·73m^2 - On stable dose of ACEi or ARB for at least 4 weeks before randomization	Randomly divided in two groups, and first treated with placebo and then with *Dapagliflozin* 10mg/day or vice versa	- GFR: significant decrease in the trial group compared to placebo - B.P.: no significant change in the trial group - Concentrations of neurohormonal biomarkers: no significant change in the trial group - Proteinuria: no significant change in the trial group - Hb and HCT: significantly increased in the trial group - FBS, potassium, calcium, and phosphate: no significant change in the trial group

Table 1. Continued

Study	Design/sample/ Duration	Inclusion criteria	Intervention	Outcome
(17) Wheeler DC, 2021, Multicenter	RCT 270 cases 2.1 years (median)	- 25<eGFR<75 mL/ min/1.73m^2 - 200<UACR≤5000 mg/g - Adults with CKD, with or without T2DM - Receiving ACEi or ARB for at least 4 wks before trial if not contraindicated	- Trial: *Dapagliflozin* 10mg/day (n=137) - Placebo: (n=133)	- Slope of change in GFR: lesser in the trial group - UACR: greater significant reduction in the trial group - BP: greater significant reduction in the trial group -Primary composite outcomes: significantly lesser in the trial group
(18) Rajasekeran H, 2017, Canada	RCT and animal study 10 cases 8 wks	- Biopsy-proven FSGS≥1mo - Cr based GFR≥45 mL/ min/1.73m^2 - Age>18yr without DM - BP≥100/60mmHg - Treatment with a RAAS inhibitor for>1 month - 30 mg/day<proteinuria<6 g/day	- Trial: *Dapagliflozin* 10mg/day (add-on to RAAS blockers)	- GFR: decreased (Not significant) - Proteinuria: decreased (Not significant) - SBP: increased (Not significant) - DBP: decreased (Not significant) - Body weight: decreased (Not significant) - Plasma renin or aldosterone: no significant change
(19) Zannad F, 2021, Multicenter	RCT 3730 cases 16 months	Class II, III, or IV HF (EF≤40%) (At baseline 53% had prevalent CKD defined by eGFR<60 mL/min/1.73m^2 or UACR>300 mg/g)	- Trial: *Empagliflozin* 10mg/day (n=879 in nonCKD and n=981 in CKD) - Placebo: (n=867 in nonCKD and n=997 in CKD) (In addition to HF therapy)	Slope of change in GFR: lesser in the trial group (Significant)
(20) Van der Beek AB, 2021, Multicenter	RCT 53 cases 6wks treatment and 6wks wash-out period	- Non-diabetic kidney disease: 500<24-hr urinary protein excretion ≤3500mg/d and eGFR≥25mL/ min/1.73m^2	Randomly assigned to placebo then *Dapagliflozin* 10mg once daily or *Dapagliflozin* 10 mg once daily then placebo (ARBs or ACEIs at least 4 wks before trial)	- UACR: greater significant reduction in trial group - mGFR: greater significant reduction in trial group - SBP: greater significant reduction in trial group - Body weight: greater significant reduction in trial group

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD, Chronic kidney disease; Cr, Creatinine; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESRD, end-stage kidney disease; FBS, fasting blood sugar; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; Hb, hemoglobin; HCT, hematocrit; HF, heart failure; mGFR, measured glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; SBP, Systolic blood pressure, T2DM, type 2 diabetes mellitus; UACR, urinary albumin: creatinine ratio

were six studies evaluating the change in GFR by SGLT2 inhibitors,[14,16-20] and four studies which measured the change in 24-hour urine protein or urine albumin to creatinine ratio (UACR), and assessed the impact of SGLT2 inhibitors on blood pressure.[16-18,20]

RESULTS

CKD patients with or without Diabetes mellitus (DM) received placebo or dapagliflozin in the DAPA-CKD trial. The study showed that dapagliflozin lowered the risk of primary composite outcome (a sustained GFR reduction of at least 50%, ESKD, and death from renal and cardiovascular causes) in all CKD participants [hazard ratio (HR) = 0.61, CI 95%: 0.51 to 0.72; $P < .001$]. In addition, GFR slopes in the dapagliflozin and placebo groups were (-2.9 ± 0.1) vs. (3.8 ± 0.1) mL/min/ 1.73m^2 /year, respectively, which reflects 0.93 mL/min/ 1.73m^2/ year difference between the two groups ($P < .050$). Whether the initial GFR improvement was reversible following discontinuation of dapagliflozin was not possible as GFR values, after the completion of the trial, were not recorded. Also, throughout the trial serious adverse events were more significant in the placebo than in the trial group ($P = .002$).[14]

A pre-specified analysis of the DAPA-CKD trial demonstrated that during the follow-up period, 247 patients died; 101 patients were treated with dapagliflozin, and 146 patients were placebo-treated (HR = 0.69, CI 95%: 0.53 to 0.88, $P = .003$). Overall, in T2DM cases, the mortality rate was 2.6

Table 2. The Results of Quality Assessment of Included Articles

Study	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Bias	Blinding (pts/ personnel)	Blinding (outcome assess)	Incomplete Outcome Data	Low	High	Unclear	Overall Score
Heerspink HJL, 2020	Low	Low	Low	Low	Low	Low	Low	7	0	0	Low
Heerspink, HJL, 2021	Low	Low	Low	Low	Low	Low	Low	7	0	0	Low
Cherney, DZI, 2020	Low	Low	Low	Low	Low	Low	Low	7	0	0	Low
Wheeler DC, 2021	Low	Low	Low	Unclear	Low	Low	Unclear	5	0	2	Moderate
Rajasekeran H, 2017	High	High	Low	High	High	High	Unclear	1	5	1	High
Zannad F, 2021	Low	Low	Low	Low	Low	Low	Low	7	0	0	Low
Van der Beek AB, 2021	Low	Low	Low	Low	Low	Low	Low	7	0	0	Low

events/100 patient-years in the dapagliflozin group and 3.5 events/100 patient-years in the placebo group (HR = 0.74, CI 95%: 0.56 to 0.98, $P < .05$). Additionally, the mortality rate of dapagliflozin and placebo among non-diabetic patients was 1.2 vs. 2.3 events/100 patient-years. (HR = 0.52, CI 95%: 0.29 to 0.93, $P < .05$) and interaction p-value for HR in people with diabetes vs. non-diabetes was 0.250. Indeed, the all-cause mortality rate in diabetic and non-diabetic cases was lower in the dapagliflozin compared with the placebo group ($P = .003$); therefore, dapagliflozin improved survival in CKD patients, regardless of diabetes mellitus status.[15]

In a cross-over trial, non-diabetic patients from Canada, Malaysia, and the Netherlands were enrolled. During six weeks of dapagliflozin treatment, the measured GFR decreased by 6.3mL/ min/ 1.73m^2 (95% CI: 4.6 to 8.0, $P < .050$) in dapagliflozin group vs. 0.3 mL/min/ 1.73m^2 (95% CI: -1.4 to 2.0, $P > .05$) in the placebo group; thus, dapagliflozin reduced mGFR by -6.6 mL/min/ 1.73m^2 (95% CI: -9.0 to -4.2, $P < ·0001$) compared to the placebo. Thereafter, in 6 weeks of washout period after discontinuation of dapagliflozin, the GFR decline fully recovered. However, there was no significant change in 24h proteinuria in the dapagliflozin compared to the placebo ($P = .93$). Furthermore, there was a significant reduction in body weight with dapagliflozin (1.5kg, 0.03 to 3.0, $P = .046$). In contrast, no significant change occurred in blood pressure and heart rate in the trial group compared to the placebo group ($P > .05$). During the treatment with dapagliflozin, three patients showed kidney-related adverse events (one acute kidney injury, one urinary tract infection, and one genital infection). [16]

In a study by Wheeler *et al.*, participants with IgA nephropathy were assigned to receive dapagliflozin or placebo. The annual change in GFR was less with dapagliflozin compared to the placebo (-2.2 ± 0.5 and -4.6 ± 0.47, respectively), with 2.4 mL/min/ 1.73m^2 /year difference between the two groups (95% CI: 1.08 to 3.71 mL/min/ 1.73m^2 /year). In addition, the GFR was not evaluated following treatment discontinuation; thus, the researchers were unable to report if GFR decline was reversible. The researchers also reported changes in UACR during the follow-up. At baseline, UACR was lower in the dapagliflozin group compared to the

placebo participants [Median (Q1 to Q3): 890.0 (558 to 1472) vs. 903.0 mg/g (501 to 1633)]; this difference continued over the course of 36 months of follow-up with the least mean difference of -26% (95% CI: -37.0 to -14.0%, $P < .001$). Additionally, it was reported that SGLT2 inhibitors reduced both systolic and diastolic blood pressure with a mean difference of 3.5mm Hg (95% CI: 5.7 to 1.3, $P = .002$) and 2.2 mmHg (95% CI: 3.7 to 0.8, $P = .003$) between systolic and diastolic blood pressures for dapagliflozin and placebo groups, respectively. Moreover, compared to placebo, dapagliflozin was associated with lower primary composite outcomes (sustained reduction in eGFR by ≥ 50%, occurrence of end-stage kidney disease and CVD or kidney-related deaths) (HR = 0.29, 95% CI: 0.12 to 0.73; $P = .005$).[17]

In another study by Rajasekeran *et al.*, FSGS-associated CKD patients received dapagliflozin to determine the changes in GFR as a primary outcome. GFR did not change significantly following eight weeks of treatment (93.9 ± 18.2 to 85.9 ± 16.9, $P = .220$), while in patients with GFR ≥ 90 mL/min/ 1.73m^2, a significant reduction in GFR was reported. Also, SGLT2 inhibitors did not significantly reduce 24-hour urine protein excretion ($P = .420$). However, in patients with 24-hour urine protein excretion of < 1.89 g/d at baseline, dapagliflozin therapy demonstrated a significant decline in proteinuria (-0.27 ± 0.21, $P = .042$). In addition, it was concluded that combined treatment of dapagliflozin and renin-angiotensin-aldosterone system (RAAS) blockers did not affect blood pressure significantly ($P = .430$). Furthermore, investigators reported that body weight, plasma renin, and aldosterone were not considerably influenced during the treatment ($P > .05$). Altogether, this trial showed no significant change in renal hemodynamics by SGLT2 inhibitors.[18]

In the EMPEROR-Reduced trial which investigated the impact of empagliflozin on heart failure, patients were classified into CKD or non-CKD, regardless of the diabetes mellitus status. Empagliflozin reduced hospitalization due to heart failure or cardiovascular death, irrespective of baseline kidney function (HR = 0.78, 95% CI: 0.65 to 0.93 in CKD; and HR = 0.72, 95% CI: 0.58 to 0.90 in non-CKD; $P = .630$). Also, a reduction in the GFR slope was reported in CKD and non-CKD groups treated with empagliflozin (1.11 vs. 2.41 mL/min/ 1.73m^2 /year, $P = .045$). Acute kidney injury occurred less frequently by SGLT2 inhibitors in patients with or without CKD (HR = 0.73, 95% CI: 0.47 to 1.15; and HR = 0.56, 95% CI: 0.28 to 1.11; respectively, $P = .530$).[19]

In another trial, non-diabetic CKD patients were enrolled to assess the pharmacokinetic profile of dapagliflozin. It was reported that every 100 ng h/ mL increase in dapagliflozin concentration led to a 0.5 mL/min/ 1.73m^2 decrease in GFR ($P < .010$), 2.8% decrease in UACR ($P = .010$), 0.4 mmHg reduction in systolic blood pressure ($P = .030$), and 0.1 kg decrease in body weight ($P = .070$); however, no change in proteinuria was observed ($P = .690$).[20]

DISCUSSION

By far, the above-mentioned studies showed that SGLT2 inhibitors have a significant role in the improvement of GFR, blood pressure, and proteinuria. Here, we reviewed the evidence about the renoprotection of SGLT2 inhibitors in non-diabetic CKD by mainly focusing on how SGLT2 inhibitors affect kidney function.

Effects of SGLT2 Inhibitors on GFR

The beneficial effect of SGLT2 inhibitors on reducing GFR in non-diabetic human models of CKD is well established from various trials. The reviewed articles reported significantly greater reduction[16,20] and fewer changes in the slope of[14,17,19] GFR in the patients who received SGLT2 inhibitors. As EMPEROR-Reduced trial indicated, both CKD and non-CKD patients benefited from the effect of Empagliflozin on preventing a decline in estimated GFR (eGFR).[19] However, Rajasekeran *et al.* reported that treatment with dapagliflozin did not significantly change eGFR in both human and rodent trials. According to this study, the beneficial effect of SGLT2 inhibitors on reducing GFR occurred only in patients with preserved kidney function. [18]

To the best of our knowledge, in the mentioned trials[14,16,17,18,19,20], GFR was not measured after treatment discontinuation. However, the DIAMOND trial demonstrated a reversible decrease in GFR in 6 weeks after washout period following discontinuation of dapagliflozin [(16)]. According to the tubular hypothesis, by increasing sodium reabsorption in the proximal tubule in hyperglycemic conditions, reduced

sodium delivery to the distal tubule is sensed by macula densa; after which, adenosine generation decreases in juxtaglomerular apparatus, that causes afferent arteriolar vasodilation. Therefore, an acute compensatory increase in GFR leads to hyperfiltration [21] which is considered a risk factor for the progression of kidney disease at the level of a single nephron.[22] SGLT2 inhibitors has been postulated to correct hyperfiltration by reversing this pathway.[18,21]

Effects of SGLT2 Inhibitors on Proteinuria

Some reviewed articles demonstrated a considerably greater reduction in UACR[17,20] following treatment with SGLT2 inhibitors; however, others reported no significant change in proteinuria.[16,18] Notably, the efficacy of SGLT2 inhibitors on reducing proteinuria was limited to patients with modest proteinuria.[18]

It has been established that proteinuria contributes to the progression of renal disease. Reducing proteinuria frequently improves kidney function, regardless of impairment in any of the glomerular wall layers.[23] Although the mechanism by which SGLT2 inhibition results in renal protection is not fully understood,[16] according to previously published trials, it might be mediated by a change in proteinuria in non-diabetic CKD caused by this new class of antihyperglycemic agents. It should be noticed that although the specific mechanism by which SGLT2 inhibitors reduce albuminuria is unknown, it is believed to occur independent of changes in GFR or blood pressure.[21]

Effects of SGLT2 Inhibitors on Blood Pressure

According to some previous studies, administration of SGLT2 inhibitors in non-diabetic CKD patients has improved[17,20] blood pressure, whereas other studies reported no significant improvement in this parameter.[16,18] In addition, no significant changes were noted in plasma renin or aldosterone by SGLT2 inhibitors.[18] Treatment with SGLT2 inhibitors leads to an early reduction in blood pressure by natriuresis and osmotic diuresis and an increase in urinary glucose excretion by inhibiting sodium-glucose cotransporter in the proximal tubule.[24] In obese individuals, dysfunctional adipose tissue contributes to the development of hypertension via overactivity in two hypertension-associated systems: RAAS and the sympathetic nervous system.[25] SGLT2 inhibition may regulate blood pressure by modulating this pathway through weight loss. By SGLT2 inhibition, the transient diuresis might activate RAAS as a compensatory mechanism, to increase sodium reuptake as a response to reduction in the extracellular volume;[26] however, the relationship between SGLT2 inhibition and RAAS activation remains unclear. Contradictory studies indicated no intrarenal RAAS activation by chronic use of SGLT2 inhibitors in T2DM.[27]

Mortality and Survival

In the DAPA-CKD trial, dapagliflozin significantly mitigated the risk of death from renal or cardiovascular causes in both diabetic and non-diabetic participants with CKD. Moreover, dapagliflozin increased survival in CKD patients, whether they have diabetes mellitus or not.[14,15] Comparing non-diabetic CKD patients with albuminuria from the REIN trial.[28] the Guangzhou trial.[29] and the DAPA-CKD trial[14] showed that a combination therapy of SGLT2 inhibitors and angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) had the most benefits on CKD patients by providing more years of event-free survival including doubling of serum creatinine, kidney failure or death.[30] To explore the long-term effects of dapagliflozin, a model analysis was performed on DAPA-CKD, which predicted that in a 10-year horizon, dapagliflozin reduces abrupt declines in kidney function, initiating kidney replacement therapy, rates of hospitalized heart failure, and all-cause mortality.[31]

Side Effects of SGLT2 Inhibitors

The treatment with SGLT2 inhibitors did not show hypoglycemia/ketoacidosis altered HbA1c/fasting plasma glucose in non-diabetic patients.[14,16] SGLT2 cotransporter in proximal tubules of the kidneys plays a significant role in glucose reabsorption, so SGLT2 inhibitors lead to glycosuria.[32] Different studies have indicated that glycosuria and diuresis result from treatment with SGLT2 inhibitors.[33,34] Inhibiting glucose reabsorption leads to osmotic diuresis and natriuresis. If adequate fluid is not replaced, SGLT2 inhibitors may cause dehydration and hypotension; volume depletion was reported slightly more significant in the dapagliflozin than in the placebo group in one of the studies.[14]

One of the most common side effects of SGLT2 inhibitors in diabetic patients is a genital mycotic infection which may be life-threatening and can influence the quality of life in older patients with comorbidities.[35] However, in most cases, the severity of infection is mild to moderate and responds to topical antifungals.[36] Only one trial reported a case of genital infection.[16] In addition, another study assumed that fracture events were more common in the dapagliflozin group, but amputations were slightly less frequent in this group compared to the placebo.[14]

However, several animal studies peruse the effect of this class of drugs on podocytes, RAAS, sympathetic nerve activity, and renal fibrosis in non-diabetic CKD models. More studies are required to clarify these effects of SGLT2 inhibitors on humans. In addition, longer follow-up periods are needed to determine the long-term impact of SGLT2 inhibitors on GFR, proteinuria, and BP following discontinuation of drugs.

CONCLUSION

SGLT2 inhibitors have beneficial effects on patients suffering from CKD, whether they have diabetes mellitus or not. These medications can provide kidney protection by improving GFR and survival, decreasing proteinuria or UACR, and reducing blood pressure. It seems that SGLT2 inhibitors might be considered as a new therapy for preserving kidney function in non-diabetic CKD.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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