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CKJ REVIEW

SGLT-2 inhibitors in nephrotic-range proteinuria: emerging clinical evidence

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ABSTRACT

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of novel oral anti-hyperglycemic agents which are increasingly used in clinical practice. SGLT-2 inhibitors improve glycemic control and cardiorenal outcomes, promote weight loss, and reduce blood pressure. Randomized controlled trials have demonstrated that SGLT-2 inhibitors reduce proteinuria and delay progression of kidney disease in patients with albuminuria. However, whether SGLT-2 inhibitors have similar benefits in patients with nephrotic-range proteinuria has not been well established. Evidence to date has been limited to case reports, case series and secondary analyses of randomized controlled trials. This is the first comprehensive review on the effectiveness of SGLT-2 inhibitors for the treatment of patients with nephrotic-range albuminuria or proteinuria. Overall findings support a likely beneficial role of SGLT-2 inhibitors in reducing proteinuria and delaying chronic kidney disease progression in patients with nephrotic-range proteinuria.

LAY SUMMARY

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors might be a promising agent in non-diabetic kidney patients with proteinuria. Lowering proteinuria may help to improve kidney disease patients' outcome by slowing kidney disease progression and decreasing the risk of new cardiovascular events.

Keywords: albuminuria, diabetic kidney disease, diabetic nephropathy, nephrotic-range proteinuria, SGLT-2 inhibitors

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INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are among the most prescribed oral antidiabetic agents globally [1, 2]. These agents have beneficial effects that extend beyond glycemic control and include weight loss, protection against major cardiovascular events, blood pressure reduction and delaying chronic kidney disease (CKD) progression [3]. While reduction in proteinuria and long-term nephroprotective effects have been established in patients with microalbuminuria [urinary albumin:creatinine ratio (UACR) 30–300 mg/g] and macroalbuminuria (>300 mg/g) [4, 5], the potential use of SGLT-2 inhibitors in patients with nephrotic-range proteinuria (NRP) was first described in a December 2017 case report of nephrotic syndrome secondary to type 2 diabetes mellitus (T2DM) successfully treated with tofogliflozin [6, 7].

Multiple hypotheses have been proposed regarding the mechanisms underlying the nephroprotective effects of SGLT-2 inhibitors including a reduction in renal hyperfiltration via tubuloglomerular feedback, reduced proximal tubule sodium reabsorption, decreased energy consumption by proximal tubular cells, protection of proximal tubular cells from glucotoxicity, enhanced erythropoiesis, improved mitochondrial function, reduced oxidative stress, and decreased autophagy, podocyte injury and renal inflammation (Fig. 1) [8–11]. Furthermore, in murine models, SGLT-2 expression was observed in podocytes and SGLT-2 inhibitors exhibit antiproteinuric effects, limiting podocyte dysfunction [12, 13]. From a clinical translation point of view, single cell transcriptomics have detected low-level expression of the *SLC5A2* gene encoding SGLT-2 in human podocytes both under control and diabetic conditions [14, 15].

Nephrotic syndrome is defined by the constellation of NRP, hypoalbuminemia, edema and hyperlipidemia. The proteinuria threshold that defines NRP varies between studies but typically refers to ≥3500 mg of proteinuria per day. Diabetic kidney disease is the leading cause of NRP, but minimal change disease and membranous nephropathy usually cause nephrotic syndrome while focal segmental glomerulosclerosis (FSGS) may cause NRP or nephrotic syndrome [16]. Nephrotic syndrome is associated with significant morbidity including infection and thromboembolic events [17], and carries with it a high risk of progression to end-stage kidney disease (ESKD). Therefore, there is interest in examining whether the benefits of SGLT-2 inhibitors on kidney outcomes may be extended to the high-risk population comprised of patients with NRP with or without nephrotic syndrome. In this review, we summarize and critically appraise current evidence on the use and effectiveness of SGLT-2 inhibitors in patients with NRP.

MATERIALS AND METHODS

A literature search of PubMed/Medline, Web of Science and Google Scholar was performed in February 2022 using the following keywords: 'proteinuria', 'albuminuria', 'nephrotic range proteinuria', 'massive proteinuria', 'nephrotic syndrome',

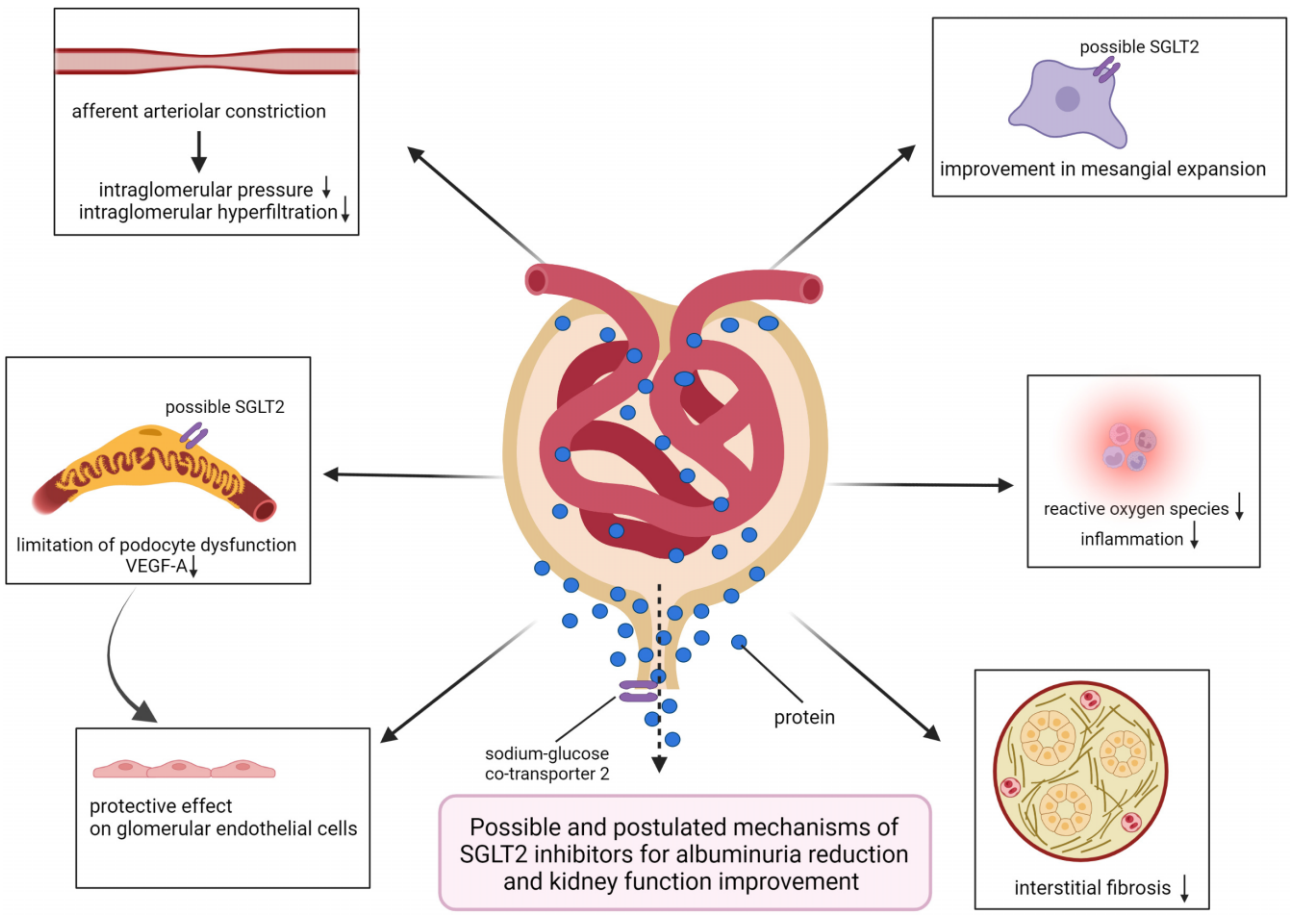

Figure 1: Postulated mechanisms for the beneficial effect of SGLT-2 inhibitors in patients with nephrotic-range proteinuria.

'UACR', 'urine albumin-creatinine ratio', 'UPCR', 'urine protein-creatinine ratio', 'sodium-glucose transporter 2 inhibitors', 'SGLT-2 inhibitors', 'gliflozin', 'canagliflozin', 'dapagliflozin', 'empagliflozin', 'ertugliflozin', 'ipragliflozin', 'luseogliflozin', 'remogliflozin', 'sergliflozin', 'sotagliflozin', 'tofogliflozin', 'diabetic nephropathy' and 'chronic kidney disease'. The title and abstract of each study were independently reviewed by each author to evaluate suitability for inclusion in this study. For completeness, reference lists of each study included were manually evaluated.

Inclusion criteria were studies evaluating the effects of SGLT-2 inhibitor therapy in patients with NRP published in a peer-reviewed journal in English. Studies not considered original investigations (i.e. systematic reviews, meta-analyses, editorials and commentaries) were excluded.

RESULTS

A total of nine clinical studies comprised of seven case reports/series and two secondary analyses from randomized controlled trials evaluating the use of SGLT-2 inhibitors in a total of 592 patients with NRP were included (Table 1) [6, 18–25]. Study protocols and patient characteristics were heterogeneous, making comparison between studies challenging. The underlying cause of kidney disease in patients included in this analysis was predominantly T2DM [6, 18, 20, 22, 24, 25], while three studies included patients with FSGS [19, 21, 23], three studies included patients with various of etiologies of nephrotic syndrome [6, 18, 19] and one study included pediatric patients with Alport syndrome and Dent disease [21]. Two studies included in this review were secondary analyses of randomized controlled trials in diabetic kidney disease [24, 25]. Significant difference in terms of estimated glomerular filtration rate (eGFR) of the participants, ranging between 30 and 105 mL/min/1.73 m², has been observed across individual studies. Methods for proteinuria quantification were heterogeneous and included 24-h urine collection, and urine albumin-creatinine ratio, and were reported in varying units including g/m², mg/g, mg/mmol, mg/dL or mg/L. The term 'nephrotic range proteinuria' was not uniformly used in all studies and the threshold for NRP varied between studies but generally was at least UACR ≥2200mg/g corresponding to≥3500 mg of proteinuria per day.

SGLT-2 inhibitors and proteinuria in patients with NRP

All studies reported varying reduction in proteinuria with SGLT-2 inhibitor treatment (Fig. 2). In the first case report in a patient with T2DM, a 76% reduction in proteinuria from 10.8 to 2.6 g/day over a 24-week follow-up period with tofogliflozin was observed [6]. Another case report also observed a 51% decrease in proteinuria from 7.8 to 3.8 g/day 4 weeks after initiating empagliflozin [20]. Imai *et al*. reported a 29% decrease in proteinuria from 7.0 to 5 g/day after 3 months [18]. Combination treatment with an SGLT-2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, and angiotensin receptor blocker reduced proteinuria by 55%, from 13.2 to 5.9 g/day over 15 weeks [22].

In a secondary analysis of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial which included 112 patients with T2DM at high cardiovascular risk, albuminuria outcomes were reported as sustained reduction by ≥30% or ≥50% from baseline and absolute reduction below 1000 mg/g (partial remission) or 500 mg/g (complete remission) [24]. In this study, NRP was defined by UACR ≥2200 mg/g and a complete remission of NRP to <500 mg/g occurred in one in six participants, while partial remission of NRP to <1000 mg/g UACR occurred in over 30% of patients and was more likely with empagliflozin compared with placebo [hazard ration (HR) 2.31; 95% confidence interval (CI) 0.98−5.42]. A sustained UACR reduction of ≥30% was more frequent in those with NRP compared to those without (*P*-value for interaction .03) occurring in 76.5% of patients with NRP on empagliflozin compared with 42.9% on placebo (HR 2.30; 95% CI 1.34–3.93). Moreover, a sustained ≥50% reduction in UACR occurred in 58.8% of those with NRP taking empagliflozin in comparison with 26.2% on placebo (HR 2.48; 95% CI 1.27−4.84), which was similar to patients without NRP [24].

A *post hoc* analysis of the CREDENCE trial evaluated 506 T2DM patients with NRP (UACR ≥3000 mg/g, which equates to a urine protein creatinine ratio of ≥5000 mg/g) treated with canagliflozin versus placebo. Three patient groups with different baselines of UACR (<1000, 1000–3000 and ≥3000 mg/g) were compared and the relative reduction in albuminuria was lower in patients with NRP (14% reduction in those with NRP versus 31% in patients with UACR <1000 mg/g and 29% in patients with UACR between 1000 and 3000 mg/g, *P*-heterogeneity = .03), whereas the absolute reduction was larger in patients with NRP (341 mg/g in those with NRP compared with 163 mg/g in patients with UACR <1000 mg/g, and 355 mg/g in patients with UACR between 1000 and 3000 mg/g) [25].

In another randomized double-blind placebo-controlled cross-over study conducted on 58 participants with non-diabetic CKD with measured GFR over 25 mL/min/1.73 m² and 24-h urinary protein excretion of 500 to 3500 mg, namely the DIAMOND trial, dapagliflozin treatment for 6 weeks had no statistically significant beneficial effect on proteinuria [26]. It is important to emphasize the consistent results of dapagliflozin treatment on proteinuria on subgroup analysis including sex, kidney diagnosis, baseline proteinuria level, systolic blood pressure and body mass index, while statistically significant difference has been observed in subgroup analysis depending on the baseline measured GFR value [26]. Dapagliflozin treatment leads to statistically significant decline in participants with baseline GFR over 60 mL/min/1.73 m^2 compared with the patients with measured GFR below 60 mL/min/1.73 m^2 [26]. Therefore, it is crucial to assess the effects of SGLT-2 inhibitors on proteinuria in accordance with the baseline measured GFR value of the patients in future studies since it appears to be independent variable.

In one case report of FSGS, UACR decreased 61% after 1 month (5100 to 2000 mg/L) and 37% after 9 months (984 to 618 mg/mmol) of empagliflozin therapy [19]. Similarly, dapagliflozin reduced proteinuria by 33% at 4 weeks and 23% at 12 weeks in nine children [21]. In two patients with FSGS, SGLT-2 inhibitors decreased UACR by 84% from 4900 to 805 mg/g at 11 months in patient 1, and there was an 18% reduction from 2719 to 2233 mg/g at 3 months in patient 4 [23].

SGLT-2 inhibitors and kidney function in patients with NRP

Studies reported an association between SGLT-2 inhibitors and various measures of kidney function (change in eGFR, sustained ≥40%–50% eGFR decline, a composite outcome of doubling of creatinine, kidney replacement therapy or renal death) (Table 2) [21, 24, 25].

In a single patient diagnosed with rapidly progressive diabetic kidney disease, treatment with an angiotensin receptor blocker, SGLT-2 inhibitor and GLP-1 receptor agonist proteinuria was reduced by 55% and eGFR increased by 4.3 mL/min/1.73 m^2 over 15 weeks, supporting a potential role for combination

Table 1: Characteristics of studies in patients with nephrotic-range proteinuria.

Author	Study design	Number of patients	Mean age (years)	Gender	Drug/dosage		Comorbidities	Bodyweight (kg)		Blood pressure (mmHg)	
					SGLT-2 inhibitors	Baseline medications		Baseline	Follow-up	Baseline	Follow-up
Imai *et al.* [18]	Case report	1	48	F	Dapagliflozin (5 mg/day)	Diuretic	Type 2 diabetes, HTN, hypercholesteremia	85–90	75	153/87	162/87
Tanaka *et al.* [6]	Case report	1	54	M	Tofogliflozin (20 mg/day)	DPP-4 inhibitors, RAAS blockade, statin, diuretic	T2DM, HTN, hypercholesteremia	92.2	80.4	150/94	130/84
Sjuls *et al.* [19]	Case report	1	28	M	Empagliflozin (10 mg/day)	RAAS blockade, diuretic, PCSK9 inhibitor, statin	FSGS, STEMI, hypercholesteremia	–	–	147/88	–
Liu *et al.* [21]	Case report	9	10.4	5M/4F	Dapagliflozin (10 mg/day $\geq$ 30 kg)	RAAS blockade	Alport disease ($n = 5$), Dent disease ($n = 1$), FSGS ($n = 1$)	34.9 (mean)	–	–	–
Li *et al.* [20]	Systematic review	1	67	M	Empagliflozin	RAAS blockade, diuretic	T2DM	–	–	–	–
Morino *et al.* [22]	Case report	1	30	F	Canagliflozin (50 mg/day)	RAAS blockade, GLP-1 analogue	T2DM	75.6	67.6	120/92	116/75
Boeckhaus *et al.* [23]	Case series	2	25	M	Empagliflozin or dapagliflozin (10 mg/day)	RAAS blockade, immunosuppressant	FSGS, IBD, HTN	–	–	–	–
			63	M	Empagliflozin or dapagliflozin (10 mg/day)	RAAS blockade	XLAS/FSGS, HTN, hearing loss	–	–	–	–
Ruggenenti *et al.* [24]	Randomized Control Trial	Empagliflozin 70	62.7	47M/23F	Empagliflozin (10 or 25 mg/day)	RAAS blockade ($n = 61$), Beta-blockers ($n = 48$), diuretics ($n = 39$), calcium channel blockers ($n = 32$), statins ($n = 57$)	T2DM ($n = 70$), coronary artery disease ($n = 46$), stroke ($n = 21$), peripheral artery disease ($n = 25$), heart failure ($n = 8$), diabetic nephropathy ($n = 42$)	–	–	146/79.2	–

Table 1: Continued

Author	Study design	Number of patients	Mean age (years)	Gender	Drug/dosage		Comorbidities	Bodyweight (kg)		Blood pressure (mmHg)	
					SGLT-2 inhibitors	Baseline medications		Baseline	Follow-up	Baseline	Follow-up
		Control 42	61	28M/14F	Placebo	RAAS blockade ($n = 30$), Beta-blockers ($n = 25$), diuretics ($n = 20$), calcium channel blockers ($n = 25$), statins ($n = 27$)	T2DM ($n = 40$) Coronary artery disease ($n = 32$) Stroke ($n = 14$) Peripheral artery disease ($n = 13$), heart failure ($n = 9$), diabetic kidney disease ($n = 25$)	–	–	148/81	–
Jardine *et al.* [25]	Randomized control trial	506[a]	60[a]	204 F[a]	Canagliflozin (100 mg/day) or placebo	Insulin ($n = 364$), sulfonylurea ($n = 114$), biguanide ($n = 247$), GLP-1 receptor agonist ($n = 19$), DPP-4 inhibitor ($n = 65$), statin ($n = 331$), antithrombotic agent ($n = 261$), RAAS blockade ($n = 505$), Beta-blocker ($n = 20$), diuretic ($n = 261$)[a]	T2DM ($n = 506$), heart failure ($n = 86$), cardiovascular disease ($n = 264$), retinopathy ($n = 261$), neuropathy ($n = 276$)[a]	–	–	143/80 (mean)[a]	–

F: female; M: male; HTN: hypertension; DPP-4 inhibitor: Dipeptidyl peptidase-4 inhibitor; RAAS blockade: renin-angiotensin-aldosterone system blockade; PCSK9 inhibitor: Proprotein convertase subtilisin/kexin type 9 inhibitor; STEMI: ST-elevation myocardial infarction; IBD: inflammatory bowel disease; XLAS: X-linked Alport syndrome.

[a]Mean number of canagliflozin-treated patients and control group.

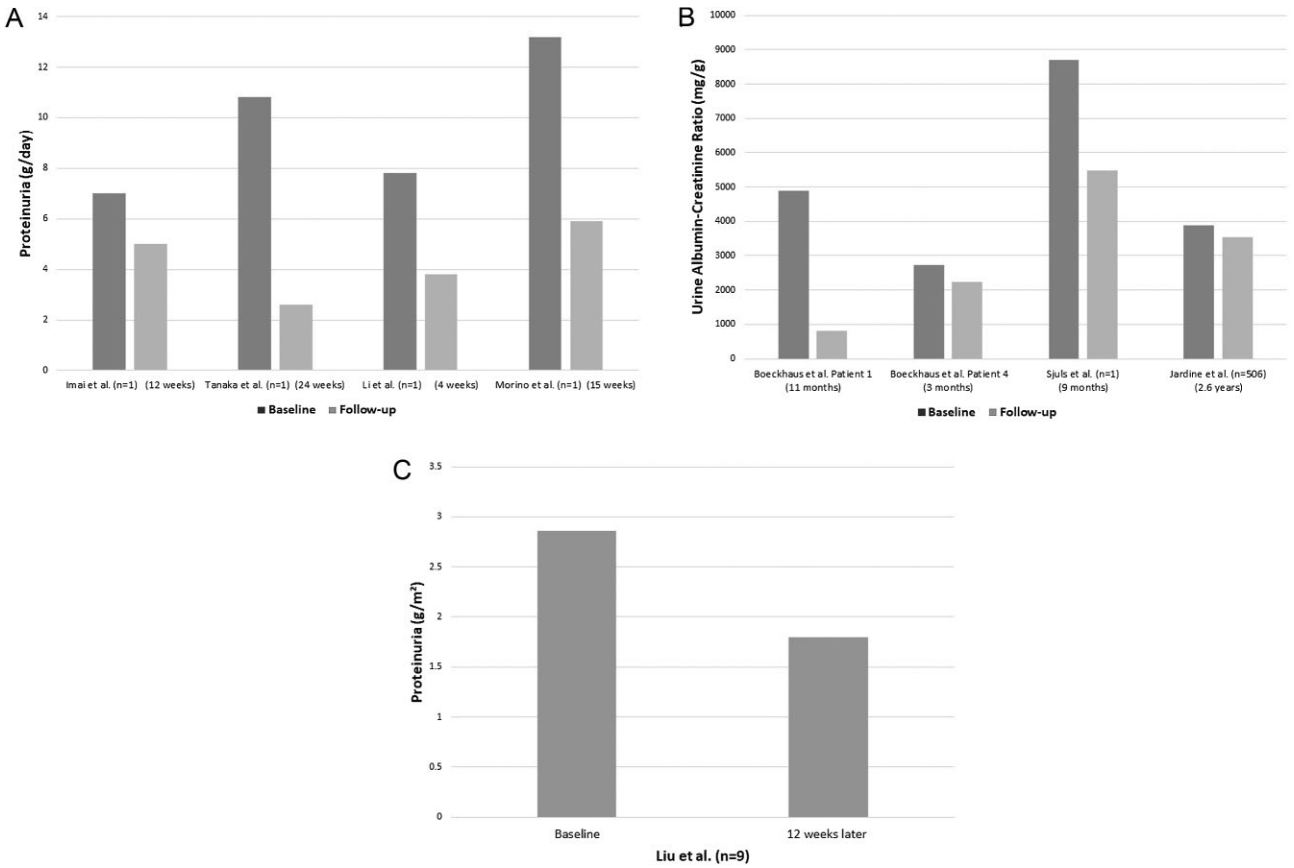

Figure 2: (**A**) Differences in proteinuria (g/day) between pretreatment and posttreatment. The follow-up period for each study is indicated in brackets [6, 18, 20, 22]. (**B**) Differences in UACR (mg/g) between pretreatment and posttreatment in two patients from Boeckhaus *et al.* and one patient from Sjuls et al. Additionally, data from subgroup analysis of the CREDENCE trial of canagliflozin in patients with T2DM are presented. The follow-up period for each patient is indicated in brackets [19, 23, 25]. (**C**) Difference between pretreatment and posttreatment in mean proteinuria (g/m²) of eight patients from Liu *et al.* [21]. The follow-up period is indicated in brackets.

therapy [14]. Another patient with FSGS treated with an SGLT-2 inhibitor experienced an increase in eGFR from 74 to 104 mL/min/1.73 m² at 11 months and a second patient with Alport syndrome and FSGS eGFR was 41 mL/min/1.73 m² at baseline and 39 mL/min/1.73 m² at 3 months. An acute dip in eGFR at 12 weeks compared with baseline was observed in nine children with FSGS, consistent with a hemodynamic effect seen in other studies [21].

The most robust evidence for the use of SGLT-2 inhibitors derives from secondary analyses of the EMPA-REG OUTCOME and CREDENCE randomized controlled trials. In the EMPA-REG OUTCOME trial, empagliflozin was associated with a 50% reduction in the composite kidney outcome of doubling of serum creatinine, kidney replacement therapy or renal death in patients with NRP, with no difference compared with those without NRP (*P*-value interaction .87). Patients with NRP were at high risk for worsening kidney function with the composite kidney outcome occurring in 20.6% treated with empagliflozin in comparison with only 1.4% in patients without NRP. Participants with NRP on empagliflozin treatment experienced an acute dip in eGFR similar to those without NRP [24]. Annual mean eGFR decline was attenuated to a greater extent in patients with NRP (–4.2 mL/min/1.73 m² on empagliflozin versus –10.2 mL/min/1.73 m² with placebo, corresponding to a between-group treatment difference of 6.0 (95% CI 2.9–9.1 mL/min/1.73 m²) compared with that in those without NPR (between-group treatment difference of 1.6 (95% CI 1.3–1.9) mL/min/1.73 m² per year: +0.3 mL/min/1.73 m² per year with empagliflozin versus –1.3 mL/min/1.73 m² per year in placebo; *P*-interaction = .005) [24]. The risk for sustained decline in eGFR ≥40% was reduced by 55% with empagliflozin in patients with NRP, which was not different from patients without NRP. In patients with NRP, extrapolating eGFR slopes increased the projected median time to ESKD from 5 to 10 years. The attenuation in annual mean eGFR slope was more pronounced in those with NRP compared with those without NRP (*P*-interaction = .005) [24]. Additionally, it is important to emphasize that approximately 80% of the participants are already on a medication that acts as renin-angiotensin-aldosterone system blocker.

A subgroup analysis of CREDENCE by albuminuria category investigated the effect of canagliflozin on eGFR slope in patients with T2DM. Higher UACR was associated with higher rates of kidney and cardiovascular events. However, the benefit was consistent across the range of albuminuria levels (<1000 mg/g, 1000–3000 mg/g, >3000 mg/g). Thus, canagliflozin reduced the primary composite outcome of ESKD, sustained doubling of serum creatinine and renal/cardiovascular death by 37% (HR 0.63; 95% CI 0.47–0.84) in those with NRP (*P*-heterogeneity = .55). Furthermore, canagliflozin reduced kidney-related adverse events, including acute kidney injury, in patients with NRP (HR 0.49; 95% CI 0.36–0.68; *P*-heterogeneity = .003). Canagliflozin decreased the annual eGFR decline in every albuminuria category. The annual eGFR decline differed by baseline UACR (*P*-heterogeneity = 0.04)

Table 2: Characteristics of case studies featuring identifiers of kidney function.

	Proteinuria				
Author	Baseline	Follow-up	GFR (mL/min/1.73 m²)	Plasma albumin (g/dL)	Follow up (months)
Imai et al. [18]	7.0 g/day	5.0 g/day	–	2.0	3
Tanaka et al. [6]	10.8 g/day	2.6 g/day	89.991	2.4	6
Sjuls et al. [19]	984 mg/mmol	618 mg/mmol	30	1.2	9
Liu et al. [21]	2.86 g/m² (mean)	1.795 g/m² (mean)	105 (mean)	3.5 ± 0.7 (mean)	3
Li et al. [20]	7.8 g/day	3.8 g/day	62	–	1
Morino et al. [22]	13.2 g/day	5.9 g/day	20	2.1	4
Boeckhaus et al. [23]	Patient 1 4.9 g/day	0.80 g/day	74	–	11
	Patient 4 2.72 g/day	2.23 g/day	41	–	3
Ruggenenti et al. [24]	Canagliflozin 3.53 g/g	–	60.3 ± 19.5 (mean)	3.84 ± 0.47 (mean)	28
	Control 3.68 g/g	–	63.6 ± 23.5 (mean)	3.75 ± 0.45 (mean)	23
Jardine et al. [25]	3.89 g/g[a]	3.55 g/g[a]	53[a]	–	31

[a]Mean number of canagliflozin-treated patients and control group.

in a nonlinear fashion. The largest annual decline in eGFR slope was observed in patients with UACR ≥3000 mg/g on placebo (8.92 mL/min/1.73 m²), and it was reduced by 28% with canagliflozin treatment [25]. Similar to the previous study, most of the patients were already on a medication that acts as renin-angiotensin-aldosterone system blocker.

DISCUSSION

The role of SGLT-2 inhibitors in patients with microalbuminuria and macroalbuminuria has been well-established. However, there is limited information on the outcomes of SGLT-2 inhibitors in patients with NRP. The studies included in this review suggest that SGLT-2 inhibitors may successfully reduce proteinuria and prevent CKD progression in patients with NRP, although outcome measures were variable across studies.

The impact of SGLT-2 inhibitors on proteinuria was variable. While 12 patients experienced complete resolution of proteinuria [23, 24], other patients continued to have NRP at follow-up [18–20, 22, 24]. Differences in proteinuria reduction may be attributable to heterogeneous underlying disease etiologies, proteinuria severity, variable follow-up duration and method of proteinuria quantification. Despite our findings suggesting reduction in proteinuria and preservation of kidney function in both diabetic and non-diabetic participants, most participants had underlying diabetic kidney disease. Therefore, future studies evaluating the effectiveness of SGLT-2 inhibitors in other etiologies of NRP are needed. Only 12 participants did not have diabetic kidney disease and these included patients with FSGS, Alport syndrome and Dent disease. Consistent with findings from randomized controlled trials, additional proteinuria reduction with SGLT-2 inhibitors was observed on a background of renin-angiotensin-aldosterone blockade [6, 19, 21, 22, 24]. The predominant SGLT-2 inhibitor prescribed was empagliflozin, although all agents demonstrated reduction in proteinuria. However, contradictory findings also exist in the literature [27]. When the effect of SGLT-2 inhibitors was explored across varying levels of proteinuria, patients with UACR >3000 mg/g demonstrated the highest absolute but lowest relative reduction in albuminuria [25]. Similarly, differences in terms of proteinuria as outcome may be attributable to the differences among studies in terms of the baseline eGFR values of the participants as shown by few clinical studies [20, 26]. A study that evaluated pediatric patients [21] provided evidence not available from randomized controlled trials as pediatric patients were excluded.

It should be noted that the DAPA-CKD trial was not included in the present analysis, although it included patients with a wide range of glomerular disease and 1484 of the participants had UACR >3000 mg/g consistent with NRP. In DAPA-CKD no heterogeneity was observed between patients with UACR ≤1000 or >1000 mg/g; however, secondary analyses have not been specifically performed in patients with NRP. However, a prespecified analysis in 104 biopsy-confirmed FSGS patients, a common cause of NRP, with a median UACR of 997 (interquartile range 736–2290 mg/g) did not observe a significant reduction in the rate of eGFR decline, although albuminuria reduction was observed and albuminuria reduction is associated with chronic eGFR slope.

Limitations to this study include the low total number of patients, varying study quality, variability in proteinuria measurement, different durations of follow-up, and low representation of diverse etiologies of nephrotic syndrome which limits generalizability beyond diabetic kidney disease. Additionally, the differences between the effects of SGLT-2 inhibitors on NRP may partially be attributable to the eGFR of the patients included in individual studies. Nevertheless, this is the first study to comprehensively review the role of SGLT-2 inhibitors in patients with NRP and supports a promising therapeutic role for these agents in this population, although larger dedicated studies for patients with NRP will be required in the future.

In conclusion, SGLT-2 inhibitors significantly decrease albuminuria and proteinuria. Thus, NRP patients might benefit from them in terms of kidney disease protection. However, clinical experience with SGLT-2 inhibitors in patients with NRP is scarce, as patients with NRP or with certain types of glomerulonephritis were excluded from some clinical trials, with kidney outcomes

and pre-specified subanalyses not always addressed this population. Despite these limitations, the present analysis supports that the kidney protective effect of SGLT-2 inhibitors extends to patients with NRP, at least for patients with diabetic kidney disease. A prospective study should be planned to evaluate the kidney and heart protective effect of SGLT-2 inhibitors in patients with NRP due to diabetes or glomerulonephritis.

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AUTHORS' CONTRIBUTIONS

Z.K., Ö.E.Ş., S.C., S.D. and M.K. contributed substantially to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work. A.O., K.Y., D.Z.I.C. and M.K. drafted the work or revised it critically for important intellectual content.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

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ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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