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The efficacy of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on renoprotection in lupus nephritis: a comprehensive review

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ABSTRACT

Lupus nephritis (LN) is a major organ condition in systemic lupus erythematosus (SLE) leading to end-stage kidney disease if not managed effectively. Two main therapeutic approaches that are successful in the management of LN include immunosuppression and non-immunosuppressive drugs, renin-angiotensin-aldosterone system inhibitors, and hydroxychloroquine (HCQ), which are supported by numerous clinical trials. Recent clinical trials with sodium-glucose cotransporter-2 inhibitors (SGLT2i) have consistently shown substantial evidence of reno-protection for those with IgA nephropathy and focal segmental glomerulosclerosis. However, emerging evidence shows the protective role of SGLT2i in renal outcomes for the management of LN. This review explores the underlying mechanisms by which SGLT2i contributes to nephroprotection, with promising evidence from both animal and human studies, and guideline recommendations regarding its utilization in LN.

Review

Implication for health policy/practice/research/medical education:
The new class of oral hypoglycemic drugs known as sodium-glucose cotransporter-2 inhibitors (SGLT2i) gained attention in modern therapies targeted at nephroprotection in patients with systemic lupus erythematosus (SLE) by increasing autophagy flux and reducing podocyte injury.

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Introduction

The complicated autoimmune illness known as systemic lupus erythematosus (SLE) releases autoantibodies and causes persistent inflammation that finally damages several organs with flare-ups and quiescence in their path.

Within five years post-diagnosis, approximately 30%-50% of individuals with SLE encounter varying degrees of organ impairment, and by the tenth year, this rises to 50% or more. Remarkably, patients with SLE commonly suffer from lupus nephritis (LN), with a 10% to 30% probability of advancing to end-stage renal disease (ESKD) within 15 years for those affected with severe LN (classified as III, IV, and V) (1). SLE patients with pre-existing traditional risk factors like dyslipidemia, smoking, and obesity, as well as non-traditional factors like proteinuria and inflammation, have high mortality rates. Among the main causes of death in persons with SLE are unambiguously infections and renal failure (2).

For individuals with LN, therapy success can be assessed using renal biopsies and other clinical indicators of damage, therefore conserving renal function and avoiding ESKD. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for LN management 2024 (3) and European Alliance of Associations for Rheumatology (EULAR) recommendations for SLE management 2023 recommendations (4) define treatment goals for SLE patients as control of disease activity and prevention of flares.

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Numerous effective and well-researched therapy alternatives are available, such as immunosuppressive and non-immunosuppressive drugs (5). One of the earliest clinically used disease-modifying anti-rheumatic medications is hydroxychloroquine (HCQ), which has immunomodulatory, anti-inflammatory, and anti-thrombotic effects. Cohort studies have demonstrated reduction in cardiovascular risk to improve long-term outcomes including damage accrual and mortality in SLE (2,6). Unless contraindicated, KDIGO 2024 LN clinical practice guideline for management advises treating patients with SLE, particularly those with LN, with HCQ or a comparable antimalarial medication (1C) (3).

The EULAR recommendations for the management of SLE: 2023 update (4) as well as KDIGO 2024 LN and CKD guidelines recommends renin-angiotensin-aldosterone system (RAAS) inhibitors (in non-pregnant patients) with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) in the management of LN for blood pressure control, CKD management (G1-G4) and any level of proteinuria (low-level as well as nephrotic range proteinuria; A2-A3) (1B) (7). RAAS-blockade in the treatment for LN is maximised when combined with a low-sodium diet at the highest tolerable dose (8). Recent data on RAAS inhibition from immunosuppression-based trials suggests that this nephroprotective drug is usually not optimised before initiating induction therapy (9).

Apart from immunosuppressive drugs, modern treatments aimed at nephroprotection in individuals with proteinuric chronic kidney disease have attracted increased interest. Among these, sodium-glucose cotransporter-2 inhibitors (SGLT2i) seem prospective.

The new class of oral hypoglycemic agents known as SGLT2i first gained attention in 2015 when the results of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study were released. This trial not only demonstrated cardiovascular safety but also showed notable renal benefits. These results have been validated over the last five years by a number of sizable randomized controlled trials, which has transformed the status of SGLT2i from another class of oral hypoglycemic agents to a paradigm-shifting class of medications with benefits to the kidneys and cardiovascular systems that go well beyond their effects on glycemic control (10). The dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial's prespecified analysis revealed that dapagliflozin therapy reduced the risk of CKD progression by 26% in patients with IgA nephropathy (11). In a case series, patients with hereditary focal segmental glomerulosclerosis showed a significant reduction in albuminuria with the use of SGLT2i (12,13). Recent animal and human studies indicate that in individuals with chronic and stable LN receiving immunosuppressive treatment and exhibiting residual proteinuria, SGLT2i may have encouraging nephroprotective effects. In this context, our comprehensive review provides an in-depth mechanism by which SGLT2i protects renal function in LN with corroborative evidence.

Nephroprotection and SGLT2i

The proximal convoluted tubule (PCT) contains a collection of glucose transporters called SGLT, which are important in the movement of glucose and sodium to the cells through the tubular lumen. There are two categories; SGLT1 (found in the distal PCT) and SGLT2 (found in the initial PCT), which together are responsible for 97% of absorption of glucose. Glycosuria and a decrease in blood glucose are caused by inhibition of SGLT2 receptors which is the physiological mechanism for SGLT2 inhibitors' ability to reduce glucose levels (14,15). SGLT2i have nephroprotective effects due to a number of pleiotropic effects in addition to enhanced glucose management which include:

- By inhibiting sodium reabsorption in the proximal tubule and enhancing sodium supply to the macula densa, SGLT2i restores tubuloglomerular feedback. This results in constriction of the afferent arterioles and a reduction in glomerular hypertension. Clinically, this is shown as a typical eGFR dip, or an abrupt, transient decrease in eGFR (estimated glomerular filtration rate) of 3-5 mL/min that becomes better by week twelve of treatment. It has been noted that using SGLT2i over time reduces the rate of eGFR fall, regardless of the occurrence or degree of the eGFR dip (16,17).
- Inhibiting SGLT2 causes sodium reabsorption to move downstream to the distal portions of the nephrons, simulating systemic hypoxia and triggering the production of factors that induce hypoxia and other protective genes. An improvement in the systemic and renal oxygen supply may follow from an increase in erythropoietin production. The fact that SGLT2i therapy has been associated with a reduced incidence of anemia along with less requirement for erythropoiesis-stimulating drugs provides clinical support for this. A lower risk of AKI has also been proposed as a possible outcome of the SGLT2 inhibition-induced decrease in proximal tubule energy consumption (18–20).
- Blood pressure is lowered by around 3-4 mm Hg for systolic and diastolic pressure by 1-2 mm Hg, respectively, by SGLT2i. The primary mechanism proposed for this impact is a reduction in plasma volume, mostly as a result of natriuresis and osmotic diuresis. However, there is not a counter-regulating rise in sympathetic tone to go along with this. Data points to the possibility of a drop in sympathetic tone through an indirect mechanism (21,22).
- SGLT2i can produce a negative energy balance and a 2-3 kg weight loss by encouraging glucosuria.

Additionally, there is a change in the utilization of free fatty acids rather than glucose, which lowers the amounts of lipid metabolites inside cells (23,24).

RAAS inhibitors and SGLT2i together provide a renoprotective approach. Reduced intra-glomerular pressure and hyperfiltration result from the actions of SGLT2i on the afferent arteriole and RAASi on the efferent arteriole, which may be additive when combined. The distal nephron may see an increase in salt load due to SGLT2i-induced natriuresis, which could encourage kaliuresis and counteract the hyperkalemia brought on by RAAS inhibitors, allowing for the continuing use of the medication.

SGLT2i for non-diabetic kidney disease

Post-hoc analysis of Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDence) and other trials revealed that SGLT2i helped to prevent poor renal outcomes independent of HbA1c levels as the baselines. Moreover, even if the glycosuric action of SGLT2i and therefore its antidiabetic effect reduces when renal function decreases, the benefits of SGLT on renal outcomes remained clear at lower levels of eGFR. These findings made research on the administration of SGLT2i in non-diabetic kidney disease possible and underlined that the renal benefits of SGLT2i are not only related to better diabetes control. The first encouraging results in this regard came from two heart failure trials: Dapagliflozin in patients with heart failure and reduced ejection fraction (DAPA-HF) and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) (25,26).

The most exciting results were from the first SGLT2i safety and efficacy trial on renal end-points in diabetic or non-diabetic CKD, Dapagliflozin, and Prevention of Adverse Consequences in CKD (DAPA-CKD). This experiment assigned patients (n=4304), one-third of which had non-diabetic kidney disease, either 10 mg of dapagliflozin or a placebo. Trial efficacy justified early termination. Dapagliflozin lowered the risk of >50% eGFR decline, ESKD, or renal or cardiovascular disease mortality by 39% over a median follow-up of 2.4 years. The benefit remained steady regardless of diabetes, eGFR, CKD stage, or proteinuria. (27,28).

The most recent randomized, controlled, phase III trial, the Empagliflozin in Patients with CKD (EMPA-KIDNEY) trial (2023), included patients(n-6609) with eGFR 20-45 mL/min/1.73 m^2 or 45-90 mL/min/1.73 m^2 with urine albumin-creatinine ration of 200 mg/g or higher in CKD with or without diabetes. The kidney disease progression was found to be significantly lower in the empagliflozin group, which also had lower hospitalization rates. This suggests that empagliflozin decreased the risk of renal disease progression in a wide spectrum of individuals with chronic kidney disease who were at risk of it progressing, including those with non-diabetic glomerular disorders (29).

SGLT2i and renoprotection in LN in animal studies

Over the past few years, researchers and clinicians building upon preliminary clinical findings in LN patients (30) have demonstrated the renoprotective effects of SGLT2i, which include a reduction in proteinuria and the preservation of renal function (2).

A few animal studies have provided substantial evidence supporting the renoprotective mechanism of SGLT2i (Figure 1). In LN, Podocyte damage and protein in the urine, sometimes known as proteinuria, might result from

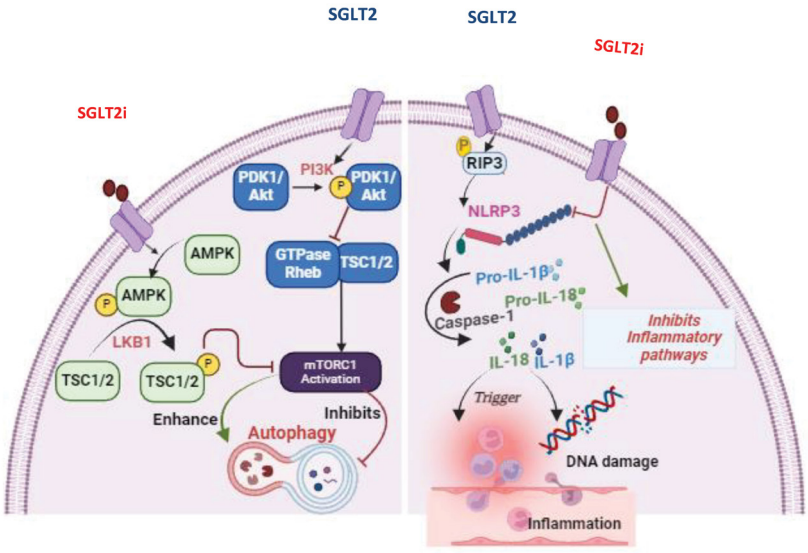

Figure 1. SGLT2i and podocyte protection. SGLT2i: Sodium-glucose cotransporter-2 inhibitors; mTORC1: mechanistic target of rapamycin complex 1; PDK1: Phosphoinositide dependent protein kinase 1; P13K: Phosphoinositide 3-kinase; AMPK: AMP-activated protein kinase; LKB1: liver kinase B1; TSC: Tuberous sclerosis complex; NLRP3: Nucleotide-binding oligomerization domain-like receptor protein 3; RIP3: Receptor-interacting kinase 3.

the activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NRRP3) inflammasome and the decrease of autophagy. SGLT2i have demonstrated the ability to regulate NLRP3 inflammasome activity in conditions such as diabetes, cardiovascular disease, and kidney disease. Clinical trials particularly on empagliflozin have been proven to diminish NLRP3 inflammasome activity and thereby protect podocytes (31,32). Similarly, studies have also shown that SGLT2i maintains cellular homeostasis by enhancing autophagic flux through activity through direct interactions with a mechanistic target of rapamycin complex 1 (mTORC1) and sirtuin1 (33,34). SGLT2i lowers intracellular glucose, which inhibits mTORC1 signaling. This effect occurs through inhibiting glucose transporter 1 (GLUT1) and GLUT4 (35,36). To better understand the effect of SGLT2 on autophagy, Xin Yu et al used MAP1LC3B KO monoclonal podocyte cell lines and an MRL/lpr mouse model and showed that empagliflozin inhibited SGLT2's effect and increased autophagy, thereby decreased podocyte injury (2). However, the mechanism by which SGLT2i acts on autophagy and podocyte injury in LN is not well understood (37), and warrants further studies.

Furthermore, Xin Yu et al in their preclinical study showed that nephritic MRL/lpr mice had higher levels of SGLT2 expression, which colocalized with lower levels of synaptopodin. In MRL/lpr mice, there was a substantial increase in synaptopodin expression following SGLT2 inhibition with empagliflozin. Subsequent in vitro research showed that SGLT2 overexpression induced podocyte damage, which was reversible in the presence of empagliflozin (2). The systemic immunomodulatory effect of SGLT2i have also been revealed Xin Yu et al study, with a significant decrease in dsDNA IgG and total IgG titers, as well as a decrease in electron-dense deposits verified by electron microscopy. This can lessen renal impairment in LN by lowering dsDNA IgG and immune complex deposition in renal tissues (2). Further research is required to ascertain the pattern of SGLT2 expression across immune cells and the impact of SGLT2 inhibitors on systemic immunity regulation as contributing to renoprotection. Additionally, SGLT2i ameliorated the defective nephrin expression in proteinuric mice, limited podocyte depletion, and limited albumin-induced α-actinin-4 remodeling and effectively limited the podocytes from losing β1-integrin (31).

Clinical administration of SGLT2i for treating patients with inherited podocytopathies is gaining attention, and positive safety and efficacy outcomes have been noted (12). Proteinuria is linked to an increased risk of ESKD and is primarily caused by podocyte injury. Notably, podocyte injury was pathogenetically caused by abnormally expressed SGLT2, and podocyte protection in LN was mediated by SGLT2i. Furthermore, by reducing inflammation, SGLT2i empagliflozin may be able to lessen podocyte damage (38).

SGLT2i and renoprotection in LN - Human studies

Transcriptome data from micro-dissected tubulointerstitial and glomerular compartments from healthy controls and patients with diabetic nephropathy, IgAN, renal vasculitis, and LN were analyzed for SGLT-2 expression and were mainly found in the tubulointerstitial area rather than the glomerular region in LN patients. Furthermore, loss of tubulointerstitial SGLT-2 expression was associated with decreased kidney function, particularly in renal vasculitis and LN. Therefore, nephroprotection by SGLT-2i may prove beneficial, especially after kidney function has stabilized and the initial phases of remission induction in LN have been reached (39). By lowering glomerular hyperfiltration and subsequently albuminuria, tubular damage, loss of kidney function, and incidence of acute renal injury, SGLT-2i has nephroprotective effects. These results imply that SGLT-2i is a potential therapeutic option for SLE patients as well, particularly with cardiac and renal involvement (40).

Among Chinese population, Wang and colleagues conducted an investigator-initiated, single-arm, open-label phase 2/3 trial of dapagliflozin involving 38 patients with SLE with or without LN. This study administered oral dapagliflozin at a daily dosage of 10 mg, alongside standard care over 6 months. The primary outcome was on evaluating the safety profile of the treatment and the secondary endpoints were composite assessments of disease activity. Patients with LN with a baseline eGFR <90 mL/min/1.73 m^2 showed improved eGFR slope, while the total eGFR remained stable. A total of 10.5% of adverse events were linked to dapagliflozin with a single case of fungal pneumonia and a significant lupus flare being the two documented serious adverse events (41).

Morales et al studied the impact of SGLT2i in LN patients receiving immunosuppressive therapy for a prolonged period along with persistent proteinuria. Empagliflozin (10 mg/d) was administered to five immunosuppressive therapy-treated patients with histologically confirmed LN and mean proteinuria of 2.2 g/d. The patients' proteinuria drastically decreased (to 49.9%) within 8 weeks of beginning medication, whereas their eGFR barely changed. These show the nephroprotective and antiproteinuric effects of SGLT2i (30).

Further, Xin Yu et al retrospectively analyzed nine patients with SLE who received more than two months of SGLT2i and had renal biopsy-proven LN to evaluate therapy responsiveness. Among them, proteinuria significantly decreased with the usage of SGLT2i, from 29.6% to 96.3% and the eGFR remained comparatively stable during the use of SGLT2i (2).

Additionally, there is one ongoing trial by Dr. Desmond Yat-Hin Yap from the University of Hong Kong wherein they are analysing the effect of SGLT2i (Dapagliflozin) on renal outcomes in LN patients with CKD, as well as the side effects, metabolic profiles, immunological functions and disease stability in 150 patients with a primary

Table 1. Human studies

Study	SGLT2 inhibitor	Study Type	Outcome measured	Results	Conclusion
Wang et al (41)	Dapagliflozin	Single-arm Phase I/II trial	Primary outcome: As per the onset of adverse events, outcomes are based on tolerability and safety. Composite lupus activity assessment using prednisone dose, proteinuria, and flare frequency.	Treated kidneys maintained eGFR for six months. Interestingly, patients with low renal function (eGFR <90 mL/min/1.73 m^2) showed improvement.	LN patients with damaged kidneys may benefit from SGLT2i
Morales et al (30)	Empagliflozin 10 mg/d	Pilot study	Investigate SGLT2i potential to reduce proteinuria and provide renal protection in LN	The treatment significantly reduced proteinuria by 49.9% within 8 weeks of initiation.	Improved renal outcomes in SLE
Xin Yu et al (2)	Dapagliflozin 10 mg, Canagliflozin 100 mg, Ertugliflozin 5 mg	Retrospective study	Patients with SLE with renal biopsy-proven LN treated with more than two months of SGLT2 inhibitors were retrospectively evaluated to evaluate therapy response.	Proteinuria dropped significantly from 29.6% to 96.3% in those on SGLT2 inhibitors. Moreover, the eGFR stayed somewhat constant during the course of SGLT2 inhibitor treatment.	Improved renal outcomes in LN
Desmond et al (42)	Dapagliflozin 10 mg	Phase 2	Primary outcome: incidence of 30% or greater eGFR drop at 24 months Secondary outcomes: ESKD incidence, eGFR, and UPC ratio changes over 24 months	Ongoing	

SGLT2i: Sodium-glucose cotransporter-2 inhibitor; ESKD: End-stage renal disease; LN: Lupus nephritis; eGFR: estimated glomerular filtration rate; UPC, urine protein creatinine.

completion by the year 2026 (42) (Table 1).

Guidelines on the administration of SGLT 2i

EULAR recommendations for the management of SLE; 2023 update

In recent years, there has been a notable focus on the development of SGLT-2i as a potential reno-protective drug in various forms of CKD. LN biopsies have shown elevated levels of SGLT-2, which has prompted interest in targeting this pathway. Hence, they suggest that patients with LN, particularly those with a reduced GFR below 60-90 mL/min/1.73 m^2 or exhibiting proteinuria greater than 0.5–1 g/day, might derive benefit from SGLT2i during the maintenance phase of their treatment regimen, in conjunction with ACEi or ARBs (38,47)

KDIGO 2024 clinical practice guideline for the management of LN and CKD

- Renoprotective medications, such as RAAS blockade, SGLT2 inhibitor, etc, in stable patients without AKI are suggested in LN patients (1A).
- Adults with eGFR ≥20 mL/min/1.73 m^2 with urine ACR ≥200 mg/g (≥20 mg/mmol), or heart failure, irrespective of level of albuminuria (1A).
- Adults with eGFR 20 to 45 mL/min/1.73 m^2 with urine ACR <200 mg/g (<20 mg/mmol) (2B).

Study Highlights

What is the current knowledge?

• The role of SGLT2i is well known in diabetic kidney disease whereas its role in other glomerular diseases is limited and the evidence is anecdotal.

What is new here?

• This review article summarizes the nephroprotection provided by SGLT2i by its mechanism of action in LN and we review the recent evidence-based animal as well as human studies as well as the guidelines on the role of SGLT2i in LN.

Conclusion

Lupus nephritis is a serious complication of SLE that can lead to ESKD. The potential clinical advantages of SGLT2i, substantiated by experimental studies and clinical trials are promising in reducing glomerular lesions, tubular damage and subsequent proteinuria in lupus patients. SGLT2i exerts its influence by regulating NLRP3 inflammasome and increased autophagy. Considering its excellent safety profile and substantial nephroprotective potential, SGLT-2 inhibition, as a straightforward and cost-effective therapeutic approach, may ultimately contribute not only to organ protection but also to enhancing the health and lifespan of affected individuals by reducing their overall cardiovascular risk. However, for clinical integration, large multicentre controlled trials are still needed.

Authors' contribution

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Validation: All authors.
Writing–original draft: All authors.
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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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