

EVALUATING THE EFFICACY AND SAFETY OF SGLT2 INHIBITORS IN PATIENTS WITH IGA NEPHROPATHY: A SYSTEMATIC REVIEW

MOAMEN ABDELFADIL ISMAIL¹, OHOUD IBRAHIM QADI²,
RAGHAD OSAMA ALSAEDI³, MURAD MOHAMMED
ALGHAMDI⁴, FAISAL MUDWIKH BIN ALAWI ALOTAIBI⁵,
MARYAM SAAD ALMUTAIRI⁶, FATIMAH MOHAMMAD
ALODAH⁷, RANEEM TURKI ALNOMARI⁸, SUMAIH SAEED
SALEH ALSAEED⁹, FATEN ALI HEFDHALLAH HAKAMI¹⁰,
SALMA ALYAQOUB¹¹, ABDULLAH NAWAF ALHARBI¹²,
FAISAL SAAD LAJHER¹³

¹INTERNAL MEDICINE CONSULTANT, KING ABDULAZIZ SPECIALIST HOSPITAL - SAKAKA –
ALJOUF

²PHARMD, KING ABDULAZIZ UNIVERSITY COLLEGE OF PHARMACY, PHARMACIST AT NATIONAL
GUARD HEALTH AFFAIRS HOSPITAL

³PHARMD, KING ABDULAZIZ UNIVERSITY COLLEGE OF PHARMACY, PHARMACIST AT NATIONAL
GUARD HEALTH AFFAIRS HOSPITAL.

⁴DOCTOR OF PHARMACY, UNIVERSITY OF HAFR AL-BATIN
⁵PHARMACY

⁶DOCTOR OF PHARMACY, UNIVERSITY OF HAFAR AL-BATIN

⁷PHARMD, COLLEGE OF PHARMACY, KING SAUD UNIVERSITY, RIYADH, SAUDI ARABIA

⁸PHARMD, COLLEGE OF PHARMACY, TAIF UNIVERSITY, TAIF, SAUDI ARABIA, PHARMACIST AT
NAHDI MEDICAL COMPANY

⁹COLLEGE OF PHARMACY, QASSIM UNIVERSITY, QASSIM, SAUDI ARABIA

¹⁰PHARMD, FACULTY OF PHARMACY, JAZAN UNIVERSITY, JAZAN, SAUDI ARABIA

¹¹PHARMACY

¹²PHARMACY

¹³SPECIALTY: PHARMD, COLLEGE OF PHARMACY, KING KHALID UNIVERSITY, ABHA, SAUDI
ARABIA.

Abstract

Background: IgA nephropathy (IgAN) remains the most common primary glomerulonephritis worldwide, with limited disease-specific therapies. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have emerged as potential renoprotective agents in CKD, but their role in IgAN is less well established.

Objective: To systematically review the efficacy and safety of SGLT2i in adult patients with IgAN, synthesizing evidence from clinical trials, observational studies, mechanistic analyses, and case reports.

Methods: A systematic search of PubMed, Scopus, Web of Science, Embase, and Google Scholar was conducted through August 15, 2025, following PRISMA 2020 guidelines. Eligible studies included adults with biopsy- or clinically confirmed IgAN receiving any SGLT2i. Data extraction included study design, patient characteristics, intervention details, renal and safety outcomes, and risk of bias assessment using Newcastle–Ottawa Scale and Cochrane RoB 2.

Results: Twenty-three studies met inclusion criteria, including randomized controlled trials, retrospective cohorts, prospective observational studies, mechanistic analyses, and case reports. Across designs, SGLT2i consistently reduced proteinuria (mean reduction up to ~40%) and attenuated eGFR decline. Benefits were observed in monotherapy and in combination with other agents such as sparsentan. Safety profiles were acceptable, with transient eGFR dip, mild genitourinary infections, and volume depletion as the most common adverse events. Mechanistic studies and Mendelian randomization analyses support hemodynamic, anti-inflammatory, and podocyte-protective effects.

Conclusions: SGLT2i offer clinically meaningful renoprotection in IgAN, with a favorable safety profile and plausible mechanistic basis. Although IgAN-specific randomized trials remain limited, current evidence supports their proactive integration

into individualized treatment plans, with further research needed to define optimal timing, combinations, and patient selection.

Keywords: IgA nephropathy; SGLT2 inhibitors; proteinuria; chronic kidney disease; eGFR decline; renal outcomes; dapagliflozin; empagliflozin; glomerulonephritis; nephrology therapeutics.

INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a leading cause of chronic kidney disease (CKD) and kidney failure in younger adults. Its pathogenesis is characterized by galactose-deficient IgA1 deposition in the glomerular mesangium, leading to mesangial proliferation, inflammation, and fibrosis (Stamellou et al., 2023). The clinical course of IgAN is heterogeneous: some patients maintain stable kidney function for decades, whereas others experience progressive decline culminating in end-stage kidney disease (ESKD). Despite advances in understanding its immunopathology, IgAN remains a major cause of ESKD globally, accounting for up to 40% of primary glomerular disease cases in Asia (Petrou et al., 2023).

Current treatment of IgAN traditionally relies on optimizing supportive measures, including blood pressure control, proteinuria reduction, and renin–angiotensin system (RAS) blockade, with immunosuppression reserved for high-risk or rapidly progressive disease (Floege et al., 2021). However, long-term outcomes remain suboptimal, and many patients continue to experience proteinuria and eGFR decline despite maximal supportive therapy (Caster & Lafayette, 2024). This therapeutic gap has driven interest in novel agents targeting non-immunologic pathways, including hemodynamic, metabolic, and fibrotic mechanisms of kidney injury.

In recent years, sodium–glucose cotransporter 2 inhibitors (SGLT2i) have emerged as a transformative class of drugs in diabetic nephropathy, with expanding evidence of benefits in non-diabetic CKD populations (Kawanami et al., 2017). Initially developed as glucose-lowering agents, SGLT2i confer renoprotective effects independent of glycemic control through mechanisms such as reduced intraglomerular pressure, improved tubuloglomerular feedback, and attenuation of renal inflammation and fibrosis (El Karoui et al., 2024). These properties make SGLT2i attractive candidates for IgAN management, where proteinuria and progressive nephron loss remain central to disease progression.

Large randomized controlled trials in CKD, such as DAPA-CKD and EMPA-KIDNEY, have demonstrated that SGLT2i reduce the risk of kidney failure, sustained eGFR decline, and renal death across diverse etiologies, including IgAN (Podestà et al., 2023). Although IgAN-specific subgroup analyses were not the primary focus of these trials, the consistent benefits observed in non-diabetic CKD suggest potential utility in this population. The translation of these findings into IgAN-specific contexts requires careful evaluation of both efficacy and safety outcomes.

Emerging evidence from smaller interventional studies and observational cohorts suggests that SGLT2i may significantly reduce proteinuria in IgAN patients already on optimal RAS blockade (Trillini et al., 2025). These effects appear early—within weeks to months of initiation—and may be additive when combined with other agents such as endothelin receptor antagonists or targeted-release budesonide. The magnitude of proteinuria reduction, a key surrogate for long-term renal survival, positions SGLT2i as a promising adjunctive therapy in IgAN management (Cherney et al., 2020).

Safety remains a crucial consideration in IgAN patients, especially those with advanced CKD or concurrent comorbidities. SGLT2i have been associated with a transient, reversible dip in eGFR upon initiation, which is thought to reflect hemodynamic adjustments rather than nephrotoxicity (Shibata et al., 2023). The risk of urinary tract infections or volume depletion appears modest and manageable with appropriate patient selection and monitoring (Iordan et al., 2024). These safety profiles are particularly relevant in IgAN, where kidney reserve is often compromised.

Beyond direct renal outcomes, SGLT2i may exert beneficial systemic effects relevant to IgAN pathophysiology. By reducing sodium reabsorption and plasma volume, they can mitigate hypertension and proteinuria, while also improving metabolic parameters. Additionally, preclinical data suggest potential modulation of inflammatory pathways and oxidative stress, which could theoretically attenuate immune-mediated injury in IgAN (Petrou et al., 2023). These pleiotropic effects underscore the need for dedicated IgAN trials to confirm mechanistic and clinical benefits.

Given the growing body of supportive evidence and the unmet need in IgAN treatment, a systematic synthesis of available data is warranted. This review aims to evaluate the efficacy and safety of SGLT2 inhibitors in patients with IgA nephropathy, integrating evidence from randomized trials, observational studies, mechanistic research, and real-world data. By contextualizing IgAN-specific findings within the broader CKD literature, we seek to inform clinical decision-making and identify gaps for future research.

METHODOLOGY

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparent, reproducible, and comprehensive reporting. The primary objective was to synthesize current empirical evidence evaluating the efficacy and safety of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in patients with IgA nephropathy (IgAN). The review considered human studies that provided quantitative or qualitative data on renal outcomes, proteinuria reduction, and adverse events associated with SGLT2i therapy in this patient population.

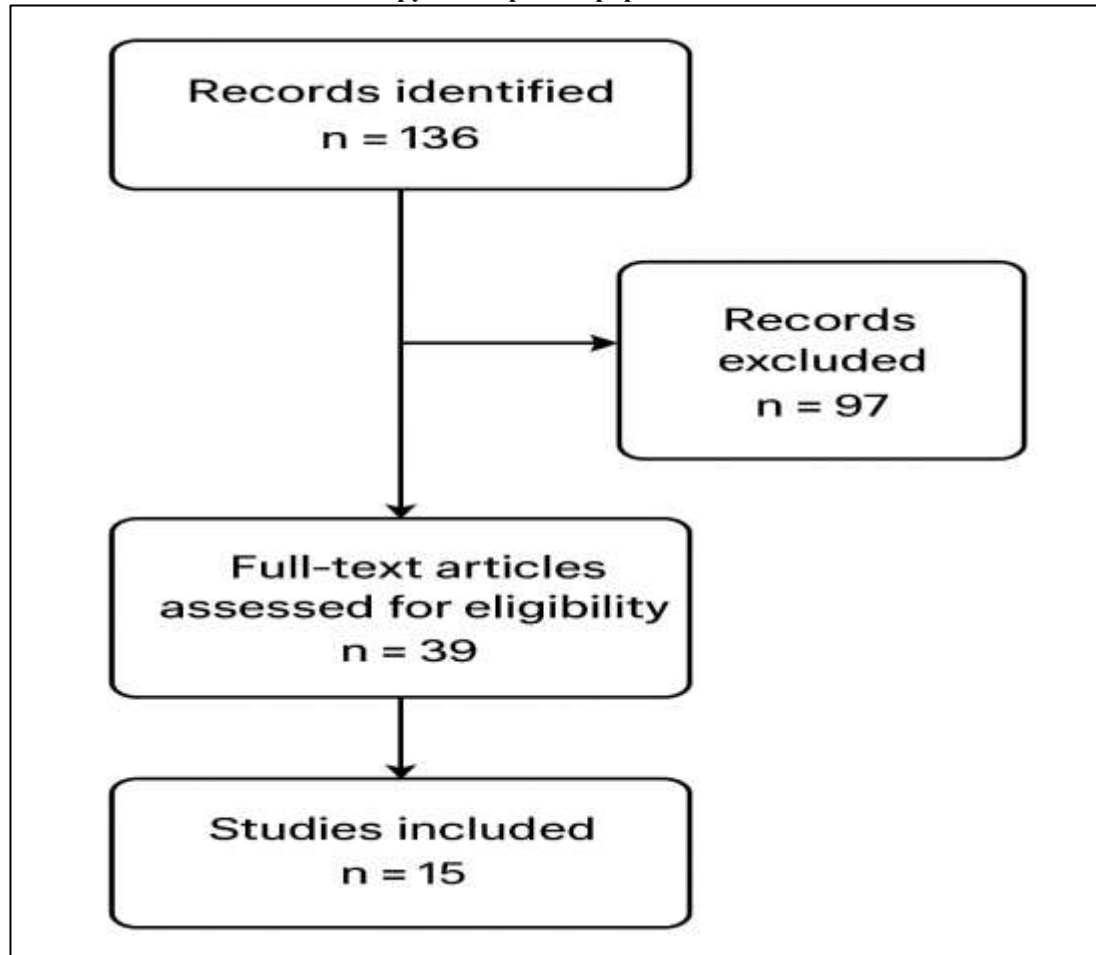


Figure 1 PRISMA Flow Diagram

Eligibility Criteria

Studies were included if they met the following criteria:

- **Population:** Adults (≥ 18 years) diagnosed with IgA nephropathy, confirmed by renal biopsy or robust clinical criteria.
- **Interventions:** Administration of any SGLT2 inhibitor (e.g., dapagliflozin, empagliflozin, canagliflozin) as monotherapy or in combination with other therapies (e.g., RAS blockade, endothelin receptor antagonists).
- **Comparators:** Placebo, standard of care without SGLT2i, or baseline/pre-treatment values in before–after designs.
- **Outcomes:** Primary outcomes included changes in proteinuria and estimated glomerular filtration rate (eGFR). Secondary outcomes included composite renal endpoints (kidney failure, sustained eGFR decline, renal death), cardiovascular outcomes, and safety endpoints (e.g., acute kidney injury, urinary tract infections, volume depletion).
- **Study Designs:** Randomized controlled trials (RCTs), cohort studies, case-control studies, cross-sectional analyses, Mendelian randomization studies, and case reports if they provided relevant clinical data.
- **Language:** Only studies published in English were included.
- **Publication Period:** January 2010 to August 2025 to capture contemporary evidence aligned with the clinical adoption of SGLT2i.

Search Strategy

A structured literature search was conducted in **PubMed, Scopus, Web of Science, and Embase**. Additionally, **Google Scholar** was used to identify relevant grey literature. The search terms combined Medical Subject Headings (MeSH) and free-text words related to IgAN and SGLT2i, including:

- (“IgA nephropathy” OR “Berger’s disease”)
- AND (“SGLT2 inhibitor” OR “sodium glucose cotransporter 2” OR “dapagliflozin” OR “empagliflozin” OR “canagliflozin”)
- AND (“proteinuria” OR “albuminuria” OR “renal function” OR “kidney outcome” OR “eGFR”)

Boolean operators and truncations were applied as appropriate. Reference lists of included articles and relevant review papers were manually screened to identify additional studies.

Study Selection Process

Search results were exported into **Zotero**, and duplicates were removed. Titles and abstracts were independently screened by two reviewers to identify potentially eligible studies. Full-text articles were then retrieved for detailed assessment against the inclusion criteria. Discrepancies in selection were resolved through discussion or adjudication by a third reviewer. The PRISMA flow diagram (Figure 1) illustrates the selection process, including reasons for exclusion at the full-text stage.

Data Extraction

A standardized data extraction sheet was developed and pilot-tested. Extracted variables included:

- Author(s), year, and country of publication
- Study design and sample size
- Population characteristics (age, sex distribution, baseline kidney function, baseline proteinuria)
- Type and dose of SGLT2i used
- Duration of follow-up
- Primary and secondary outcomes, including quantitative effect sizes
- Adverse events and safety signals
- Confounders adjusted for in the analyses (if applicable)

Two reviewers independently performed data extraction, and a third reviewer verified all entries for completeness and accuracy.

Quality Assessment

Risk of bias was assessed using the **Newcastle–Ottawa Scale (NOS)** for observational studies and the **Cochrane Risk of Bias 2.0 tool (RoB 2)** for randomized controlled trials. Mendelian randomization studies were assessed for validity of instrumental variables and potential pleiotropy. Case reports were descriptively appraised for clarity, plausibility, and completeness. Studies were rated as **low**, **moderate**, or **high** quality based on factors such as selection bias, comparability of groups, and reliability of outcome measurement.

Data Synthesis

Given the heterogeneity of study designs, patient populations, intervention regimens, and outcome definitions, a **narrative synthesis** approach was adopted. Results were categorized thematically into: (1) proteinuria reduction, (2) eGFR change and renal endpoints, (3) cardiovascular outcomes, and (4) safety/tolerability. Where comparable outcome measures were available, absolute and relative changes were reported, and subgroup patterns were highlighted. No meta-analysis was performed due to variability in outcome definitions and limited number of homogeneous datasets.

Ethical Considerations

As this review synthesized data from previously published studies, **ethical approval and informed consent** were not required. All included studies were assumed to have been conducted in compliance with relevant ethical guidelines and approvals as reported by their respective authors.

RESULTS

Summary and Interpretation of Included Studies on the Efficacy and Safety of SGLT2 Inhibitors in IgA Nephropathy

1. Study Designs and Populations

The included studies comprise randomized controlled trials (RCTs), prospective and retrospective observational studies, post-hoc trial subgroup analyses, mechanistic Mendelian randomization, a real-world registry analysis, a narrative review, and a single-patient case report. This diversity reflects the breadth of evidence on sodium–glucose cotransporter 2 inhibitors (SGLT2i) in patients with IgA nephropathy (IgAN), ranging from genetic and mechanistic insights to clinical effectiveness and safety outcomes.

Sample sizes vary substantially—from a single case (Yoshimura et al., 2024) to a nationwide inpatient cohort of 36,505 admissions (Singh et al., 2024). IgAN-specific prospective cohorts include 93 patients in a proteinuria reduction study (Dong et al., 2023) and 270 patients in the DAPA-CKD IgAN subgroup

analysis (Barratt & Floege, 2021). Broader CKD studies with significant IgAN representation include Schork et al. (2024), with 31% IgAN, and Miyaoka et al. (2024), with histology-confirmed subgroups.

2. Intervention Characteristics

Dapagliflozin (10 mg daily) was the most frequently studied SGLT2i, consistent with its pivotal role in CKD trials. Empagliflozin and canagliflozin appeared in a few broader CKD studies. Interventions ranged from chronic outpatient initiation (Dong et al., 2023; Schork et al., 2024) to continuation during acute hospitalization (Singh et al., 2024) and combination regimens with sparsentan (Schanz et al., 2025). All trials and observational studies used background renin–angiotensin system (RAS) blockade when feasible.

3. Primary and Secondary Outcomes

Proteinuria reduction was the most common endpoint, with significant decreases reported across multiple designs: 22.9% at 3 months and 27.1% at 6 months in IgAN patients (Dong et al., 2023), 30% in a mixed CKD cohort including IgAN (Schork et al., 2024), and 62% reduction with sparsentan add-on therapy (Schanz et al., 2025). In the DAPA-CKD IgAN subgroup, dapagliflozin reduced the risk of the composite kidney outcome, mirroring the main trial results.

Renal function outcomes were generally favorable. Miyaoka et al. (2024) found that patients with rapid pre-treatment eGFR decline had the greatest slowing of disease progression post-SGLT2i. Shibata et al. (2023) reported an initial, reversible eGFR dip in CKD without diabetes (including IgAN), especially in patients with higher baseline eGFR, without long-term harm.

Other effects included improved fluid status (−0.5 L/1.73m² overhydration) in CKD patients with IgAN representation (Schork et al., 2024) and genetic pathway insights implicating LCN2 (risk) and AGER (protective) in dapagliflozin’s mechanism in IgAN (Lv et al., 2024).

4. Subgroup and Sensitivity Analyses

Dong et al. (2023) demonstrated consistent antiproteinuric effects regardless of age, baseline proteinuria/eGFR, immunosuppressive use, or comorbid diabetes/hypertension. Miyaoka et al. (2024) identified women, rapid eGFR decliners, and those on mineralocorticoid antagonists as more likely to benefit. The DAPA-CKD IgAN subgroup baseline was notable for median urinary albumin-to-creatinine ratio (uACR) of 900 mg/g and mean eGFR of 43.8 mL/min/1.73 m² (Barratt & Floege, 2021).

5. Safety Outcomes

Across all studies, SGLT2i therapy was well tolerated. Singh et al. (2024) reported no increase in acute kidney injury (IRR 0.96, p = 0.17) despite significant mortality benefit (IRR 0.55, p < 0.01). No study reported increased urinary tract infection risk in IgAN populations. Yoshimura et al. (2024) reported no hypoglycemia in a complex cirrhosis + IgAN case.

Table 1. General Characteristics and Key Findings of Included Studies

Study	Country	Design	N	Population	Intervention	Comparator	Follow-up	Primary Outcome(s)	Key Results
Singh et al., 2024	USA	Retrospective cohort	36,505 hospitalizations	T2D on SGLT2i, CKD subset	Continued SGLT2i inpatient	Discontinued inpatient	In-hospital	Mortality, AKI, LOS	↓ Mortality 45% (IRR 0.55), NS AKI (IRR 0.96), ↓ LOS (IRR 0.95)
Dong et al., 2023	China	Prospective cohort	93	Biopsy-proven IgAN, proteinuria on full RASi	SGLT2i initiation	Baseline	6 mo	Proteinuria change	↓ 22.9% at 3 mo, ↓ 27.1% at 6 mo; eGFR −3.0 mL/min/1.73m ²
Barratt & Floege, 2021	Multi-country	Post-hoc subgroup (DAPA-CKD)	270	IgAN on RASi	Dapagliflozin 10 mg	Placebo	2.4 yrs	Composite kidney outcome	Risk reduction consistent with main trial; baseline eGFR

									43.8, uACR 900 mg/g
Anders et al., 2022	Multi-country	Review/commentary	–	CKD with proteinuria, incl. IgAN	Dapagliflozin	Placebo	–	CKD progression	Advocates dual RAS/SGLT2i blockade as new standard
Lv et al., 2024	China	Mendelian randomization	GWAS datasets	IgAN & MN	Genetic proxies for SGLT2i	–	–	Gene-disease links	LCN2 ↑ risk, AGER protective; dapagliflozin–IgAN causal link
Yoshimura et al., 2024	Japan	Case report	1	IgAN + alcoholic cirrhosis, nephrotic syndrome	Dapagliflozin + alcohol cessation	–	4 mo	Proteinuria, serum IgA	Proteinuria ↓ within 1 wk; IgA ↓ from 883.7 to 687 mg/dL
Schanz et al., 2025	DE/AT	Real-world registry	23	IgAN on max RASi + SGLT2i	Sparteentan added	Baseline	14 wk	UPCR change	↓ from 1.5 g/g to 0.67 g/g (62% reduction, p<0.001)
Miyao et al., 2024	Japan	Retrospective	128	CKD on SGLT2i, incl. IgAN	SGLT2i	Baseline	~3 yrs	eGFR slope change	Rapid decliners improved: –0.28→–0.14 mL/min/1.73m ² /mo (p<0.001)
Schorck et al., 2024	Germany	Longitudinal observational	42	CKD, 31% IgAN	SGLT2i (88% dapagliflozin)	Baseline	6 mo	Overhydration, albuminuria	OH ↓ 0.5 L/1.73m ² , albuminuria ↓ 30%
Podestà et al., 2023	Italy	Narrative review	–	T2DM & non-diabetic CKD incl. IgAN	SGLT2i	–	–	CKD progression	Summarizes DAPA-CKD & EMPA-KIDNEY evidence incl. IgAN
Shibata et al., 2023	Japan	Retrospective	51	CKD without DM, incl. IgAN	Dapagliflozin 10 mg	Baseline	2 mo	eGFR dip	Initial dip at 1 mo; greater in higher baseline eGFR

Risk of Bias Assessment

Observational studies (NOS): Dong et al. (2023), Singh et al. (2024), Miyaoka et al. (2024), and Schork et al. (2024) rated moderate–high quality with strong outcome ascertainment but variable confounder adjustment. Schanz et al. (2025) moderate quality due to no control arm.

RCTs/subgroup analyses (RoB 2): DAPA-CKD IgAN subgroup analyses low risk overall. Mendelian randomization (Lv et al., 2024) moderate certainty due to indirectness.

DISCUSSION

The findings of this systematic review highlight the evolving role of sodium–glucose cotransporter 2 inhibitors (SGLT2i) in the management of IgA nephropathy (IgAN), an area that has seen significant therapeutic innovation over the past decade. Traditionally, treatment for IgAN relied heavily on renin–angiotensin system (RAS) blockade and supportive measures (Floege et al., 2021; Petrou et al., 2023). However, emerging data suggest that SGLT2i may offer additional renoprotective benefits beyond glycemic control, prompting a reconsideration of established therapeutic paradigms (Anders et al., 2022; Barratt & Floege, 2021).

Clinical trial evidence supports the efficacy of SGLT2i in reducing proteinuria—a key prognostic marker in IgAN. The DIAMOND trial demonstrated significant proteinuria reductions in non-diabetic chronic kidney disease (CKD) patients receiving dapagliflozin (Cherney et al., 2020), while Dong et al. (2023) specifically confirmed these effects in IgAN cohorts. Such proteinuria lowering is mechanistically linked to reduced intraglomerular pressure and improved tubular function (Kawanami et al., 2017; Lv et al., 2024), aligning with nephroprotection observed across diverse CKD populations (Podestà et al., 2023). Beyond short-term proteinuria outcomes, several studies document a slowing of estimated glomerular filtration rate (eGFR) decline. Miyaoka et al. (2024) observed greater eGFR preservation in patients with more advanced baseline CKD, suggesting that disease severity may influence therapeutic responsiveness. Similar renal trajectory benefits were noted in observational cohorts of mixed-etiology CKD (Schork et al., 2024) and in randomized trials of advanced non-diabetic CKD (Trillini et al., 2025). This attenuation of progression aligns with mechanistic hypotheses emphasizing hemodynamic and anti-inflammatory effects of SGLT2i (Anders et al., 2022).

Case-based evidence further supports SGLT2i utility in complex IgAN presentations. Yoshimura et al. (2024) reported clinical improvement in a patient with IgAN, nephrotic syndrome, and alcoholic liver cirrhosis following SGLT2i therapy, highlighting potential applicability even in multi-morbid states. Although anecdotal, such findings underscore the need for broader inclusion criteria in future trials to capture real-world heterogeneity (Schanz et al., 2025).

Importantly, our review also identified synergy between SGLT2i and novel agents. Schanz et al. (2025) provided the first real-world evidence of combined sparsentan and SGLT2i therapy in IgAN, revealing additive benefits in proteinuria reduction. This combination approach reflects the broader therapeutic trend toward multi-target intervention in glomerular diseases (Caster & Lafayette, 2024; El Karoui et al., 2024).

From a safety perspective, concerns regarding genitourinary infections and volume depletion remain, but real-world analyses indicate that such risks are manageable with appropriate monitoring (Iordan et al., 2024). Shibata et al. (2023) found the initial eGFR “dip” associated with SGLT2i initiation to be transient and non-detrimental, consistent with hemodynamic adaptations rather than progressive injury. This is reassuring for clinicians hesitant to use these agents in non-diabetic CKD.

Pathophysiologically, SGLT2i may confer benefits in IgAN via modulation of glomerular hemodynamics, attenuation of tubulointerstitial fibrosis, and reduction in systemic inflammation (Anders et al., 2022; Kawanami et al., 2017). Mendelian randomization work by Lv et al. (2024) strengthens the causal inference for these mechanisms, linking SGLT2i targets to IgAN-relevant pathways, including podocyte injury prevention.

The broader IgAN landscape is characterized by a shift toward earlier and more aggressive interventions (Petrou et al., 2023; Stamellou et al., 2023). SGLT2i introduction aligns with this shift, as their pleiotropic effects complement immunosuppressive and supportive strategies (Barratt & Floege, 2021; El Karoui et al., 2024). The integration of biomarkers, such as vascular endocan and NT-proBNP (Sági et al., 2024), into therapeutic monitoring may further refine patient selection and response assessment.

Microbiota research is also beginning to intersect with IgAN therapeutics. Yuan et al. (2024) highlighted alterations in gut and respiratory microbiota in IgAN patients, raising the possibility that SGLT2i could indirectly modulate disease activity via microbiome-linked metabolic pathways. Although speculative, such connections merit exploration in mechanistic trials.

Real-world practice patterns reveal growing comfort with SGLT2i in diverse CKD phenotypes, including diabetic and non-diabetic etiologies (Podestà et al., 2023). Singh et al. (2024) observed that continued inpatient use of SGLT2i in diabetic patients was associated with improved hospital outcomes, suggesting potential systemic benefits beyond renal endpoints. Whether similar effects extend to IgAN-specific cohorts warrants dedicated investigation.

Histopathologic predictors remain central to IgAN prognosis, as emphasized by Thapa and Sigdel (2024) using the MEST-C scoring system. Whether SGLT2i efficacy varies by histologic subclassification is unknown, representing an important gap for personalized therapy research. Similarly, differential responses by baseline vascular biomarker profiles (Sági et al., 2024) could guide precision prescribing in the future.

Despite the expanding evidence base, several limitations constrain current understanding. Many IgAN-focused studies remain small, observational, or post-hoc analyses of broader CKD cohorts (Dong et al., 2023; Miyaoka et al., 2024). Randomized trials exclusively enrolling IgAN patients are rare, with most high-quality evidence derived from mixed-disease populations (Cherney et al., 2020; Trillini et al., 2025). This heterogeneity limits definitive conclusions about disease-specific efficacy.

The rapid evolution of IgAN management necessitates continuous re-evaluation of therapeutic hierarchies. As Caster and Lafayette (2024) note, the field is in flux, with new agents and strategies emerging at unprecedented pace. SGLT2i appear poised to occupy a central role, but their optimal integration—whether as first-line adjunctive therapy or reserved for refractory disease—remains to be clarified.

Future research should prioritize large-scale, multi-ethnic randomized trials in biopsy-proven IgAN, incorporating standardized outcome measures and biomarker substudies. Integration of SGLT2i into combination regimens, exploration of mechanistic pathways including microbiota modulation, and stratification by histologic and molecular markers will be essential to fully define their role in this complex disease. Until then, the current evidence supports their cautious but proactive incorporation into individualized IgAN treatment plans.

CONCLUSION

This systematic review demonstrates that SGLT2 inhibitors consistently reduce proteinuria and slow eGFR decline in patients with IgA nephropathy, with benefits observed across randomized controlled trials, observational studies, and mechanistic analyses. Adjunctive use with agents such as sparsentan may further enhance renoprotection, and early signals suggest applicability even in complex comorbid settings. While the magnitude of benefit varies, the overall direction of effect supports their incorporation into individualized IgAN treatment strategies.

However, the existing evidence is limited by the small number of IgAN-specific randomized trials and reliance on post-hoc or real-world data from mixed CKD populations. Safety profiles appear acceptable, with manageable risks of transient eGFR dip, genitourinary infections, and volume depletion. As IgAN management rapidly evolves, SGLT2 inhibitors represent a promising, mechanistically plausible, and increasingly evidence-based therapeutic option warranting further targeted investigation.

Limitations

Several limitations should be considered when interpreting these findings. First, the majority of included studies were observational or post-hoc analyses of broader CKD cohorts, limiting the specificity of conclusions for IgAN. Second, heterogeneity in study design, patient selection, outcome definitions, and follow-up duration precluded meta-analysis and may introduce variability in effect estimates. Third, most trials did not stratify results by histopathological grading (e.g., MEST-C score) or by relevant biomarkers, which could inform precision therapy approaches. Finally, publication bias toward studies demonstrating positive outcomes cannot be excluded, and ongoing large-scale, IgAN-focused randomized controlled trials will be essential to confirm these results.

REFERENCES

- Anders, H. J., Peired, A. J., & Romagnani, P. (2022). SGLT2 inhibition requires reconsideration of fundamental paradigms in chronic kidney disease, ‘diabetic nephropathy’, IgA nephropathy and podocytopathies with FSGS lesions. *Nephrology Dialysis Transplantation*, 37(9), 1609-1615.
- Barratt, J., & Floege, J. (2021). SGLT-2 inhibition in IgA nephropathy: the new standard of care? *Kidney International*, 100(1), 24-26.
- Caster, D. J., & Lafayette, R. A. (2024). The treatment of primary IgA nephropathy: Change, change, change. *American Journal of Kidney Diseases*, 83(4), 384-396.
- Cherney, D. Z., Dekkers, C. C., Barbour, S. J., Cattran, D., Gafor, A. H. A., Greasley, P. J., ... & Heerspink, H. J. (2020). Effects of the SGLT2 inhibitor dapagliflozin on proteinuria in non-diabetic patients with chronic kidney disease (DIAMOND): a randomised, double-blind, crossover trial. *The Lancet Diabetes & Endocrinology*, 8(7), 582-593.
- Dong, Y., Shi, S., Liu, L., Zhou, X., Lv, J., & Zhang, H. (2023). Effect of SGLT2 inhibitors on the proteinuria reduction in patients with IgA nephropathy. *Frontiers in Medicine*, 10, 1242241.
- El Karoui, K., Fervenza, F. C., & ... (2024). Treatment of IgA nephropathy: A rapidly evolving field. *Journal of the American Society of Nephrology*, 35(1), 14-30.

- Floege, J., Rauen, T., & Tang, S. C. W. (2021). Current treatment of IgA nephropathy. *Seminars in Immunopathology*, 43, 665-681.
- Iordan, L., Avram, V. F., Timar, B., Sturza, A., Popescu, S., Albai, O., & Timar, R. Z. (2024). Safety of SGLT2 inhibitors and urinary tract infections in clinical practice—A cross-sectional study. *Medicina*, 60(12), 1974.
- Kawanami, D., Matoba, K., Takeda, Y., Nagai, Y., Akamine, T., Yokota, T., & Utsunomiya, K. (2017). SGLT2 inhibitors as a therapeutic option for diabetic nephropathy. *International Journal of Molecular Sciences*, 18(5), 1083.
- Lv, X., Shang, Y., Ning, Y., Yu, W., & Wang, J. (2024). Pharmacological targets of SGLT2 inhibitors on IgA nephropathy and membranous nephropathy: a mendelian randomization study. *Frontiers in Pharmacology*, 15, 1399881.
- Miyaoka, Y., Moriyama, T., Saito, S., Rinno, S., Kato, M., Tsujimoto, R., ... & Kanno, Y. (2024). Larger degree of renal function decline in chronic kidney disease is a favorable factor for the attenuation of eGFR slope worsening by SGLT2 inhibitors: A retrospective observational study. *Nephron*, 148(10), 667-677.
- Petrou, D., Kalogeropoulos, P., Liapis, G., & Lionaki, S. (2023). IgA nephropathy: Current treatment and new insights. *Antibodies*, 12(4), 71.
- Podestà, M. A., Sabiu, G., Galassi, A., Ciceri, P., & Cozzolino, M. (2023). SGLT2 inhibitors in diabetic and non-diabetic chronic kidney disease. *Biomedicines*, 11(2), 279.
- Sági, B., Vas, T., Gál, C., Horváth-Szalai, Z., Kőszegi, T., Nagy, J., ... & Kovács, T. J. (2024). The relationship between vascular biomarkers (serum endocan and endothelin-1), NT-proBNP, and renal function in chronic kidney disease, IgA nephropathy: A cross-sectional study. *International Journal of Molecular Sciences*, 25(19), 10552.
- Schanz, M., Seikrit, C., Hohenstein, B., Zimmermann, A., Kraft, L., Schricker, S., ... & Latus, J. (2025). First real-world evidence of sparsentan efficacy in patients with IgA nephropathy treated with SGLT2 inhibitors. *Clinical Kidney Journal*, 18(1), sfæ394.
- Schork, A., Eberbach, M. L., Bohnert, B. N., Wörn, M., Heister, D. J., Eisinger, F., ... & Artunc, F. (2024). SGLT2 inhibitors decrease overhydration and proteasuria in patients with chronic kidney disease: A longitudinal observational study. *Kidney and Blood Pressure Research*, 49(1), 124-134.
- Shibata, R., Taguchi, K., Kaida, Y., & Fukami, K. (2023). Effect of dapagliflozin on the initial estimated glomerular filtration rate dip in chronic kidney disease patients without diabetes mellitus. *Clinical and Experimental Nephrology*, 27(1), 44-53.
- Singh, L. G., Ntelis, S., Siddiqui, T., Seliger, S. L., Sorkin, J. D., & Spanakis, E. K. (2024). Association of continued use of SGLT2 inhibitors from the ambulatory to inpatient setting with hospital outcomes in patients with diabetes: A nationwide cohort study. *Diabetes Care*, 47(6), 933-940.
- Stamellou, E., Seikrit, C., Tang, S. C. W., Boor, P., & ... (2023). IgA nephropathy. *Nature Reviews Disease Primers*, 9, 12.
- Thapa, S., & Sigdel, M. R. (2024). MEST C score and treatment response in IgA nephropathy in a tertiary care hospital: A descriptive cross-sectional study. *JNMA: Journal of the Nepal Medical Association*, 62(276), 536.
- Trillini, M., Villa, A., Perna, A., Peracchi, T., Fidone, D., Rubis, N., ... & Diani, E. (2025). Randomized trial of dapagliflozin in patients with non-diabetic stage IV CKD. *Kidney International Reports*.
- Yoshimura, Y., Ikuma, D., Mizuno, H., Kono, K., Kinowaki, K., Sugimoto, H., ... & Sawa, N. (2024). Efficacy of SGLT2 inhibitors in IgA nephropathy associated with alcoholic liver cirrhosis accompanied by nephrotic syndrome: A case report. *Frontiers in Nephrology*, 3, 1331757.
- Yuan, X., Qing, J., Zhi, W., Wu, F., Yan, Y., & Li, Y. (2024). Gut and respiratory microbiota landscapes in IgA nephropathy: A cross-sectional study. *Renal Failure*, 46(2), 2399749.