

Beyond haemodynamics: Do SGLT2 inhibitors protect the podocyte?

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Over the past decade, sodium-glucose cotransporter 2 (SGLT2) inhibitors have evolved from glucose-lowering agents into a cornerstone of kidney-protective therapy. Landmark trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, demonstrated reductions in kidney disease progression across a broad spectrum of patients with chronic kidney disease (CKD), beyond those attributable to glycaemic control.¹⁻³ A subsequent collaborative meta-analysis of 13 large placebo-controlled trials reported an approximately 37% reduction in the risk of kidney disease progression, with benefits observed irrespective of diabetes status.⁴ These findings have reshaped contemporary CKD management, with SGLT2 inhibitors now strongly recommended by the KDIGO 2024 guidelines for eligible patients with CKD.⁵

The renoprotective effects of SGLT2 inhibition have traditionally been attributed largely to the restoration of tubuloglomerular feedback. Increased sodium delivery to the macula densa promotes afferent arteriolar vasoconstriction, reducing glomerular hyperfiltration and intraglomerular pressure. However, an expanding body of evidence suggests that kidney protection may extend beyond haemodynamic effects, with proposed mechanisms including reduced tubular workload and hypoxia, modulation of inflammatory and fibrotic pathways, attenuation of inflammasome activation and oxidative stress, and favourable metabolic adaptations.⁶

Podocytes are particularly relevant in this context. These highly specialised, terminally differentiated epithelial cells form a critical component of the glomerular filtration barrier and provide structural support to the glomerular capillary wall. Because their capacity for regeneration is limited, sustained podocyte injury and loss can disrupt the filtration barrier, resulting in proteinuria and progressive glomerulosclerosis. Podocyte dysfunction is therefore considered a central feature of diabetic kidney disease (DKD) progression. While the haemodynamic effects of SGLT2 inhibition are well established, whether these agents confer additional protection through direct or indirect effects on podocytes remains less certain.⁷

Against this background, a randomised, double-blind, placebo-controlled trial by Gu et al. in this issue of the *Annals* provides a valuable clinical opportunity to examine the relationship between SGLT2 inhibition and markers of podocyte injury.⁸ The investigators randomised 180 patients with type 2 diabetes and DKD to 12 weeks of standard therapy plus either canagliflozin or placebo; 172 completed the study and were included in the analysis. Glycaemic control during follow-up was comparable between groups, allowing differences in kidney outcomes and podocyte-associated biomarkers to be interpreted with less concern that they reflected differential glucose-lowering.

A notable strength of this study is the assessment of podocyte-associated biomarkers alongside conventional measures of kidney injury. In addition to blood urea nitrogen, serum creatinine, urinary albumin-to-creatinine ratio (UACR), and 24-hour urinary protein (24h-UP), the investigators serially assessed urinary podocyte count and the urinary podocalyxin-to-creatinine ratio (UPCX/Ucr) as markers of podocyte injury. Canagliflozin was associated with progressive reductions in urinary podocyte shedding, UACR, and 24h-UP over 12 weeks, with significant treatment-by-time interactions. By week 12, urinary podocyte counts were approximately 52% lower and UACR approximately 28% lower than in the control group. Serum creatinine also followed a different trajectory between groups, although the between-group difference was no longer statistically significant at week 12. Taken together, the parallel changes in podocyte-associated biomarkers and proteinuria support the possibility that reduced podocyte injury may contribute to the kidney-protective effects of SGLT2 inhibition.

Several considerations are important when interpreting these findings. The 12-week follow-up and single-centre design necessarily focused the study on short-term biomarker responses rather than sustained preservation of kidney function. The study population was also relatively selected: patients with rapid estimated glomerular filtration rate (eGFR) decline (>5 mL/min/1.73 m² per year), a doubling or

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Accepted: 17 September 2026

Published Online First: 17 September 2026

greater increase in UACR within 2 years, nephrotic syndrome, or other features suggestive of non-diabetic kidney disease were excluded. While these criteria increase confidence that the enrolled cohort had a relatively well-defined DKD phenotype, they also select for a more clinically stable cohort and may limit extrapolation to patients with rapidly progressive disease. The relatively preserved mean baseline eGFR of approximately 74–76 mL/min/1.73 m² should also be considered when applying the findings to patients with more advanced CKD. Urinary podocyte count and UPCX/Ucr should also be regarded as surrogate markers of podocyte injury rather than direct measures of podocyte structure or function. In the absence of complementary structural assessment, reductions in urinary biomarkers should therefore be interpreted as consistent with reduced podocyte injury rather than definitive evidence of preservation of podocyte architecture. Manual podocyte quantification may also introduce measurement variability, although the high reported inter-observer agreement provides reassurance regarding measurement consistency.

The mediation analysis represents a particularly interesting aspect of the study. Rather than asking only whether canagliflozin reduces proteinuria, mediation analysis examines whether part of the treatment effect may operate through an intermediate variable in the proposed pathway between treatment and outcome. Here, treatment assignment was considered the exposure; change in UPCX/Ucr the mediator; and changes in UACR, 24h-UP, and serum creatinine the outcomes. Under the assumptions of the mediation model, the statistically significant indirect effects, with estimated mediation proportions of 84.39% for UACR and 86.42% for 24h-UP, support the hypothesis that reduced podocyte injury may lie on the pathway linking canagliflozin treatment with reduced proteinuria.

These estimates, however, require careful interpretation. Although treatment allocation was randomised, the mediator itself was not, and randomisation therefore does not eliminate potential confounding of the mediator–outcome relationship.⁹ In addition, mediator and outcome changes were assessed over the same follow-up interval, making temporal ordering difficult to establish. For the UACR model, the mediator and outcome also share urinary creatinine as the denominator, potentially introducing correlated measurement variation, although the similar finding for 24h-UP is less susceptible to this concern. Mediation analysis in this setting, therefore, strengthens a biologically plausible mechanistic hypothesis but does not, by itself, establish that reduced podocyte injury causally mediates the antiproteinuric effect of canagliflozin.

These findings also raise a broader question regarding residual kidney risk despite contemporary SGLT2 inhibitor therapy. Even with substantial reductions in kidney disease progression, some patients continue to experience progressive loss of kidney function, reflecting the multiple haemodynamic, inflammatory, fibrotic, metabolic, and structural pathways involved in CKD progression.¹⁰ If reductions in podocyte injury contribute to the clinical effects of SGLT2 inhibition, persistent podocyte injury despite therapy may represent 1 component of this residual risk. Further studies incorporating longer follow-up, serial assessments of podocyte biomarkers and kidney function trajectories, and, where feasible, complementary structural or molecular assessments could help determine whether podocyte preservation is a mediator, biomarker, or consequence of SGLT2 inhibitor-associated kidney protection.

Large cardiovascular and kidney outcome trials have established that SGLT2 inhibitors protect the kidney. The present study contributes to the complementary question of how that protection may occur, providing clinical evidence linking canagliflozin treatment with reduced podocyte injury and proteinuria. Clarifying the causal relationships between these processes will be an important next step in understanding the full spectrum of SGLT2 inhibitor-mediated kidney protection.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors declare that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *canagliflozin, diabetes mellitus type 2, diabetic nephropathies, podocalyxin, podocytes*

REFERENCES

1. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;380:2295-306.
2. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; 383:1436-46.
3. Group TEKC, Herrington WG, Staplin N, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2022; 388:117-27.
4. Staplin N, Haynes R, Mayne KJ, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022;400:1788-801.

5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024;105:S117-314.
6. Upadhyay A. SGLT2 Inhibitors and Kidney Protection: Mechanisms Beyond Tubuloglomerular Feedback. *Kidney360* 2024;5:771-82.
7. Jiang B, Cheng Z, Wang D, et al. Unveiling the podocyte-protective effect of sodium-glucose cotransporter-2 inhibitors. *Kidney Res Clin Pract* 2024;44:69-78.
8. Gu S, Zhu N, Hang G, et al. A randomised controlled study of canagliflozin in improving diabetic kidney disease through podocyte protection mechanism. *Ann Acad Med Singap* 2026;OnlineFirst.
9. Lee H, Cashin AG, Lamb SE, et al. A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies. *JAMA* 2021;326:1045-56.
10. Chaudhry K, Karalliedde J. Chronic kidney disease in type 2 diabetes: The size of the problem, addressing residual renal risk and what we have learned from the CREDENCE trial. *Diabetes Obes Metab* 2024;26:25-34.