DYNAMICS OF NEPHRIN AND CYSTATIN C DURING DIFFERENT GLUCOSE-LOWERING THERAPIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Z.A.Rakhimberdiyeva
B.Kh.Shagazatova
Tashkent State Medical University, Tashkent, Uzbekistan
https://doi.org/10.5281/zenodo.22043695

ARTICLE INFO

Received: 16th August 2026
Accepted: 18th August 2026
Online: 20th August 2026

KEYWORDS

type 2 diabetes mellitus, diabetic kidney disease, nephrin, cystatin C, SGLT2 inhibitor, DPP-4 inhibitor, metformin, nephroprotection

ABSTRACT

Background. Diabetic kidney disease is a major complication of type 2 diabetes mellitus (T2DM). Current evidence supports the kidney-protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with diabetes and chronic kidney disease [1–4]. Nephrin reflects podocyte injury, whereas cystatin C is a sensitive marker of changes in glomerular filtration. Their combined assessment may provide information on both structural and functional renal changes during treatment.

Objective. To compare changes in nephrin and cystatin C during different glucose-lowering treatment regimens in patients with T2DM.

Materials and Methods. The study included 140 patients with T2DM receiving combination glucose-lowering therapy. Of these, 62 patients received a DPP-4 inhibitor plus metformin and 78 patients received an SGLT2 inhibitor plus metformin. After 12 months, patients were evaluated according to three treatment regimens: DPP-4 inhibitor + metformin, SGLT2 inhibitor + metformin, and SGLT2 inhibitor + DPP-4 inhibitor + metformin. Clinical, metabolic and renal parameters were assessed, with particular attention to serum nephrin and cystatin C.

Results. At baseline, serum nephrin was 8.10 ± 0.78 ng/mL in the DPP-4 inhibitor + metformin group and 6.85 ± 0.95 ng/mL in the SGLT2 inhibitor + metformin group ($p<0.05$). Serum cystatin C was 16.0 ± 1.03 versus 16.5 ± 0.93 mg/L, respectively ($p>0.05$).

After 12 months, nephrin levels were 6.92 ± 0.64, 4.98 ± 0.58 and 3.86 ± 0.47 ng/mL in the DPP-4 inhibitor + metformin, SGLT2 inhibitor + metformin and triple-therapy groups, respectively ($p<0.05$). Cystatin C levels were 14.8 ± 0.84, 13.2 ± 0.76 and 12.4 ± 0.69 mg/L, respectively.

The greatest reduction in nephrin was observed with triple

therapy (43.6%), compared with 27.3% with SGLT2 inhibitor + metformin and 14.6% with DPP-4 inhibitor + metformin. Cystatin C decreased by 24.8%, 20.0% and 7.5%, respectively.

Conclusion. Treatment regimens containing an SGLT2 inhibitor were associated with greater reductions in nephrin and cystatin C. The most pronounced biomarker changes were observed with triple therapy combining an SGLT2 inhibitor, DPP-4 inhibitor and metformin. These findings suggest that simultaneous measurement of nephrin and cystatin C may be useful for monitoring structural and functional renal biomarker responses during therapy in patients with T2DM..

Introduction

Patients with T2DM and CKD are at increased risk of kidney failure and cardiovascular complications. Contemporary management therefore aims not only to achieve adequate glycemic control but also to preserve kidney function and reduce cardiorenal risk.

The ADA–KDIGO consensus recommends a comprehensive strategy incorporating therapies with demonstrated kidney and cardiovascular benefits, including SGLT2 inhibitors in appropriate patients with T2DM and CKD [1].

Large randomized clinical trials have established the kidney-protective effects of SGLT2 inhibitors. In DAPA-CKD, dapagliflozin significantly reduced the primary composite kidney/cardiovascular outcome compared with placebo [2]. The EMPA-KIDNEY trial subsequently demonstrated that empagliflozin reduced progression of kidney disease across a broad population with CKD [3].

The KDIGO 2024 guideline consequently incorporates SGLT2 inhibitors as an important component of kidney-protective treatment.

However, conventional parameters may not fully characterize early structural renal changes. Nephrin reflects podocyte and slit-diaphragm integrity, while cystatin C provides a sensitive measure related to glomerular filtration.

A meta-analysis by Liao et al. including 26 studies reported pooled sensitivity of 0.86, specificity of 0.89, and an area under the SROC curve of 0.94 for serum cystatin C in diabetic nephropathy, supporting its diagnostic value [5].

The combined evaluation of nephrin and cystatin C may therefore provide complementary information on structural and functional renal changes.

Materials and Methods

Of 160 initially examined patients, 140 patients with T2DM who met the study criteria and were receiving combination glucose-lowering therapy were selected for the therapeutic analysis.

Patients were initially divided into two groups: DPP-4 inhibitor + metformin (n=62) and SGLT2 inhibitor + metformin (n=78).

Clinical assessment included age, duration of T2DM, HbA1c, serum creatinine, urea, total cholesterol, triglycerides, systolic and diastolic blood pressure, and heart rate.

After 12 months, the treatment groups included patients continuing DPP-4 inhibitor + metformin, those receiving SGLT2 inhibitor + metformin, and patients requiring intensified triple therapy with an SGLT2 inhibitor + DPP-4 inhibitor + metformin.

Serum nephrin and cystatin C were assessed as biomarkers of structural and functional renal alterations.

Results and Discussion

At baseline, the treatment groups were generally comparable with respect to age, diabetes duration, renal function, lipid profile and hemodynamic parameters. HbA1c was lower in patients receiving SGLT2 inhibitor + metformin (7.6 ± 0.47%) compared with the DPP-4 inhibitor + metformin group (8.6 ± 0.41%; $p<0.05$).

After 12 months, improvements in metabolic and renal parameters were observed, with the most favorable values reported in the triple-therapy group. HbA1c reached 6.5 ± 0.24%, compared with 6.9 ± 0.29% with SGLT2 inhibitor + metformin and 7.8 ± 0.36% with DPP-4 inhibitor + metformin.

Particular attention was paid to nephrin and cystatin C. Nephrin showed the greatest relative reduction with triple therapy (43.6%), while the decrease with SGLT2 inhibitor + metformin was 27.3% and with DPP-4 inhibitor + metformin 14.6%. Cystatin C demonstrated a similar pattern, with reductions of 24.8%, 20.0%, and 7.5%, respectively.

These findings are directionally consistent with the established kidney-protective role of SGLT2 inhibitors demonstrated in large outcome trials, although the biomarker findings of the present study should not be interpreted as equivalent to hard renal outcomes such as kidney failure or sustained eGFR decline. DAPA-CKD and EMPA-KIDNEY provide independent clinical evidence that SGLT2 inhibition slows CKD progression.

Cystatin C may add further information to conventional kidney markers. The meta-analysis by Liao et al. reported high overall diagnostic accuracy of serum cystatin C for diabetic nephropathy, while an earlier meta-analysis also found cystatin C to be more sensitive than serum creatinine for identifying renal dysfunction in diabetic patients [5,6].

Conclusion

SGLT2 inhibitor-containing regimens were associated with greater reductions in serum nephrin and cystatin C than DPP-4 inhibitor + metformin in the studied cohort. The greatest changes were observed among patients receiving triple therapy with an SGLT2 inhibitor, DPP-4 inhibitor and metformin.

The parallel reduction of nephrin and cystatin C suggests improvement in biomarkers reflecting both podocyte injury and renal filtration. Their combined measurement may therefore be useful as an additional approach for monitoring renal status during treatment of patients with T2DM.

Further prospective randomized studies are required to determine whether treatment-related changes in nephrin independently predict long-term renal outcomes.

References:

1.de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022;45(12):3075–3090. doi:10.2337/dci22-0027.

2.Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–1446. doi:10.1056/NEJMoa2024816.
3.The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388:117–127. doi:10.1056/NEJMoa2204233.
4.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(Suppl 4S):S117–S314.
5.Liao X, Zhu Y, Xue C. Diagnostic value of serum cystatin C for diabetic nephropathy: a meta-analysis. BMC Endocr Disord. 2022;22:149. doi:10.1186/s12902-022-01052-0.
6.Shagazatova, B. H., & Rakhimberdieva, Z. A. (2024). EARLY BIOMARKERS OF DIABETIC KIDNEY DISEASE. Eurasian Journal of Medical and Natural Sciences , 4 (9), 34-44.
7.AKZAMOVNA, Z. R., XABIBULLAYEVNA, S. B., KAMARDINOVNA, N. D., & TOXTABAYEVICH, B. Q. (2019). THE STUDY OF THE POLYMORPHIC GENE AGTR1 1166 A> C AND A MARKER OF NEPHRINE WITH DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 1 DIABETES IN THE UZBEK POPULATION. International Journal of Pharmaceutical Research (09752366), 11(3), 187.
8.Nazhmutdinova, D. K., Rakhimberdieva, Z. A., & Maksudova, D. R. (2017). Relationship of autoimmune thyroids with violations of reproductive function in women of childbearing age. Eurasian Union of Scientists , (2 (35)), 31-34.