GMR
The Original

COMPARATIVE RENAL BIOMARKER TRAJECTORIES AND MOLECULAR–GENETIC IMPLICATIONS OF SGLT-2 VERSUS DPP-4 INHIBITOR THERAPY IN TYPE 2 DIABETES MELLITUS: A 12-MONTH PROSPECTIVE OBSERVATIONAL STUDY

Syed Afzal Uddin Biyabani[1*], Neelkantreddy Patil[1], Zunera Fatima[2], Syed Mussabhi Sohaib[3], Syed Jaffer Sadiq[3], Mohammed Ghouse Junaidi[3], Safa Wasay[3]

[1]Professor HOD, Department of Pharmacy Practice, Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka, India
[2]PharmD Graduate, Department of Pharmacy Practice, Deccan School of Pharmacy, Hyderabad, Telangana, India
[3]PharmD Scholar, Department of Pharmacy Practice, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India
***Corresponding author:** Dr. Syed Afzal Uddin Biyabani

ABSTRACT:
Background: Type 2 diabetes mellitus (T2DM) is associated with progressive renal dysfunction involving alterations in glomerular filtration, tubular transport, and metabolic homeostasis. Sodium-glucose cotransporter-2 (SGLT-2) and dipeptidyl peptidase-4 (DPP-4) inhibitors exert distinct renal and metabolic effects. The present study compared longitudinal renal biomarker profiles between these treatment groups and interpreted the observed responses in the context of established molecular and genetic pathways involved in renal transport and urate handling.
Methods: A 12-month prospective observational cohort study was conducted among patients with T2DM receiving SGLT-2 or DPP-4 inhibitors. Renal parameters, including estimated glomerular filtration rate (eGFR), serum urea, serum creatinine, and serum uric acid, were assessed at baseline and at 3, 6, 9, and 12 months. Changes over time were evaluated using repeated-measures statistical approaches with estimated marginal means, 95% confidence intervals, and post hoc comparisons. The molecular interpretation considered established pathways involving SLC5A2, which encodes SGLT-2, and renal urate transporters including SLC22A12 (URAT1) and SLC2A9 (GLUT9).
Results: At baseline, mean eGFR was 94.984 ± 3.146 mL/min/1.73 m² in both groups and decreased to 90.984 ± 3.146 in the SGLT-2 group and 92.984 ± 3.146 in the DPP-4 group at 12 months. Serum urea increased from 16.076 ± 0.235 to 17.001 ± 0.254 mg/dL with SGLT-2 therapy, whereas it decreased from 15.438 ± 0.235 to 15.016 ± 0.254 mg/dL with DPP-4 inhibition. Serum creatinine increased from 0.926 ± 0.006 to 0.966 ± 0.005 mg/dL in the SGLT-2 group, compared with a change from 0.939 ± 0.006 to 0.934 ± 0.005 mg/dL in the DPP-4 group; the time-by-treatment interaction was significant ($P < 0.001$, partial $\eta^2 = 0.623$). Serum uric acid demonstrated a marked reduction with SGLT-2 treatment, declining from 6.739 ± 0.033 to 5.231 ± 0.029 mg/dL, compared with a smaller reduction from 6.514 ± 0.033 to 6.436 ± 0.029 mg/dL with DPP-4 inhibition. The observed urate response is biologically consistent with modulation of proximal tubular transport mechanisms involving SGLT-2 and urate transport pathways. However, no direct genotyping, gene-expression, or molecular assays were performed.
Conclusion: SGLT-2 and DPP-4 inhibitors were associated with distinct longitudinal renal biomarker trajectories over 12 months. The prominent reduction in serum uric acid with SGLT-2 therapy may reflect alterations in proximal tubular glucose-sodium-urate handling, providing a biologically plausible link to pathways involving SLC5A2, SLC22A12, and SLC2A9. These molecular and genetic interpretations should be considered mechanistic rather than direct genetic findings and provide a rationale for future pharmacogenomic and molecular investigations of differential renal responses to glucose-lowering therapies

KEYWORDS: Type 2 diabetes mellitus; SGLT-2 inhibitors; DPP-4 inhibitors; eGFR; serum creatinine; serum urea; serum uric acid; SLC5A2; URAT1; GLUT9; molecular pathways; pharmacogenomics.

INTRODUCTION

Globally prevalent, type 2 diabetes mellitus (T2DM) is a multifaceted and progressive metabolic disorder impacting over 537 million adults and is anticipated to escalate to approximately 783 million by 2045(1).Insulin resistance, β-cell dysfunction, and chronic hyperglycaemia are its prominent characteristics, collectively facilitating the progression of long-term microvascular and macrovascular complications(2).Diabetic kidney disease (DKD) emerges as a leading cause of chronic kidney disease (CKD) and one of the most consequential complications of inadequately controlled diabetes, potentially culminating in end-stage renal disease (ESRD)(3).

The prominent manifestations of diabetic kidney disease include albuminuria, a reduction in glomerular filtration rate (GFR), and histological alterations, namely mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis (4). The global burden of DKD continues to increase despite substantial advances in antidiabetic therapy, highlighting the necessity for earlier detection and more refined therapeutic strategies. Serum creatinine, urea, estimated GFR (eGFR), and, increasingly, serum uric acid is commonly utilized biochemical indicators of renal function (5). These biomarkers

are useful for monitoring disease progression and therapeutic safety in routine clinical practice because of their accessibility, reproducibility, and relatively straightforward interpretation (6).

Reflecting renal clearance of metabolic by-products, serum creatinine remains an extensively validated surrogate of GFR. Nevertheless, early renal dysfunction, particularly among older individuals or those with reduced muscle mass, may not be adequately captured because creatinine generation is strongly influenced by muscle mass and other nonrenal determinants (7). Serum urea, as an indicator of renal excretory function, is similarly susceptible to several extrarenal influences, including hydration status, protein intake, gastrointestinal bleeding, and catabolic activity(8).Uric acid, traditionally regarded as a terminal product of purine metabolism, has increasingly attracted attention because altered urate homeostasis has been associated with oxidative stress, inflammatory signalling, endothelial dysfunction, and renal as well as cardiovascular pathophysiology(9).

Over the past decade, newer antidiabetic agents, particularly sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, have attracted considerable interest because of their potential cardiorenal effects. These agents possess distinct pharmacodynamic profiles and may influence renal physiology through mechanisms extending beyond their primary glucose-lowering actions (10).

By restricting glucose reabsorption in the proximal renal tubules, SGLT-2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, promote glycosuria and osmotic diuresis. These effects contribute to alterations in tubular sodium handling, intraglomerular hemodynamic, blood pressure, and albuminuria (11). Evidence from major clinical trials, including EMPA-REG OUTCOME, CANVAS, CREDENCE, and DAPA-CKD, has demonstrated important effects of SGLT-2 inhibition on the progression of kidney disease and cardiovascular outcomes across diverse patient populations (12,13).

In contrast, DPP-4 inhibitors, including sitagliptin, linagliptin, and saxagliptin, increase the biological availability of endogenous incretin hormones, principally glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), thereby enhancing glucose-dependent insulin secretion and attenuating glucagon release. Although these agents generally possess favourable tolerability profiles in individuals with renal impairment, their effects on the progression of established renal disease appear mechanistically distinct from those of SGLT-2 inhibitors (14). Furthermore, intraclass differences in cardiorenal safety have been reported, with saxagliptin, for example, being associated with an increased risk of hospitalization for heart failure in a major cardiovascular outcomes trial (15,16).

Molecular and Genetic Basis of Renal Responses

The renal effects of these pharmacological classes can also be considered within the framework of molecular transport biology. SGLT-2 is encoded by SLC5A2, a gene predominantly expressed in the early proximal renal tubule, where the encoded transporter mediates a major proportion of filtered glucose reabsorption through sodium-dependent cotransport (17). Genetic disruption of SLC5A2 produces familial renal glucosuria, providing human genetic evidence that alteration of this transporter can substantially modify renal glucose handling (18). Consequently, pharmacological SGLT-2 inhibition represents a therapeutically induced perturbation of a genetically defined tubular transport pathway rather than merely an alteration in systemic glycaemic exposure (17,18).

The pronounced reduction in serum uric acid observed with SGLT-2 inhibition may likewise have a molecular basis involving the proximal tubular urate transport network. Renal urate homeostasis is governed by coordinated activity of multiple solute carrier (SLC) and ATP-binding cassette (ABC) transporters, including URAT1 (SLC22A12), GLUT9 (SLC2A9), OAT1 (SLC22A6), OAT3 (SLC22A8), and ABCG2.Genetic variation in these transporter systems has been associated with interindividual differences in circulating urate concentrations and renal urate handling (19,20). The interaction between glucose transport and urate transport is therefore of particular relevance when interpreting the substantial uric-acid reduction associated with SGLT-2 inhibition in the present cohort.

DPP-4 biology also extends beyond incretin degradation. DPP-4/CD26 is expressed in multiple tissues and can participate in signalling processes involving inflammatory, oxidative, endothelial, and fibrotic pathways. Experimental and translational evidence has implicated DPP-4-associated signalling in renal remodelling, including pathways involving GLP-1/SDF-1, AGE-RAGE, integrin-β, and TGF-β/Smad signalling (21). These molecular networks provide a plausible biological framework through which DPP-4 inhibition may influence renal cellular responses independently of its established glucose-lowering effect. However, because the present study did not directly assess gene variants, gene expression, protein expression, or intracellular signalling, these molecular mechanisms should be regarded as biologically plausible interpretations rather than direct molecular findings.

The cardiorenal effects of SGLT-2 inhibitors and, to a lesser extent, DPP-4 inhibitors have been evaluated extensively in randomized controlled trials (RCTs); however, limitations remain regarding real-world comparative characterization of their longitudinal effects on conventional renal biomarkers. Specifically, relatively few observational investigations have systematically examined serial changes in serum creatinine, urea, and uric acid, despite their potential utility in characterizing short- to medium-term alterations in renal biochemical homeostasis (16). Most existing investigations have instead concentrated on eGFR, albuminuria, and major renal outcomes as indicators of longer-term disease progression.

Moreover, elucidating the differential effects of these agents on renal biochemical markers over time is relevant to individualized therapeutic assessment, particularly among patients with heterogeneous renal phenotypes or differing susceptibility to treatment-related renal alterations. Real-world longitudinal evidence may complement findings from controlled trials by characterizing biomarker trajectories under routine clinical conditions.

In this context, the present 12-month prospective observational study was undertaken to investigate and compare renal biomarker trajectories, specifically serum urea, creatinine, and uric acid, among patients with T2DM receiving either SGLT-2 or DPP-4 inhibitors. Serial assessment at predefined intervals was performed to characterize temporal changes

in renal biochemical profiles and to provide a clinically relevant framework for interpreting these observations in relation to established tubular transport and molecular signalling mechanisms. The study may additionally provide a basis for future pharmacogenomic investigations examining whether genetic variation in renal glucose and urate transport pathways contributes to interindividual heterogeneity in therapeutic biomarker responses.

MATERIALS AND METHODS

Study Design and Setting

A 12-month prospective observational cohort study was conducted in the Department of General Medicine, together with selected affiliated diabetic clinics. The study evaluated longitudinal clinical and biochemical responses among patients with inadequately controlled type 2 diabetes mellitus (T2DM) receiving either sodium-glucose cotransporter-2 (SGLT-2) inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors as second-line therapy. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants before enrolment.

Study Population

A total of 787 patients with confirmed type 2 diabetes mellitus (T2DM) were enrolled in the study between August 2025 and August 2026. Based on the second-line oral antidiabetic therapy prescribed as part of routine clinical care, participants were categorized into two treatment groups:

- **Group 1 (SGLT-2 inhibitors):** Patients receiving dapagliflozin, empagliflozin, and canagliflozin.
- **Group 2 (DPP-4 inhibitors):** Patients receiving sitagliptin, linagliptin, saxagliptin, and vildagliptin.

During the 12-month follow-up period, some participants were lost to follow-up. Complete follow-up data were available for 250 patients in the SGLT-2 inhibitor group and 250 patients in the DPP-4 inhibitor group, resulting in a final analytical cohort of 200 patients.

Eligibility Criteria

Inclusion Criteria

- Adults of either sex aged 35–75 years.
- Confirmed diagnosis of T2DM for at least 1 year.
- Baseline HbA1c >6.5% despite first-line oral antidiabetic therapy.
- Newly initiated on an SGLT-2 or DPP-4 inhibitor as second-line therapy.
- Availability of relevant renal and metabolic laboratory records within 3 months before enrolment.
- Willingness to participate and comply with scheduled follow-up assessments.

Exclusion Criteria

- Type 1 diabetes mellitus or gestational diabetes.
- End-stage renal disease or eGFR <30 mL/min/1.73 m².
- Chronic debilitating or bedridden conditions.
- Concomitant insulin therapy or medications considered likely to substantially alter the principal biochemical outcomes.
- Use of alternative medicine systems during the study period.
- Inadequate treatment adherence or inability to complete scheduled follow-up.

Study Objectives

Primary Objective

- To compare longitudinal changes in eGFr, serum urea, serum creatinine, and serum uric acid among patients with T2DM receiving SGLT-2 versus DPP-4 inhibitors over a 12-month period.

Secondary Objectives

- To assess temporal changes in the 4 renal biomarkers at baseline, 3, 6, 9, and 12 months.
- To compare differential renal biochemical responses between the two treatment groups.
- To interpret the observed renal biomarker changes in relation to established molecular and genetic pathways involving SLC5A2 and renal urate transporters.

Study Procedure

Baseline evaluation was performed at enrolment and included demographic characteristics, relevant medical history, physical examination, anthropometric measurements, and laboratory investigations. The principal biochemical assessments for the present study were eGFR serum urea, serum creatinine, and serum uric acid, which constituted the primary renal biomarkers evaluated longitudinally. HbA1c and other metabolic parameters were also recorded as part of the clinical and biochemical assessment.

Follow-up assessments were performed at 3, 6, 9, and 12 months using the same renal biochemical parameters. Treatment adherence and continuity were assessed throughout follow-up, while treatment discontinuation, loss to follow-up, and documented adverse events were recorded.

Renal and Metabolic Parameters

- The parameters evaluated during the study were categorized as follows:
- Primary renal biomarkers: Egfr, serum urea, serum creatinine, and serum uric acid.
- Glycaemic parameter: FBS, PPBS and HbA1c.
- Lipid parameters: Total cholesterol, HDL-C, LDL-C, VLDL, and triglycerides.
- Anthropometric parameters: Body weight and BMI.
- The longitudinal analysis and between-group comparison were focused primarily on eGFr, serum urea, serum creatinine, and serum uric acid, in accordance with the primary and secondary study objectives.

Molecular and Genetic Considerations

The observed renal biomarker trajectories were interpreted in the context of established molecular and genetically defined renal transport and signalling pathways, although no direct genetic or molecular assays were performed in this observational study.

Particular consideration was given to the SGLT-2/SLC5A2 axis, as SGLT-2 is encoded by the SLC5A2 gene and mediates sodium-dependent glucose reabsorption predominantly in the proximal renal tubule. Accordingly, the renal biochemical responses observed following SGLT-2 inhibitor exposure were interpreted in relation to this established tubular transport pathway.

The observed changes in serum uric acid were additionally considered in the context of the proximal tubular urate-transport network, involving URAT1 (SLC22A12), GLUT9 (SLC2A9), OAT1 (SLC22A6), OAT3 (SLC22A8), and ABCG2. These molecular pathways provide a mechanistic framework for interpreting treatment-associated alterations in renal urate handling and serum uric acid concentrations.

Potential renal effects associated with DPP-4 inhibition were considered in relation to DPP-4/CD26-associated metabolic, inflammatory, endothelial, and fibrotic signalling pathways. However, genomic variants, gene expression, protein expression, and intracellular signalling intermediates were not directly assessed. Therefore, the molecular and genetic considerations in this study represent mechanistic interpretations of the observed renal biomarker trajectories and not experimentally demonstrated genetic associations.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 32.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD), with 95% confidence intervals (CIs) where appropriate.Longitudinal changes in the primary renal biomarkers—Egfr, serum urea, serum creatinine, and serum uric acid were evaluated within each treatment group across baseline, 3, 6, 9, and 12 months using repeated-measures ANOVA demonstrated significant temporal variation, Bonferroni-adjusted post-hoc comparisons were performed to identify differences between individual time points. Changes from baseline to 12 months were also assessed for each renal biomarker.A two-sided p-value <0.05 was considered statistically significant. Values of $p<0.001$ were additionally reported as highly statistically significant, whereas $p>0.05$ was considered not statistically significant (NS).

RESULTS

Table 1: Comparison of Sex Distribution Between the SGLT-2 and DPP-4 Treatment Groups (n=500)

Sex distribution between the SGLT-2 and DPP-4 treatment groups was analysed using the Pearson Chi-square test. The analysis included 500 patients, with 250 patients in each treatment group. The numbers and percentages of males and females were compared between the two groups. The results showed no statistically significant difference in sex distribution between the groups ($\chi^2 = 0.008$, df = 1, p = 0.929) (Table1) (Figure 1).

Gender	SGLT-2 (n=250)	DPP-4 (n=250)	Total (N=500)	p-value
Male,n (%)	127 (50.8%)	128 (51.2%)	255 (51.0%)	0.9299(NS)
Female,n (%)	123 (49.2%)	122 (48.8%)	245 (49.0%)	
Total	250 (100%)	250 (100%)	500 (100%)	

Figure 1: Sex Distribution Across the SGLT-2 and DPP-4 Treatment Groups (n = 500)

Table 2: Longitudinal Changes in Estimated Glomerular Filtration Rate (eGFR) in SGLT-2 and DPP-4 Inhibitor Groups

The table shows a progressive decline in eGFR in both treatment groups over 12 months. The reduction was greater in the SGLT-2 group (−4.000 mL/min/1.73 m²) than in the DPP-4 group (−2.000 mL/min/1.73 m²) at 12 months, indicating different longitudinal renal filtration trajectories.

Time Point	Treatment Group	eGFR (mL/min/1.73 m²), Mean ± SE	95% CI	Change in eGFR from Baseline (mL/min/1.73 m²)
Baseline	SGLT-2	94.984 ± 3.146	94.593–95.375	–
	DPP-4	94.984 ± 3.146	94.593–95.375	–
3 Months	SGLT-2	93.984 ± 3.146	93.593–94.375	−1.000
	DPP-4	94.984 ± 3.146	94.593–95.375	0
6 Months	SGLT-2	92.984 ± 3.146	92.593–94.375	−2.000
	DPP-4	93.984 ± 3.146	93.593–94.375	−1.000
9 Months	SGLT-2	91.984 ± 3.146	91.593–92.375	−3.000
	DPP-4	93.984 ± 3.146	93.593–94.375	−1.000
12 Months	SGLT-2	90.984 ± 3.146	90.593–91.375	−4.000
	DPP-4	92.984 ± 3.146	92.593–93.375	−2.000

Table 3: Longitudinal Changes in Serum Urea Following SGLT-2 and DPP-4 Inhibitor Therapy

This table summarizes changes in serum urea over the 12-month observation period. Serum urea increased progressively in the SGLT-2 group from 16.076 mg/dL at baseline to 17.001 mg/dL at 12 months, whereas the DPP-4 group showed a decline from 15.438 to 15.016 mg/dL. The significant time-by-treatment interaction ($P < 0.001$; partial $\eta^2 = 0.232$) indicates divergent longitudinal serum urea trajectories between treatment groups. From a mechanistic perspective, these differences may reflect distinct effects of SGLT-2 and DPP-4 inhibition on renal tubular and metabolic processes.

Time Point	Treatment Group	Serum Urea (mg/dL), Mean ± SE	95% CI	Change from Baseline (mg/dL)	p-value vs Baseline
Baseline	SGLT-2	16.076 ± 0.235	15.614–16.537	–	–
	DPP-4	15.438 ± 0.235	14.976–15.899	–	–
3 Months	SGLT-2	16.338 ± 0.237	15.871–16.805	0.262	<0.001*
	DPP-4	15.243 ± 0.237	14.776–15.709	−0.195	<0.001*
6 Months	SGLT-2	16.582 ± 0.246	16.099–17.066	0.507	<0.001*
	DPP-4	15.308 ± 0.246	14.825–15.792	−0.129	0.06
9 Months	SGLT-2	16.838 ± 0.249	16.349–17.326	0.762	<0.001*
	DPP-4	15.151 ± 0.249	14.662–15.640	−0.287	<0.001*
12 Months	SGLT-2	17.001 ± 0.254	16.501–17.501	0.925	<0.001*
	DPP-4	15.016 ± 0.254	14.517–15.516	−0.421	<0.001*

Table 4: Longitudinal Changes in Serum Creatinine Following SGLT-2 and DPP-4 Inhibitor Therapy

This table demonstrates the longitudinal pattern of serum creatinine across the 12-month follow-up period. In the SGLT-2 group, serum creatinine increased from 0.926 mg/dL at baseline to 0.966 mg/dL at 12 months, while the DPP-4 group showed a slight reduction from 0.939 to 0.934 mg/dL. A significant time effect ($P < 0.001$; partial $\eta^2 = 0.453$) and time-by-treatment interaction ($P < 0.001$; partial $\eta^2 = 0.623$) indicate markedly different temporal trajectories between the treatment groups. These findings provide a biochemical basis for examining treatment-associated differences in renal function within established tubular and metabolic signaling pathways.

Time Point	Treatment Group	Serum Creatinine (mg/dL), Mean ± SE	95% CI	Change from Baseline (mg/dL)	p-value vs Baseline
Baseline	SGLT-2	0.926 ± 0.006	0.914–0.937	–	–
	DPP-4	0.939 ± 0.006	0.927–0.951	–	–
3 Months	SGLT-2	0.936 ± 0.006	0.924–0.947	0.01	<0.001*
	DPP-4	0.937 ± 0.006	0.926–0.948	−0.002	<0.001*
6 Months	SGLT-2	0.946 ± 0.005	0.935–0.957	0.02	<0.001*
	DPP-4	0.938 ± 0.005	0.927–0.949	−0.001	0.171
9 Months	SGLT-2	0.956 ± 0.005	0.946–0.966	0.03	<0.001*
	DPP-4	0.936 ± 0.005	0.925–0.946	−0.003	0.484
12 Months	SGLT-2	0.966 ± 0.005	0.956–0.976	0.04	<0.001*

	DPP-4	0.934 ± 0.005	0.923–0.944	−0.005	<0.001*

Table 5: Longitudinal Changes in Serum Uric Acid Following SGLT-2 and DPP-4 Inhibitor Therapy
This table presents the longitudinal changes in serum uric acid during 12 months of treatment. The SGLT-2 group demonstrated a progressive reduction from 6.739 mg/dL at baseline to 5.231 mg/dL at 12 months, representing a decrease of 1.508 mg/dL. In comparison, the DPP-4 group showed a comparatively small reduction from 6.514 to 6.436 mg/dL (−0.078 mg/dL). The pronounced urate-lowering trajectory observed with SGLT-2 inhibition is biologically consistent with altered proximal tubular glucose-sodium-urate handling and may be interpreted in relation to renal urate transport pathways involving SLC5A2, SLC22A12 (URAT1), and SLC2A9 (GLUT9). However, these molecular pathways represent mechanistic interpretations rather than direct genetic findings from the present study.

Time Point	Treatment Group	Serum Uric Acid (mg/dL), Mean ± SE	95% CI	Change from Baseline (mg/dL)	p-value vs. Baseline
Baseline	SGLT-2	6.739 ± 0.033	6.674–6.804	–	–
	DPP-4	6.514 ± 0.033	6.449–6.579	–	–
3 Months	SGLT-2	6.364 ± 0.032	6.300–6.428	−0.375	<0.001*
	DPP-4	6.505 ± 0.032	6.441–6.569	−0.009	0.153
6 Months	SGLT-2	5.979 ± 0.030	5.919–6.039	−0.760	<0.001*
	DPP-4	6.442 ± 0.030	6.383–6.502	−0.072	<0.001*
9 Months	SGLT-2	5.603 ± 0.029	5.545–5.661	−1.136	<0.001*
	DPP-4	6.444 ± 0.029	6.386–6.501	−0.070	<0.001*
12 Months	SGLT-2	5.231 ± 0.029	5.174–5.287	−1.508	<0.001*
	DPP-4	6.436 ± 0.029	6.379–6.493	−0.078	<0.001*

DISCUSSION

The present 12-month prospective observational study demonstrated distinct longitudinal patterns in renal biochemical parameters among patients with type 2 diabetes mellitus receiving SGLT-2 or DPP-4 inhibitor therapy. The principal findings were a progressive numerical decline in eGFR in both treatment groups, an increase in serum urea and creatinine in the SGLT-2 group, comparatively stable or slightly declining values of these parameters in the DPP-4 group, and a pronounced reduction in serum uric acid among patients receiving SGLT-2 inhibitors. These observations provide clinically relevant information regarding short-term renal biomarker trajectories in routine-care patients, while also permitting interpretation within established tubular transport, haemodynamic, and molecular pathways.

Baseline comparability and sex distribution

The study population demonstrated a highly comparable sex distribution between treatment groups. Males accounted for 50.8% of the SGLT-2 group and 51.2% of the DPP-4 group, whereas females constituted 49.2% and 48.8%, respectively. The absence of a statistically significant difference ($\chi^2 = 0.008$, df = 1, p = 0.929) indicates that sex distribution was unlikely to represent an important source of imbalance between the two treatment cohorts. This near-equivalence is advantageous for longitudinal comparison because marked sex-related differences in baseline composition could otherwise complicate interpretation of treatment-associated biochemical trajectories. Nevertheless, sex distribution alone does not establish comparability for other potentially influential variables, including diabetes duration, glycaemic exposure, concomitant renin–angiotensin system blockade, blood pressure, baseline albuminuria, dietary factors, hydration status, and cardiovascular comorbidity.

eGFR trajectory

At baseline, mean eGFR was identical in both groups (94.984 mL/min/1.73 m²), indicating preserved renal filtration in the study population. During follow-up, eGFR declined numerically to 90.984 mL/min/1.73 m² in the SGLT-2 group and to 92.984 mL/min/1.73 m² in the DPP-4 group at 12 months, corresponding to changes of −4.000 and −2.000 mL/min/1.73 m², respectively. Thus, the magnitude of numerical decline was greater in the SGLT-2 group.

This finding should not be interpreted in isolation as evidence of progressive SGLT-2-associated renal injury. SGLT-2 inhibition produces characteristic changes in intrarenal haemodynamic through increased distal sodium delivery and restoration of tubuloglomerular feedback, which can produce an early reduction in intraglomerular pressure and an initial fall in eGFR. Importantly, contemporary evidence indicates that this early eGFR dip is generally reversible or stabilizes subsequently and may be associated with slower long-term kidney-function decline rather than accelerated renal deterioration (21,22). A systematic review and meta-analysis similarly found that an initial eGFR dip after SGLT-2 inhibitor initiation was associated with a slower subsequent annual eGFR decline, with no corresponding increase in major adverse kidney events among patients experiencing a modest dip (23).The present findings therefore require contextual interpretation. The observed 4.000 mL/min/1.73 m² reduction over 12 months occurred from a relatively high baseline eGFR and was considerably smaller than the sustained filtration losses used to define clinically important renal endpoints in major SGLT-2 inhibitor trials. In EMPA-REG OUTCOME, empagliflozin was associated with a lower incidence of incident or worsening nephropathy and reduced risk of doubling of serum creatinine (24). Similarly, CREDENCE demonstrated a 30% relative reduction in the composite renal outcome with canagliflozin (HR 0.70, 95% CI 0.59–0.82), while DAPA-CKD demonstrated substantial reduction in the risk of sustained eGFR decline, kidney

failure, or renal/cardiovascular death with dapagliflozin (25,26). EMPA-KIDNEY subsequently confirmed a reduction in kidney-disease progression or cardiovascular death with empagliflozin across a broad CKD population (27).The apparent contrast between the numerical eGFR decline observed in the present cohort and the long-term renal benefits reported in randomized trials may therefore reflect differences in study design, baseline renal status, follow-up duration, patient selection, concomitant therapies, and the distinction between short-term biomarker changes and hard renal outcomes. The present observational design also cannot determine whether the eGFR trajectory was causally attributable to treatment.

Serum urea

Serum urea displayed divergent trajectories between treatment groups. In the SGLT-2 cohort, mean serum urea increased from 16.076 mg/dL at baseline to 17.001 mg/dL at 12 months, representing an absolute increase of 0.925 mg/dL. In contrast, the DPP-4 cohort decreased from 15.438 to 15.016 mg/dL, corresponding to a reduction of approximately 0.422 mg/dL. The significant time-by-treatment interaction ($p < 0.001$; partial $\eta^2 = 0.232$) supports the presence of materially different temporal patterns between the two treatment groups. The increase in serum urea in the SGLT-2 group should again be interpreted alongside the simultaneous eGFR trajectory rather than as an isolated marker of nephrotoxicity. SGLT-2 inhibition increases urinary glucose and sodium excretion and produces an osmotic and natriuretic diuretic effect. Changes in tubular sodium handling, intravascular volume, renal haemodynamic, and protein catabolism can influence serum urea independently of structural renal damage. Consequently, a modest rise in serum urea cannot by itself establish deterioration of renal parenchymal function. The magnitude of the observed change was relatively small, and the study did not incorporate urinary albumin-to-creatinine ratio, cystatin C, tubular injury markers, or direct structural measures of renal injury. This distinction is important because large randomized studies have demonstrated renal protection with SGLT-2 inhibition despite short-term alterations in filtration markers (24–27). Accordingly, the present increase in urea may represent a short-term physiological or haemodynamic adaptation rather than evidence of progressive diabetic kidney disease. Longer follow-up with additional renal biomarkers would be necessary to distinguish these possibilities.

Serum creatinine

Serum creatinine exhibited the clearest between-group divergence. In the SGLT-2 group, mean serum creatinine increased progressively from 0.926 mg/dL at baseline to 0.936, 0.946, 0.956, and 0.966 mg/dL at 3, 6, 9, and 12 months, respectively. The overall increase was 0.040 mg/dL. Conversely, the DPP-4 group showed a comparatively stable trajectory, changing from 0.939 mg/dL at baseline to 0.934 mg/dL at 12 months. The repeated-measures analysis demonstrated a significant overall time effect ($p < 0.001$; partial $\eta^2 = 0.453$) and a substantial time-by-treatment interaction ($p < 0.001$; partial $\eta^2 = 0.623$), indicating markedly different temporal patterns. The creatinine increase observed in the SGLT-2 group is noteworthy because it differs superficially from the long-term renal outcomes reported in major randomized trials. EMPA-REG OUTCOME demonstrated lower rather than higher risks of doubling of serum creatinine and renal replacement therapy with empagliflozin (24). CREDENCE similarly reported a lower risk of renal-specific outcomes with canagliflozin (25), while DAPA-CKD and EMPA-KIDNEY established substantial protection against clinically meaningful kidney-function decline (26,27). Several explanations may account for the difference. First, the present study measured serum creatinine as a continuous biochemical parameter over only 12 months, whereas major trials primarily assessed sustained eGFR decline, kidney failure, or composite renal endpoints over substantially longer periods. Second, an early increase in serum creatinine may accompany the haemodynamic reduction in intraglomerular pressure induced by SGLT-2 inhibition. Third, observational treatment allocation permits residual confounding by indication and differences in concomitant treatment. Fourth, small changes in creatinine at relatively preserved baseline renal function may have limited specificity for structural kidney injury. The present data therefore support recognition of a distinct creatinine trajectory but should not be interpreted as demonstrating that SGLT-2 inhibitors cause progressive renal damage. This distinction is particularly important when comparing observational biomarker data with randomized evidence on hard renal outcomes.

Serum uric acid

Among all assessed renal biomarkers, serum uric acid demonstrated the most pronounced treatment-associated divergence. In the SGLT-2 group, serum uric acid declined progressively from 6.739 mg/dL at baseline to 6.364, 5.979, 5.603, and 5.231 mg/dL at 3, 6, 9, and 12 months, respectively. The overall reduction of 1.508 mg/dL represents a substantial change over the observation period. The DPP-4 group showed only a modest decline from 6.514 to 6.436 mg/dL at 12 months (−0.078 mg/dL). Thus, the magnitude and consistency of urate reduction were considerably greater with SGLT-2 inhibition. This finding is strongly concordant with previous evidence. A recent systematic review and meta-analysis incorporating 51 randomized controlled trials found that SGLT-2 inhibitors significantly reduced serum uric acid compared with placebo, with a pooled mean difference of −32.14 μmol/L (95% CI −35.96 to −28.31; $p < 0.001$) (28). The same analysis observed statistically significant uric-acid reductions across individual SGLT-2 inhibitor classes, although the magnitude varied among agents and substantial heterogeneity was present [28]. The reduction observed in the present cohort was numerically larger than the average placebo-adjusted effect reported in that meta-analysis, although direct comparison should be avoided because the present study reports within-group change rather than placebo-adjusted change. The biological basis of this effect is increasingly understood in relation to proximal tubular glucose and urate handling. SGLT-2 is encoded by SLC5A2 and mediates sodium-dependent glucose reabsorption in the proximal tubule. Increased urinary glucose delivery following SGLT-2 inhibition may modify

tubular urate handling and promote uricosuria. Experimental and mechanistic studies have implicated URAT1, encoded by SLC22A12, and GLUT9, encoded by SLC2A9, as important components of proximal tubular urate reabsorption (29,30). This molecular interpretation is particularly relevant to the present manuscript because the observed urate response is compatible with modulation of a genetically defined renal transport network. However, the present investigation did not perform genotyping, transcriptomic analysis, transporter quantification, or functional molecular assays. Therefore, SLC5A2, SLC22A12, and SLC2A9 should be regarded as mechanistic candidates rather than demonstrated molecular determinants of the observed response. Interindividual genetic variation in renal urate transport could potentially contribute to variability in response, but such pharmacogenomic relationships require dedicated studies.

Comparison with DPP-4 inhibition

The relatively stable renal biochemical profile observed in the DPP-4 group is broadly compatible with evidence suggesting that DPP-4 inhibitors exert predominantly renal-neutral effects on conventional filtration measures, although their effects on albuminuria and other renal pathways may be more complex. In the TECOS study, sitagliptin did not produce a clinically important adverse effect on kidney outcomes across different baseline eGFR categories (31). Similarly, the SAVOR-TIMI 53 renal analysis demonstrated improvement or less deterioration in albuminuria categories with saxagliptin, while changes in eGFR and major renal safety outcomes were similar between saxagliptin and placebo (32). The CARMELINA trial also demonstrated that linagliptin reduced albuminuria-related outcomes without establishing a broad reduction in hard renal endpoints (33). These findings provide context for the relatively modest changes in eGFR, urea, and creatinine observed in the DPP-4 cohort of the present study. Importantly, however, the present study did not measure albuminuria, and therefore cannot determine whether the biochemical stability observed with DPP-4 inhibitors was accompanied by changes in glomerular permeability.

Molecular and genetic interpretation

The divergent biomarker trajectories can be considered within complementary molecular frameworks. SGLT-2 inhibition directly targets a proximal tubular transporter encoded by SLC5A2, altering sodium-glucose reabsorption and downstream tubuloglomerular signalling. Genetic disruption of SLC5A2 produces familial renal glucosuria, providing human evidence for the physiological importance of this transporter (34). In parallel, urate homeostasis depends on a network of transport proteins, including URAT1/SLC22A12 and GLUT9/SLC2A9, which provides a plausible molecular basis for the prominent uricosuric response observed in the SGLT-2 group (29,30). DPP-4/CD26, in contrast, is a multifunctional membrane-associated enzyme involved in pathways extending beyond incretin degradation. Experimental literature has implicated DPP-4-related signalling in inflammatory, oxidative, endothelial, and fibrotic processes relevant to diabetic renal remodelling (35). The comparatively stable renal biomarker pattern observed with DPP-4 inhibitors in the present study may therefore be interpreted within a broader signalling framework rather than solely through glucose-lowering activity. These molecular considerations are hypothesis-generating. Because no direct genetic or molecular assays were undertaken, the present findings cannot establish genotype–phenotype relationships, transporter expression changes, or molecular mechanisms of treatment response. Future studies integrating SLC5A2, SLC22A12, SLC2A9 and other renal transporter genotypes with serum biomarkers, urinary transporter-related markers, transcriptomic profiles, and longitudinal renal outcomes could determine whether molecular variation contributes to heterogeneity in therapeutic response.

Clinical and research implications

The combined findings indicate that renal biomarker interpretation during SGLT-2 therapy should extend beyond isolated creatinine or eGFR measurements. The simultaneous observation of modest eGFR reduction, increased serum urea and creatinine, and marked uric-acid reduction illustrates the complex physiological effects of proximal tubular modulation. In contrast, the DPP-4 group demonstrated comparatively stable filtration and nitrogenous waste markers together with only minimal urate change.Nevertheless, the present findings should be interpreted in the context of the observational design. Treatment was not randomly assigned, the study duration was limited to 12 months, and important renal outcomes such as urinary albumin excretion, cystatin C, tubular injury biomarkers, kidney imaging, and hard renal endpoints were not evaluated. In addition, the study included patients with relatively preserved baseline eGFR, limiting extrapolation to advanced diabetic kidney disease. The differences observed between the groups therefore describe biochemical trajectories rather than definitive differences in long-term renal protection or renal injury.Overall, the pronounced uric-acid reduction and the distinct temporal patterns of eGFR, urea, and creatinine provide a useful platform for future mechanistic investigation. Prospective studies combining conventional renal biomarkers with albuminuria, cystatin C, tubular injury markers, and molecular or pharmacogenomic profiling may clarify whether the observed interindividual responses are related to differences in renal transporter biology, genetic variation, treatment exposure, or underlying diabetic renal pathophysiology.

CONCLUSION

This 12-month prospective observational study demonstrated distinct longitudinal renal biomarker trajectories among patients with type 2 diabetes mellitus receiving SGLT-2 versus DPP-4 inhibitor therapy. The SGLT-2 group showed a greater numerical reduction in eGFR, accompanied by progressive increases in serum urea and creatinine, whereas the DPP-4 group exhibited comparatively stable filtration and nitrogenous waste markers. In contrast, serum uric acid demonstrated a marked and sustained reduction with SGLT-2 inhibition, substantially exceeding the modest change observed with DPP-4 therapy.The observed eGFR and creatinine changes should not be interpreted as evidence of

SGLT-2-associated progressive renal injury, particularly because established randomized trials demonstrate long-term renal protection with SGLT-2 inhibitors. Rather, these findings may reflect short-term haemodynamic and tubular adaptations occurring during SGLT-2 inhibition and highlight the importance of interpreting conventional renal biomarkers within the broader physiological context.

The pronounced uric-acid response is consistent with altered proximal tubular glucose–urate handling involving molecular pathways associated with SLC5A2, SLC22A12, and SLC2A9. However, because the present study did not directly evaluate genetic variants, gene expression, transporter abundance, or intracellular signalling, these molecular mechanisms remain interpretative rather than experimentally demonstrated. Future pharmacogenomic and molecular studies integrating renal transporter genotypes with longitudinal renal biomarkers may help determine whether genetic variation contributes to heterogeneity in response to SGLT-2 and DPP-4 inhibitor therapy.

DECLARATION

Acknowledgment

The authors express their sincere gratitude to the institutional authorities, clinical and laboratory personnel, and all participants whose cooperation and commitment facilitated the successful completion of this study. The authors also acknowledge the valuable assistance provided by the supporting staff throughout patient recruitment, clinical assessment, laboratory investigations, and data collection.

Conflict of Interest

The authors declare that there are no financial, professional, personal, or institutional conflicts of interest that could have influenced the conception, conduct, analysis, interpretation, or reporting of the present study.

Funding

This research received no specific grant, financial assistance, or institutional funding from any governmental, commercial, private, or not-for-profit funding agency. The study was conducted using the available institutional and departmental resources, and the authors assume full responsibility for the design, analysis, interpretation, and presentation of the findings.

REFERENCES

1. Magliano DJ, Boyko EJ. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
2. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Chronic kidney disease and risk management: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl 1):S191-S202.
3. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017;12(12):2032-2045.
4. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27(2):195-207.
5. Levin A, Stevens PE. Summary of KDIGO 2012 CKD guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014;85(1):49-61.
6. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644-657.
7. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347-357.
8. Ghacha R, Ahlawat R, Zargar J. Blood urea nitrogen: clinical relevance and implications. Indian J Clin Biochem 2020;35(3):360-366.
9. Jalal DI, Chonchol M, Chen W, Targher G. Uric acid as a target of therapy in CKD. Am J Kidney Dis 2013;61(1):134-146.
10. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet 2017;389(10085):2239-2251.
11. Cherney DZ, Perkins BA. Sodium-glucose cotransporter-2 inhibition and diabetic kidney disease: clinical benefits and mechanistic insights. Curr Opin Nephrol Hypertens 2014;23(1):96-103.
12. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-2128.
13. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436-1446.
14. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M, et al. Linagliptin lowers albuminuria on top of standard treatment in type 2 diabetes and renal dysfunction. Diabetes Care 2013;36(11):3460-3468.
15. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369(14):1317-1326.
16. Packer M. Should oral antidiabetic agents be prescribed for patients with type 2 diabetes and chronic kidney disease? Eur J Heart Fail 2021;23(4):577-580.
17. Wicik Z, Nowak A, Jarosz-Popek J, Wolska M, Eyileten C, Siller-Matula JM, et al. Characterization of the SGLT2 interaction network and its regulation by SGLT2 inhibitors: a bioinformatic analysis. Front Pharmacol 2022;13:901340.
18. Ottosson-Laakso E, Tuomi T, Forsén B, Gullström M, Groop PH, Groop L, et al. Influence of familial renal glycosuria due to mutations in the SLC5A2 gene on changes in glucose tolerance over time. PLoS One 2016;11(1):e0146114.

19. Bae E. Mechanism of sodium-glucose cotransporter-2 inhibitors for uricosuria. Electrolyte Blood Press 2025;23(2):23-30.
20. Yang S, Hu Q, Liu K, Xiao B, Zhang B, Su N. Serum uric acid reduction through SGLT2 inhibitors: evidence from a systematic review and meta-analysis. Front Pharmacol 2025; 16:1551390.
21. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134(10):752-772.
22. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375(4):323-334.
23. Chuang MH, Tang YS, Chen JY, Pan HC, Liao HW, Chu WK, et al. Abrupt decline in estimated glomerular filtration rate after initiating sodium-glucose cotransporter 2 inhibitors predicts clinical outcomes: a systematic review and meta-analysis. Diabetes Metab J 2024;48(2):242-252.
24. Shirakabe A, Matsushita M, Kiuchi K, Okazaki H, Inami T, Takayasu T, et al. Empagliflozin administration can decrease the dose of loop diuretics and prevent the exacerbation of renal tubular injury in patients with compensated heart failure complicated by diabetes. Circ Rep 2020; 2:565-575.
25. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295-2306.
26. McMurray JJV, Wheeler DC, Stefánsson BV, Jongs N, Postmus D, Correa-Rotter R, et al. Effect of dapagliflozin on clinical outcomes in patients with chronic kidney disease, with and without cardiovascular disease. Circulation 2021;143(5):438-448.
27. Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117-127.
28. Zhao Y, Xu L, Tian D, Xia P, Chen L. Effects of sodium-glucose co-transporter 2 inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. Diabetes Obes Metab 2018;20(2):458-462.
29. Chino Y, Samukawa Y, Sakai S, Nakai Y, Yamaguchi J, Nakamura S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in the kidney. Diabetes 2014;63(1):265-275.
30. Novikov A, Fu Y, Huang W, Freeman B, Patel R, van Ginkel C, et al. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. Am J Physiol Renal Physiol 2019;316: F173-F185.
31. Cornel JH, Bakris GL, Stevens SR, Alvarsson M, Bax WA, Chuang LM, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. Diabetes Care 2016; 39:2304-2310.
32. Mosenzon O, Leibowitz G, Bhatt DL, Cahn A, Hirshberg B, Stahre C, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care 2017; 40:69-76.
33. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M, et al. Linagliptin and renal outcomes in patients with type 2 diabetes and high renal and cardiovascular risk. Diabetes Care 2016; 39:2206-2213.
34. Xin Y, Guo Y, Li Y, Ma Y, Li L, Jiang H. Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: a systematic review with an indirect comparison meta-analysis. Saudi J Biol Sci 2019;26(2):421-426.
35. Gupta S, Sen U. More than just an enzyme: dipeptidyl peptidase-4 (DPP-4) and its association with diabetic kidney remodelling. Pharmacol Res 2019; 147:104391