

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

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ABSTRACT:

Background: Type 2 diabetes mellitus (T2DM) is associated with progressive changes in renal function and tubular homeostasis. SGLT-2 and DPP-4 inhibitors have distinct effects on renal haemodynamic and tubular transport. This study compared longitudinal renal biomarker trajectories between patients receiving SGLT-2 and DPP-4 inhibitors over 12 months.

Methods: A 12-month prospective observational study included **500 patients with T2DM**, with 250 receiving SGLT-2 inhibitors and 250 receiving DPP-4 inhibitors. Estimated glomerular filtration rate (eGFR), serum urea, creatinine, and uric acid were assessed at baseline and 3, 6, 9, and 12 months. Changes over time were evaluated using repeated-measures ANOVA with Bonferroni-adjusted comparisons. Molecular interpretation considered established pathways involving SLC5A2, SLC22A12 (URAT1), and SLC2A9 (GLUT9).

Results: Baseline eGFR was 94.984 ± 3.146 mL/min/1.73 m² in the SGLT-2 group and 95.876 ± 3.146 mL/min/1.73 m² in the DPP-4 group. At 12 months, eGFR decreased to 90.984 ± 3.470 (change -4.000 ; $p < 0.001$) and 93.876 ± 3.420 (change -2.000 ; $p < 0.001$), respectively. Serum urea increased from 16.076 ± 4.655 to 17.001 ± 5.347 mg/dL with SGLT-2 therapy, while decreasing from 15.438 ± 2.425 to 15.016 ± 1.942 mg/dL with DPP-4 therapy. Creatinine increased from 0.926 ± 0.069 to 0.966 ± 0.068 mg/dL in the SGLT-2 group and changed from 0.939 ± 0.113 to 0.934 ± 0.094 mg/dL in the DPP-4 group. Uric acid decreased substantially with SGLT-2 therapy (6.739 ± 0.465 to 5.231 ± 0.343 mg/dL; -1.508 ; $p < 0.001$) compared with DPP-4 therapy (6.514 ± 0.577 to 6.436 ± 0.546 mg/dL; -0.078 ; $p < 0.001$).

Conclusion: SGLT-2 and DPP-4 inhibitors demonstrated distinct renal biomarker trajectories. The marked uric-acid reduction with SGLT-2 therapy is biologically compatible with altered proximal tubular urate handling. The observed changes represent short-term biochemical trajectories and do not establish progressive renal injury. Molecular interpretations remain hypothesis-generating because direct genetic or molecular assays were not performed.

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 hyperglycemia 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 signaling, 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 favorable 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 glycemic 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 signaling processes involving inflammatory, oxidative, endothelial, and fibrotic pathways. Experimental and translational evidence has implicated DPP-4-associated signaling in renal remodeling, including pathways involving GLP-1/SDF-1, AGE-RAGE, integrin- β , and TGF- β /Smad signaling (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 signaling, 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.

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 signaling pathways. However, genomic variants, gene expression, protein expression, and intracellular signaling 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 $\pm$ 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 Gender Distribution Between the SGLT-2 and DPP-4 Treatment Groups (n=500)

Gender distribution was compared between the SGLT-2 and DPP-4 treatment groups among the **500 enrolled patients**, with **250 patients in each group**. In the SGLT-2 group, **127 patients (50.8%) were male and 123 (49.2%) were female**, whereas the DPP-4 group comprised **128 males (51.2%) and 122 females (48.8%)**. Overall, males accounted for **255 (51.0%)** and females for **245 (49.0%)** of the study population. The proportions of males and females were therefore **very similar between the two treatment groups**, with only a small difference in male representation (50.8% vs 51.2%) and female representation (49.2% vs 48.8%). The **Pearson Chi-square test showed $\chi^2 = 0.008$, $df = 1$, and $P = 0.929$** , indicating that the observed difference in gender distribution was **not statistically significant**. Thus, there was **no evidence of an association between treatment group and gender** in this study population. The nearly balanced male-to-female distribution also indicates that both treatment groups had a **comparable gender composition at baseline**, reducing concern that gender imbalance could substantially influence subsequent between-group comparisons.

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%)	0.929 (NS)
Female, n (%)	123 (49.2%)	122 (48.8%)	245 (49.0%)	
Total	250 (100%)	250 (100%)	500 (100%)	

Table 2: Descriptive Statistics and Statistical Significance of eGFR Changes Over Time for SGLT-2 Inhibitors (n=250) and DPP-4 Inhibitors (n=250)

The table presents eGFR levels at baseline and at 3, 6, 9, and 12 months in the SGLT-2 and DPP-4 inhibitor groups, expressed as mean $\pm$ SD. Changes in eGFR levels over time were assessed using repeated-measures ANOVA with Bonferroni-adjusted pairwise comparisons. A p -value < 0.05 was considered statistically significant.

Time Point	Treatment Group	Serum eGFR (mL/min/1.73 m ²), Mean $\pm$ SD	95% CI	Change from Baseline (mL/min/1.73 m ²)	p-value vs. Baseline
Baseline	SGLT-2	94.984 $\pm$ 3.146	94.593–95.375	–	–
	DPP-4	95.876 $\pm$ 3.146	95.484–96.268	–	–
3 Months	SGLT-2	93.984 $\pm$ 3.230	93.593–94.375	–1.000	<0.001*
	DPP-4	95.376 $\pm$ 3.320	94.962–95.790	-0.5	1(NS)
6 Months	SGLT-2	92.984 $\pm$ 3.310	92.593–93.375	–2.000	<0.001*
	DPP-4	94.876 $\pm$ 3.280	94.467–95.285	–1.000	<0.001*
9 Months	SGLT-2	91.984 $\pm$ 3.390	91.593–92.375	–3.000	<0.001*
	DPP-4	94.376 $\pm$ 3.350	93.959–94.793	–1.500	<0.001*
12 Months	SGLT-2	90.984 $\pm$ 3.470	90.593–91.375	–4.000	<0.001*
	DPP-4	93.876 $\pm$ 3.420	93.450–94.302	–2.000	<0.001*

Table 3: Descriptive Statistics and Statistical Significance of Serum Urea Changes Over Time for SGLT-2 Inhibitors (n=250) and DPP-4 Inhibitors (n=250)

The table presents Serum Urea levels at baseline and at 3, 6, 9, and 12 months in the SGLT-2 and DPP-4 inhibitor groups, expressed as mean $\pm$ SD. Changes in Serum Urea levels over time were assessed using repeated-measures ANOVA with Bonferroni-adjusted pairwise comparisons. A p -value < 0.05 was considered statistically significant.

Time Point	Treatment Group	Serum Urea (mg/dL), Mean $\pm$ SD	95% CI	Change from Baseline (mg/dL)	p-value vs Baseline
Baseline	SGLT-2	16.076 $\pm$ 4.655	15.614–16.537	–	–
	DPP-4	15.438 $\pm$ 2.425	14.976–15.899	–	–
3 Months	SGLT-2	16.338 $\pm$ 4.799	15.876–16.800	0.262	<0.001*
	DPP-4	15.243 $\pm$ 2.272	14.781–15.704	–0.195	<0.001*
6 Months	SGLT-2	16.582 $\pm$ 4.979	16.120–17.045	0.507	<0.001*
	DPP-4	15.308 $\pm$ 2.340	14.846–15.771	–0.129	0.06
9 Months	SGLT-2	16.838 $\pm$ 5.129	16.375–17.300	0.762	<0.001*
	DPP-4	15.151 $\pm$ 2.155	14.689–15.614	–0.287	<0.001*
12 Months	SGLT-2	17.001 $\pm$ 5.347	16.538–17.463	0.925	<0.001*
	DPP-4	15.016 $\pm$ 1.942	14.554–15.479	–0.421	<0.001*

Table 4: Descriptive Statistics and Statistical Significance of Serum Creatinine Changes Over Time for SGLT-2 Inhibitors (n=250) and DPP-4 Inhibitors (n=250)

The table presents Serum Creatinine levels at baseline and at 3, 6, 9, and 12 months in the SGLT-2 and DPP-4 inhibitor groups, expressed as mean $\pm$ SD. Changes in Serum Creatinine levels over time were assessed using repeated-measures ANOVA with Bonferroni-adjusted pairwise comparisons. A p -value < 0.05 was considered statistically significant.

Time Point	Treatment Group	Serum Creatinine (mg/dL), Mean $\pm$ SD	95% CI	Change from Baseline (mg/dL)	p-value vs Baseline
Baseline	SGLT-2	0.926 $\pm$ 0.069	0.914–0.937	–	–
	DPP-4	0.939 $\pm$ 0.113	0.927–0.951	–	–
3 Months	SGLT-2	0.936 $\pm$ 0.069	0.924–0.947	0.01	$<0.001^*$
	DPP-4	0.937 $\pm$ 0.108	0.926–0.948	–0.002	$<0.001^*$
6 Months	SGLT-2	0.946 $\pm$ 0.069	0.935–0.957	0.02	$<0.001^*$
	DPP-4	0.938 $\pm$ 0.102	0.927–0.949	–0.001	0.171
9 Months	SGLT-2	0.956 $\pm$ 0.069	0.946–0.966	0.03	$<0.001^*$
	DPP-4	0.936 $\pm$ 0.097	0.925–0.946	–0.003	0.484
12 Months	SGLT-2	0.966 $\pm$ 0.068	0.956–0.976	0.04	$<0.001^*$
	DPP-4	0.934 $\pm$ 0.094	0.923–0.944	–0.005	$<0.001^*$

Table 5: Descriptive Statistics and Statistical Significance of Serum Uric Acid Changes Over Time for SGLT-2 Inhibitors (n=250) and DPP-4 Inhibitors (n=250)

The table presents Serum Uric Acid levels at baseline and at 3, 6, 9, and 12 months in the SGLT-2 and DPP-4 inhibitor groups, expressed as mean $\pm$ SD. Changes in Serum Uric Acid levels over time were assessed using repeated-measures ANOVA with Bonferroni-adjusted pairwise comparisons. A p -value < 0.05 was considered statistically significant

Time Point	Treatment Group	Serum Uric Acid (mg/dL), Mean $\pm$ SD	95% CI	Change from Baseline (mg/dL)	p-value vs. Baseline
Baseline	SGLT-2	6.739 $\pm$ 0.465	6.674–6.804	–	–
	DPP-4	6.514 $\pm$ 0.577	6.449–6.579	–	–
3 Months	SGLT-2	6.364 $\pm$ 0.425	6.300–6.428	–0.375	$<0.001^*$
	DPP-4	6.505 $\pm$ 0.588	6.441–6.569	–0.009	0.153
6 Months	SGLT-2	5.979 $\pm$ 0.404	5.919–6.039	–0.760	$<0.001^*$
	DPP-4	6.442 $\pm$ 0.548	6.383–6.502	–0.072	$<0.001^*$
9 Months	SGLT-2	5.603 $\pm$ 0.372	5.545–5.661	–1.136	$<0.001^*$
	DPP-4	6.444 $\pm$ 0.544	6.386–6.501	–0.070	$<0.001^*$
12 Months	SGLT-2	5.231 $\pm$ 0.343	5.174–5.287	–1.508	$<0.001^*$
	DPP-4	6.436 $\pm$ 0.546	6.379–6.493	–0.078	$<0.001^*$

Discussion

The present 12-month prospective observational study evaluated longitudinal changes in renal biochemical parameters among patients with type 2 diabetes mellitus receiving SGLT-2 or DPP-4 inhibitor therapy. The findings demonstrated **distinct temporal patterns in eGFR, serum urea, serum creatinine, and serum uric acid** between the two treatment groups. The SGLT-2 group showed a progressive numerical reduction in eGFR together with increases in serum urea and creatinine, whereas the DPP-4 group demonstrated a smaller reduction in eGFR and comparatively stable serum urea and creatinine levels. The most pronounced difference between the groups was observed for **serum uric acid, which decreased substantially in the SGLT-2 group but changed only minimally in the DPP-4 group**. These findings provide useful information regarding short-term renal biomarker trajectories during routine clinical treatment, while their interpretation requires consideration of the known haemodynamic and tubular effects of SGLT-2 inhibition.

Baseline comparability and sex distribution

The study included **500 patients, with 250 patients in each treatment group**. The gender distribution was highly comparable between the two groups. In the SGLT-2 group, **127 patients (50.8%) were male and 123 (49.2%) were female**, compared with **128 males (51.2%) and 122 females (48.8%)** in the DPP-4 group. The Pearson Chi-square test demonstrated no statistically significant difference in gender distribution ($\chi^2 = 0.008$, $df = 1$, $p = 0.929$). Thus, there was no evidence of an association between treatment group and sex in this study population. The near-balanced sex distribution provides a favourable basis for longitudinal comparison; however, sex distribution alone does not establish complete baseline comparability because other clinical factors, such as diabetes duration, glycaemic status, concomitant medications, blood pressure, hydration status, cardiovascular disease, and baseline renal characteristics, may also influence renal biomarker trajectories.

eGFR trajectory

At baseline, mean eGFR was **94.984 ± 3.146 mL/min/1.73 m² in the SGLT-2 group and 95.876 ± 3.146 mL/min/1.73 m² in the DPP-4 group**, indicating relatively preserved renal filtration in both cohorts. Over 12 months, eGFR progressively declined to **90.984 ± 3.470 mL/min/1.73 m² in the SGLT-2 group**, representing a change of **-4.000 mL/min/1.73 m²**, while the DPP-4 group declined to **93.876 ± 3.420 mL/min/1.73 m²**, corresponding to a change of **-2.000 mL/min/1.73 m²**. Thus, the numerical decline was greater in the SGLT-2 group. The reduction in eGFR in the SGLT-2 group was statistically significant from 3 months onward ($p < 0.001$), while the DPP-4 group showed a smaller decline that was also statistically significant at subsequent follow-up points.

The observed decline in eGFR in the SGLT-2 group should not, however, be interpreted in isolation as evidence of progressive renal injury. SGLT-2 inhibition increases distal sodium delivery and enhances tubuloglomerular feedback, resulting in reduced intraglomerular pressure and an early reduction in eGFR. This initial haemodynamic response is a recognized physiological effect of SGLT-2 inhibition and may subsequently stabilize, with evidence suggesting that an early eGFR dip can be associated with slower long-term kidney-function decline rather than progressive renal deterioration (21,22). A systematic review and meta-analysis similarly reported that an initial eGFR decline after initiation of SGLT-2 inhibitors was associated with a slower subsequent annual eGFR decline without a corresponding increase in major adverse kidney events among patients experiencing a modest initial decline (23).

The present findings therefore require cautious interpretation. The **4.000 mL/min/1.73 m² reduction in eGFR over 12 months in the SGLT-2 group occurred from a relatively preserved baseline renal function**. Major randomized clinical trials have demonstrated renal benefits of SGLT-2 inhibitors despite the possibility of an early eGFR reduction. EMPA-REG OUTCOME reported a lower incidence of incident or worsening nephropathy and reduced risk of doubling of serum creatinine with empagliflozin (24). 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 significant reduction in sustained eGFR decline, kidney failure, or renal/cardiovascular death with dapagliflozin (25,26). EMPA-KIDNEY subsequently demonstrated reduced risk of kidney-disease progression or cardiovascular death with empagliflozin across a broad CKD population (27).

The apparent difference between the numerical eGFR decline observed in the present study and the long-term renal benefits reported in randomized trials may relate to differences in study design, patient characteristics, baseline renal function, treatment exposure, concomitant therapy, duration of follow-up, and outcome definitions. Importantly, the present observational study evaluated **continuous changes in eGFR over 12 months rather than hard renal endpoints such as kidney failure or sustained severe eGFR decline**. Therefore, the present findings demonstrate a renal biomarker trajectory but cannot establish that the observed eGFR reduction was causally attributable to SGLT-2 therapy.

Serum urea

Serum urea demonstrated different temporal patterns between the two treatment groups. In the SGLT-2 group, mean serum urea increased from **16.076 ± 4.655 mg/dL at baseline to 17.001 ± 5.347 mg/dL at 12 months**, representing an

increase of **0.925 mg/dL**. In contrast, the DPP-4 group showed a reduction from **15.438 ± 2.425 mg/dL to 15.016 ± 1.942 mg/dL**, corresponding to a decrease of approximately **0.421 mg/dL**. The SGLT-2 group therefore demonstrated a gradual numerical increase in serum urea, whereas the DPP-4 group remained comparatively stable with a small reduction.

The increase in serum urea in the SGLT-2 group should be interpreted together with the eGFR and creatinine findings rather than considered an isolated marker of nephrotoxicity. SGLT-2 inhibition increases urinary glucose and sodium excretion and produces an osmotic and natriuretic diuretic effect. These changes can influence intravascular volume, renal haemodynamic, and tubular handling of nitrogenous compounds. Consequently, a modest increase in serum urea does not by itself establish structural renal injury.

The magnitude of the observed increase was relatively small. Moreover, the present study did not include urinary albumin-to-creatinine ratio, cystatin C, tubular injury biomarkers, renal imaging, or direct measures of structural renal damage. Therefore, the increase in urea should be interpreted as a **biochemical change occurring during SGLT-2 therapy rather than definitive evidence of progressive diabetic kidney disease**. This interpretation is also consistent with evidence from large randomized trials demonstrating renal protection with SGLT-2 inhibitors despite early changes in conventional renal filtration markers (24–27). Longer follow-up incorporating additional renal biomarkers would be required to determine the clinical significance of the observed urea trajectory.

Serum creatinine

Serum creatinine showed a progressive increase in the SGLT-2 group during the 12-month follow-up. Mean creatinine increased from **0.926 ± 0.069 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 from baseline was **0.040 mg/dL**. In comparison, the DPP-4 group showed a comparatively stable pattern, with creatinine changing from **0.939 ± 0.113 mg/dL at baseline to 0.934 ± 0.094 mg/dL at 12 months**, corresponding to a small decrease of **0.005 mg/dL**.

The progressive increase in creatinine observed in the SGLT-2 group represents an important finding of the present study, particularly because it occurred alongside the numerical decline in eGFR. Nevertheless, this pattern should not automatically be interpreted as progressive structural renal injury. SGLT-2 inhibitors alter intrarenal haemodynamic through restoration of tubuloglomerular feedback and reduction of intraglomerular pressure. Such haemodynamic changes can produce an early reduction in filtration and a small accompanying increase in serum creatinine.

The present findings differ superficially from the long-term renal outcomes observed in major randomized trials. EMPA-REG OUTCOME reported lower risks of doubling of serum creatinine and renal replacement therapy with empagliflozin (24). CREDENCE similarly demonstrated lower renal-specific outcomes with canagliflozin (25), while DAPA-CKD and EMPA-KIDNEY demonstrated protection against clinically meaningful kidney-function decline (26,27). Several factors may explain this apparent difference, including the **12-month observational design**, differences in baseline renal characteristics, concomitant treatment, and the distinction between continuous biochemical measurements and long-term clinical renal endpoints.

Importantly, the absolute creatinine increase in the SGLT-2 group was **0.040 mg/dL**, which is a relatively small numerical change. Therefore, the current findings support recognition of a distinct creatinine trajectory during follow-up but do not establish SGLT-2-associated progressive renal damage. The observational nature of the study also permits residual confounding and prevents a definitive causal interpretation.

Serum uric acid

Serum uric acid demonstrated the **most prominent biochemical difference between the two treatment groups**. In the SGLT-2 group, serum uric acid decreased progressively from **6.739 ± 0.465 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 was **1.508 mg/dL**. In contrast, the DPP-4 group showed only a small reduction from **6.514 ± 0.577 mg/dL to 6.436 ± 0.546 mg/dL**, representing a change of **–0.078 mg/dL** at 12 months. Thus, the magnitude and consistency of uric-acid reduction were considerably greater in the SGLT-2 group.

This finding is consistent with previous evidence demonstrating urate-lowering effects of SGLT-2 inhibitors. A systematic review and meta-analysis incorporating 51 randomized controlled trials reported a significant reduction in serum uric acid with SGLT-2 inhibitors compared with placebo, with a pooled mean difference of **–32.14 μmol/L (95% CI –35.96 to –28.31; p < 0.001)** (28). Reductions were observed across individual SGLT-2 inhibitor classes, although the magnitude varied between agents and substantial heterogeneity was reported (28).

The reduction observed in the present study was numerically greater than the pooled placebo-adjusted effect reported in the meta-analysis; however, direct comparison should be made cautiously because the present study reports **within-group change**, whereas the meta-analysis reports a **between-group placebo-adjusted treatment effect**. Nevertheless, the

consistent progressive reduction across all follow-up points supports a strong association between SGLT-2 therapy and lower serum uric acid in this cohort.

The biological explanation may involve altered proximal tubular glucose and urate handling. SGLT-2 is encoded by **SLC5A2** and mediates sodium-dependent glucose reabsorption in the proximal tubule. SGLT-2 inhibition increases urinary glucose delivery and may alter proximal tubular urate handling, thereby promoting uricosuria. URAT1, encoded by **SLC22A12**, and GLUT9, encoded by **SLC2A9**, are important components of renal urate transport and reabsorption (29,30). These pathways provide a plausible molecular framework for the marked uric-acid reduction observed in the present study.

However, the present study did **not perform genotyping, gene-expression analysis, transporter quantification, or functional molecular assays**. Therefore, SLC5A2, SLC22A12, and SLC2A9 should be considered mechanistic candidates rather than experimentally demonstrated determinants of the observed response. Possible contributions from genetic variation remain hypotheses requiring dedicated pharmacogenomic investigation.

Comparison with DPP-4 inhibition

The DPP-4 group demonstrated a comparatively stable renal biochemical profile, particularly for serum urea and creatinine, together with a relatively small reduction in eGFR and minimal change in serum uric acid. These findings are broadly compatible with evidence suggesting that DPP-4 inhibitors generally have relatively 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 reported 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). CARMELINA also demonstrated effects on albuminuria-related outcomes with linagliptin without establishing a broad reduction in hard renal endpoints (33).

These findings provide useful context for the comparatively stable urea and creatinine pattern observed in the DPP-4 group. However, the present study did not measure urinary albumin excretion or albumin-to-creatinine ratio. Therefore, the current results cannot determine whether the biochemical stability observed with DPP-4 therapy was accompanied by changes in glomerular permeability or albuminuria.

Molecular and genetic interpretation

The divergent renal biomarker patterns can be considered within complementary molecular and physiological frameworks. SGLT-2 inhibition directly targets the 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).

The marked reduction in serum uric acid observed in the present study may also be interpreted in relation to the proximal tubular urate transport network, particularly **URAT1/SLC22A12 and GLUT9/SLC2A9** (29,30). These pathways provide a biologically plausible explanation for the prominent uricosuric response associated with SGLT-2 inhibition.

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 biochemical profile observed in the DPP-4 group may therefore be considered within this broader biological framework.

Nevertheless, these molecular interpretations remain **hypothesis-generating**. Because the present investigation did not include genetic testing, gene-expression analysis, transporter quantification, or intracellular signalling assays, the findings cannot establish genotype–phenotype relationships or demonstrate direct molecular mechanisms underlying treatment response. Future studies incorporating renal transporter genotypes, serum and urinary biomarkers, transcriptomic profiles, and longitudinal renal outcomes may clarify whether molecular variation contributes to differences in response to SGLT-2 and DPP-4 inhibitor therapy.

Clinical and research implications

Taken together, the findings demonstrate that renal biomarker interpretation during SGLT-2 therapy should not rely on a single parameter such as serum creatinine or eGFR. In the present study, SGLT-2 therapy was associated with a **4.000 mL/min/1.73 m² decline in eGFR, a 0.925 mg/dL increase in serum urea, a 0.040 mg/dL increase in serum creatinine, and a pronounced 1.508 mg/dL reduction in serum uric acid over 12 months**. In comparison, the DPP-4 group showed a **2.000 mL/min/1.73 m² reduction in eGFR, a 0.421 mg/dL reduction in urea, a 0.005 mg/dL reduction in creatinine, and only a 0.078 mg/dL reduction in uric acid**.

The simultaneous occurrence of modest changes in filtration and nitrogenous waste markers together with substantial uric-acid reduction illustrates the complex physiological consequences of proximal tubular SGLT-2 inhibition. However, these observations should not be interpreted as evidence of long-term renal harm because the study was observational, treatment allocation was not randomized, and follow-up was limited to 12 months. Furthermore, important renal outcomes including urinary albumin excretion, cystatin C, tubular injury biomarkers, renal imaging, and hard clinical renal endpoints were not assessed.

The relatively preserved baseline eGFR of the study population also limits extrapolation of these findings to patients with advanced diabetic kidney disease. Accordingly, the present results describe **short-term biochemical trajectories rather than definitive differences in long-term renal protection or renal injury**. Future prospective studies with longer follow-up and inclusion of albuminuria, cystatin C, tubular injury biomarkers, and molecular or pharmacogenomic parameters would provide a more comprehensive assessment of renal response and may help explain interindividual differences in treatment-associated biomarker changes.

CONCLUSION

This 12-month prospective observational study demonstrated **distinct longitudinal renal biomarker trajectories in patients with type 2 diabetes mellitus receiving SGLT-2 versus DPP-4 inhibitor therapy**. The SGLT-2 group showed a greater numerical decline in eGFR, from **94.984 to 90.984 mL/min/1.73 m² (–4.000 mL/min/1.73 m²)**, compared with a decline from **95.876 to 93.876 mL/min/1.73 m² (–2.000 mL/min/1.73 m²)** in the DPP-4 group. Serum urea increased by **0.925 mg/dL** and serum creatinine by **0.040 mg/dL** in the SGLT-2 group, whereas the DPP-4 group demonstrated small reductions of **0.421 mg/dL and 0.005 mg/dL**, respectively.

In contrast, **serum uric acid showed the most pronounced treatment-associated difference**, declining by **1.508 mg/dL in the SGLT-2 group**, compared with only **0.078 mg/dL in the DPP-4 group**. This marked uric-acid reduction is consistent with the recognized effects of SGLT-2 inhibition on proximal tubular glucose and urate handling and may involve pathways associated with SLC5A2, SLC22A12, and SLC2A9.

The numerical reductions in eGFR and increases in serum urea and creatinine observed with SGLT-2 therapy should **not be interpreted as definitive evidence of progressive renal injury**, particularly because established randomized clinical trials have demonstrated long-term renal benefits of SGLT-2 inhibitors. The present findings are more appropriately interpreted as short-term renal biochemical trajectories that may reflect haemodynamic and tubular adaptations during SGLT-2 inhibition. The comparatively stable renal biochemical profile observed with DPP-4 therapy provides a useful comparative context but does not establish superiority of either treatment with respect to long-term renal outcomes.

Finally, the molecular interpretation remains **hypothesis-generating**, because the present study did not directly evaluate genetic variants, gene expression, transporter abundance, or molecular signalling. Further long-term prospective studies incorporating albuminuria, cystatin C, tubular injury biomarkers, clinical renal endpoints, and pharmacogenomic or molecular profiling are warranted to determine whether differences in renal transporter biology contribute to the variability of response to SGLT-2 and DPP-4 inhibitor therapy.

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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.

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