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Initial changes of kidney functional tests and tubular injury biomarkers following SGLT2 inhibitors therapy in patients with diabetic kidney disease; a prospective cohort study

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ABSTRACT

Introduction: Diabetic kidney disease (DKD) is one of the leading causes of chronic kidney failure. Sodium-glucose cotransporter-2 (SGLT2) inhibitors indicated marked renoprotective effects, but their mechanisms and benefits remain unclear.

Objectives: The objective of this study is to assess initial changes in kidney functional and tubular injury biomarkers following the consumption of the SGLT2 inhibitor in DKD patients.

Materials and Methods: This study was designed as a prospective cohort conducted at Al-Basrah Teaching hospital in Basrah, Iraq, from January to December 2025. Patients with DKD were included and classified into two groups according to their treatment regimen; those with a stable antidiabetic treatment including an SGLT2 inhibitor and those with similar regimens without SGLT2 inhibitors. The samples from blood and urine were collected to measure standard kidney functional tests, including blood urea nitrogen (BUN), creatinine, and estimated glomerular filtration rate (eGFR), urine albumin-to-creatinine ratio (UACR), and tubular injury biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). The data were compared between two groups.

Results: Results demonstrated that 60 DKD patients with a mean age of 53.28 ± 8.08 years were included. Patients who received SGLT2 inhibitors had a better renal profile, with better conventional kidney function measurements (BUN, creatinine, and eGFR), lower albumin-to-creatinine ratio (UACR), and consistently reduced levels of tubular injury markers, including urinary KIM-1 and NGAL, in comparison to those who do not receive these agents, and these differences were statistically significant ($P < 0.05$).

Conclusion: Our study found, SGLT2 inhibitor therapy was accompanied by improvements in kidney functional tests and lower levels of tubular injury markers in DKD patients. These findings suggest that SGLT2 inhibitors may begin to confer renoprotective effects, particularly at the level of the renal tubules, supporting their use as an important component of care in this high-risk population.

Implication for health policy/practice/research/medical education:
This cohort study has shown that patients with diabetes who received sodium-glucose cotransporter-2 (SGLT2) inhibitors had a healthier kidney profile, including better traditional kidney function test results, lower albuminuria, and lower levels of tubular injury markers. In summary, these findings indicated that SGLT2 inhibitors have a protective effect on both glomerular and tubular structures, suggesting a plausible biological explanation for the longer-term renal benefits.

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Introduction

Diabetic kidney disease (DKD) is one of the most common complications of type 2 diabetes mellitus (T2DM) and is one of the common causes for end-stage renal disease (ESRD) globally (1-4). Although initially studies focused on glomerular injury as one of the central drivers of renal decline, most evidence now points to tubular compartment disorder as a critical determinant of DKD progression

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(5,6). In patients with T2DM, hyperglycemia drives excessive glucose reabsorption by up-regulated sodium-glucose cotransporter-2 (SGLT2) in the proximal tubule, which predisposes tubular epithelial cells to oxidative stress, hypoxia, inflammation, and apoptosis (7). Over time, these harmful changes make the tubular cells swell, thicken the supporting (basement) membrane around the tubules, and lead to scarring in the spaces between them, and these tubulointerstitial lesions are actually better predictors of how fast kidney function will decline than glomerular scarring by itself (5). Most researchers increasingly rely on urinary and plasma biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL)for recognizing tubular injury before the appearance of microalbuminuria (8). Previous studies have indicated that KIM-1 and the inflammation markers TNF receptors 1 and 2 (TNFR1 and TNFR2) may predict the occurrence of kidney failure requiring replacement therapy in adults with T2DM and an estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2, underscoring the prognostic value of tubular biomarkers beyond conventional parameters (9,10).

The SGLT2 inhibitors as a group of glucose-lowering drugs have fundamentally improved the therapeutic aspects of DKD in the past decade (11). These agents conduct cardiorenal protection by inhibiting proximal tubular sodium and glucose reabsorption, restoring tubuloglomerular feedback, reducing intraglomerular hypertension, lessening the tubular metabolic workload, and dampening inflammation and fibrosis (7,11). Previous randomized controlled trials (RCTs) demonstrated marked evidence for their effectiveness in kidney protection (12). Two studies by Wanner et al (12) and Ji et al (13) indicated that using empagliflozin reduced incident or worsening nephropathy in about 40% of T2DM patients. A trial subsequently showed that canagliflozin lowered the risk of the composite renal endpoint, including ESRD, doubling of serum creatinine, and renal death, by 34% in patients with T2DM and established nephropathy (14). These findings were further consolidated by the Wanner et al trial, in which dapagliflozin reduced the primary composite kidney and cardiovascular outcome across patients with chronic kidney disease, regardless of diabetes status (12).

Beyond their well-established effects on glomerular hemodynamics and albuminuria, recent RCT-based biomarker studies have offered direct evidence that SGLT2 inhibitors attenuate renal tubular injury at the molecular level (15). A post-hoc analysis of a trial reported that ertugliflozin produced a sustained and significant reduction in plasma KIM-1 levels at both 26 and 52 weeks in patients with T2DM and stage 3 CKD, independent of baseline eGFR or albuminuria (15). Complementary findings emerged from the study by Sen et al, in which canagliflozin reduced plasma KIM-1 by 26.7% and modestly attenuated TNFR-1 and TNFR-2 concentrations compared with placebo. Importantly, early reductions in TNFR-1 and TNFR-2 were independently associated with a lower risk of kidney disease progression, suggesting these biomarkers may serve as pharmacodynamic indicators of tubular protection (16). Earlier RCT evidence from the dapagliflozin study similarly showed a 22.6% decrease in urinary KIM-1 excretion alongside a reduction in the inflammatory marker interleukin-6 (IL-6), with biomarker changes correlated with albuminuria reduction (17). Collectively, these findings suggest that early biomarker-based assessment of tubular injury may offer a clinically meaningful window for capturing the nephroprotective effects of SGLT2 inhibitors at the tubular level, a question that the present prospective cohort study aims to examine in patients with DKD.

Objectives

This study aimed to evaluate the effectiveness of SGLT2 inhibitor therapy among patients with DKD. The objective is to assess the changes in kidney function and renal tubular injury biomarkers following SGLT2 inhibitor therapy.

Patients and Methods

Study design and participants

This prospective cohort study was conducted in a clinical setting at Al-Basrah teaching hospital in Basrah, Iraq, during 12 months from January to December 2025. During routine outpatient visits, adults with T2DM and established DKD who met the eligibility criteria were invited to participate and, after providing written informed consent, were enrolled in the study. Participants were then classified into two cohorts according to their ongoing treatment plan: those receiving SGLT2 inhibitor therapy and those managed with standard care without an SGLT2 inhibitor.

Inclusion and exclusion criteria

In this study, we enrolled adults aged 30 to 70 years with T2DM and a documented diagnosis of established DKD, defined according to the diagnostic thresholds of the American diabetes association (18), and all participants provided written informed consent before inclusion. Eligible patients were required to be on a stable antidiabetic regimen, either with or without an SGLT2 inhibitor (dapagliflozin 10 mg/day or empagliflozin 10 mg/day), to reduce the potential influence of recent treatment changes. Individuals who were unwilling to continue participation at any stage, as well as those with incomplete or missing laboratory data, were excluded from the final analysis.

Group classification

In this study, we grouped patients according to the treatment decisions made in everyday clinical practice rather than by random allocation. Adults with established

DKD who were taking an SGLT2 inhibitor (SGLT2i) for at least six months (either dapagliflozin 10 mg/d or empagliflozin 10 mg/d) were included in the SGLT2i group. Those with a similar clinical profile who continued on standard care without any SGLT2 inhibitor were classified as the non-SGLT2i group.

Data collection

Data for this study were collected prospectively from adult patients with a diagnosis of DKD who were receiving routine care at our center. Eligible patients were identified from clinic records and invited to participate, and those who agreed and provided informed written consent were then allocated to one of two cohorts based on their current treatment plan: individuals for whom the treating physician had initiated an SGLT2 inhibitor, and those managed without these agents. Demographic characteristics and key diabetes-related data, including gender, age, body mass index (BMI), glycated hemoglobin (HbA1c), and duration of diabetes mellitus were collected through the patients' interview or clinical documents. The sample for blood and urine were collected to measure conventional kidney function tests such as blood urea nitrogen (BUN), creatinine, and eGFR, urine albumin-to-creatinine ratio (UACR), and tubular injury biomarkers such as KIM-1 and NGAL.

Outcomes measurements

The primary outcomes were comparison of kidney function tests (BUN, creatinine, and eGFR) and tubular injury biomarkers (UACR, KIM-1, and NGAL) between patients who received SGLT2 inhibitors and those managed without this agent.

Statistical analysis

Data analysis was conducted by SPSS version 27 (IBM Corp., USA). Data normality was assessed by the Shapiro–Wilk. Comparison between the SGLT2 inhibitor and non–SGLT2 inhibitor groups was conducted by independent-samples t tests for quantitative variables, while chi-square tests were used for categorical variables. Because of this issue that parametric and nonparametric tests had similar P values, the parametric tests were chosen for their higher statistical efficiency. A $P < 0.05$ was considered significant.

Results

This study included 60 DKD patients with a mean age of 53.28 ± 8.08 years in two equal groups of 30 patients. The majority of participants were male with an average BMI of 30.35 kg/m^2. The average diabetes duration was more than ten years. Their HbA1C indicating partial diabetic control (Table 1).

The comparative analysis demonstrated that demographic data and diabetic profile information were similar between the two groups of SGLT2 consumers and those without. Demographic profile such as age, BMI, and gender, and diabetic characteristics (HbA1c and diabetic duration), found no statistically significant difference among two treatment groups (Table 2).

Table 1. Demographic data and diabetic profile of studied participants

Qualitative variables	Frequency	Percent
Gender		
Male	35	58.3
Female	25	41.7
SGLT2i consumer		
Yes	30	50
No	30	50
Quantitative variables	**Mean**	**SD**
Age (year)	53.28	8.08
BMI (kg/m^2)	30.35	3.60
HbA1c (%)	8.10	1.22
T2DM duration (year)	11.66	4.08

SGLT2i: Sodium-glucose cotransporter-2 inhibitors, BMI: Body mass index, HbA1c: Glycosylated hemoglobin, T2DM: Type 2 diabetes mellitus, SD: Standard deviation.

Comparative analysis of kidney function test and tubular injury biomarkers illustrated that patients who received SGLT2 inhibitors consistently indicated improved kidney function tests and lower tubular injury biomarkers in comparison to those without. The serum creatinine and BUN had lower level in patients under treatment of SGLT2i and eGFR indicated a higher level. Glomerular damage biomarkers, including UACR, also were reduced in the SGLT2i consumers. Furthermore, biomarkers indicating tubular injury, such as urinary NGAL and KIM-1, were significantly lower in patients with SGLT2i, indicating a protective effect of SGLT2 inhibition on tubular integrity. All between-group differences for all parameters indicated statistical significance (Table 3 and Figure 1).

Discussion

The present results demonstrated that DKD patients receiving SGLT2 inhibitor therapy had significantly more favourable renal profiles compared with those on similar regimens without SGLT2 inhibitors, encompassing lower BUN, serum creatinine, and UACR, better-preserved eGFR, and reduced urinary KIM-1 and NGAL levels. These findings are broadly consistent with, and provide corroboration of, a growing body of evidence from landmark randomized controlled trials. The improvements in conventional kidney function parameters observed in the SGLT2 inhibitor group are in line with results from several pivotal trials. The trial study by Wanner et al demonstrated that empagliflozin significantly reduced the risk of incident or worsening nephropathy and slowed eGFR decline compared with placebo in patients with T2DM and established cardiovascular disease (12). Another trial study, by Ji et al indicated that empagliflozin has a cardiorenal protective effect and reduces the mortality risk (13). The trial conducted by Chertow et al, subsequently reported that dapagliflozin was associated

Table 2. Comparative analysis of demographic data and diabetic profile between two groups

Qualitative variables		Treatment group		*P* value*
		SGLT2i consumer (n = 30) N (%)	Non SGLT2i consumer (n = 30) N (%)	
Gender	Male (n = 35)	18 (51.4)	17 (48.6)	0.793
	Female (n = 25)	12 (48)	13 (52)	
Quantitative variables		**Mean ± SD**	**Mean ± SD**	***P* value****
Age (year)		52.66 ± 7.83	53.91 ± 8.41	0.553
BMI (kg/m²)		30.21 ± 3.61	30.49 ± 3.66	0.764
HbA1c (%)		7.85 ± 1.41	8.34 ± 1.28	0.119
T2DM duration (year)		11.01 ± 4.30	12.33 ± 3.81	0.208

SGLT2i: Sodium-glucose cotransporter-2 inhibitors, BMI: Body mass index, HbA1c: Glycosylated hemoglobin, T2DM: Type 2 diabetes mellitus, SD: Standard deviation. *Chi-square, **Independent T-test.

Table 3. Comparative analysis of kidney function test and tubular injury biomarkers between the two treatment groups

Qualitative variables	Treatment group		Mean difference (95% CI)	*P* value*
	SGLT2i consumer Mean ± SD	Non SGLT2i consumer Mean ± SD		
BUN (mg/dL)	20.25 ± 5.42	29.30 ± 6.64	9.05 (5.91–12.18)	<0.001
Creatinine (mg/dL)	1.24 ± 0.22	1.65 ± 0.46	0.41 (0.22–0.60)	<0.001
eGFR (mL/min/1.73m²)	56.01 ± 10.26	48.54 ± 15.05	7.47 (0.79–14.11)	0.029
UACR (mg/g)	134.15 ± 34.02	226.39 ± 54.44	92.24 (68.68–115.80)	<0.001
Urinary KIM-1 (ng/mL)	1.86 ± 0.49	2.81 ± 0.78	0.95 (0.60–1.28)	<0.001
Urinary NGAL (ng/mL)	60.13 ± 20.97	108.86 ± 21.26	48.73 (37.81–59.64)	<0.001

SGLT2i: Sodium-glucose cotransporter-2 inhibitors, eGFR: estimated glomerular filtration rate, BUN: Blood urea nitrogen, UACR: Urine albumin-to-creatinine ratio, KIM-1: Kidney injury molecule-1, NGAL: Neutrophil gelatinase-associated lipocalin, SD: Standard deviation, *Chi-square, **Independent T-test.

with a significantly slower mean annual eGFR decline and a reduction in the composite renal endpoint (19). The clinical trial similarly showed that canagliflozin, another type of SGLT2 inhibitor, reduced the composite of kidney failure (16). The renal hemodynamic mechanisms underlying these benefits are well characterized: SGLT2 inhibitors restore tubuloglomerular feedback by increasing sodium delivery to the macula densa, leading to afferent arteriolar vasoconstriction and a reduction in intraglomerular hypertension, a pivotal driver of DKD progression (20). Hemodynamically, these agents decrease renal oxygen using by decreasing the metabolic burden of proximal tubular glucose–sodium co-transport, thereby alleviating tubular hypoxia (21).

The lower level of UACR in patients' under-treatment of SGLT2 inhibitor the current study is in line with antialbuminuric effects reported in previous studies. An analysis of the dapagliflozin-CKD study found a 35.1% reduction in UACR level in T2DM patients who treated with dapagliflozin, with patients indicating macroalbuminuria at baseline being significantly more likely to regress to lower albuminuria categories (22). In a 12-week randomized controlled trial by Satirapoj et al, dapagliflozin produced a significant between-group difference in UACR reduction compared with standard treatment (−23.3 versus +19.9 mg/g creatinine), independent of glycemic control (23), suggesting that the antialbuminuric effect is at least partly mediated through non-glycaemic pathways, including reduced intraglomerular pressure and improved podocyte integrity.

A particularly notable aspect of the present findings is the reduction in urinary KIM-1 and NGAL in the SGLT2 inhibitor group. These biomarkers reflect injury at distinct nephron segments: KIM-1 is shed from injured proximal tubular cells following ischemic or toxic insult (24), while NGAL is expressed in the loop of Henle and collecting duct under conditions of oxidative stress and inflammation (25). Elevated levels of both markers have been shown to independently predict rapid eGFR decline and progression to ESRD in prospective cohort studies of patients with diabetic nephropathy. In a prospective cohort study of 257 T2DM patients, high urinary KIM-1 and NGAL were associated with hazard ratios for ESRD of 2.77 and 2.53, respectively (26). SGLT2 inhibitors are thought to reduce tubular injury through several mechanisms: by lowering proximal tubular glucose and sodium co-transport, they reduce the metabolic workload and oxygen demand of tubular cells, thereby alleviating hypoxia-induced injury signalling upstream of KIM-1 expression (27). Satirapoj et al demonstrated a significant between-group reduction in urinary KIM-1:creatinine ratio with dapagliflozin versus standard care (−26.7 versus +422.2 ng/g creatinine), independent of HbA1c changes, providing direct evidence for a tubular cytoprotective effect of this drug class (23). It is worth noting that a biomarker sub-study of a clinical trial by Malijan et al reported no significant effect of empagliflozin on urinary KIM-1 or monocyte chemoattractant protein-1 (MCP-1) in a broad CKD population (28). This apparent discrepancy likely reflects differences in patient population, disease stage, and the

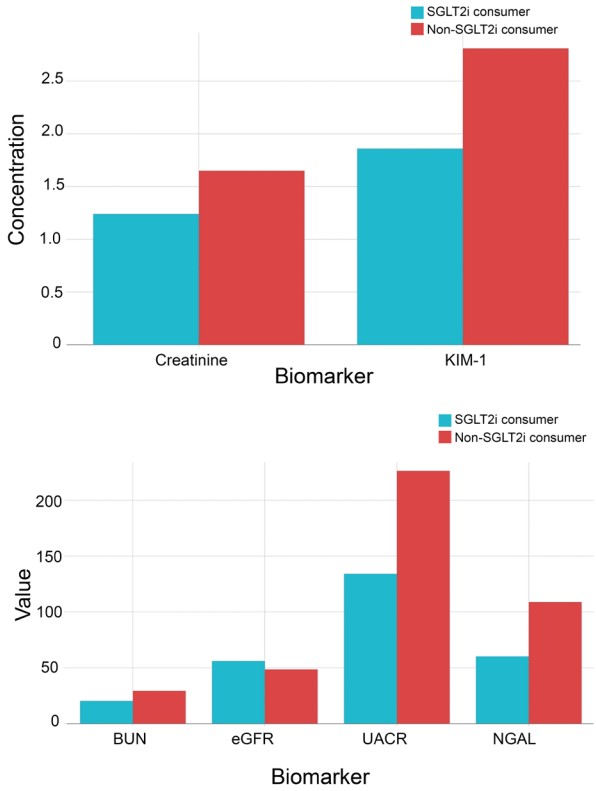

Figure 1. Comparison of kidney function tests and tubular injury biomarkers among treatment groups. SGLT2i: Sodium-glucose cotransporter-2 inhibitors, eGFR: estimated glomerular filtration rate, BUN: Blood urea nitrogen, UACR: Urine albumin-to-creatinine ratio, KIM-1: Kidney injury molecule-1, NGAL: Neutrophil gelatinase-associated lipocalin.

duration of biomarker follow-up and does not diminish the biological plausibility or significance of the tubular benefits observed in the present DKD-specific cohort.

Overall, the present study demonstrates that SGLT2 inhibitor therapy is associated with significantly improved kidney function parameters, reduced albuminuria, and lower urinary tubular injury biomarkers in patients with DKD. These findings, taken alongside the broader body of trial and mechanistic evidence, suggest that SGLT2 inhibitors exert early renoprotective effects at the tubular level, and support their integration as an essential component of care in patients with DKD.

Conclusion

Using SGLT2 inhibitor treatment in DKD patients was related with a markedly favorable renal profile in comparison to the standard care. SGLT2 inhibitors consumers had lower levels of kidney function tests, alongside higher eGFR, indicating a modest but meaningful early improvement in overall kidney function. Tubular injury biomarkers, such as urinary NGAL and KIM-1, were clearly lower in the SGLT2i group, pointing toward reduced tubular stress or damage in the early phase after treatment initiation. In summary, our findings found that that SGLT2 inhibitors exert Reno-protective effects, particularly at the level of the kidney tubules, and provide biological plausibility for the longer-term kidney benefits. Our results concluded that early monitoring of tubular biomarkers could offer additional insight into treatment response and may help clinicians better understand which patients derive the greatest renal benefit from using of SGLT2 inhibitor.

Limitations of the study

Single-center setting, small sample size, non-randomization allocation, raising the possibility of residual confounding by unmeasured factors despite the overall similarity of baseline characteristics, and relied on single-time laboratory measurements are the most common limitation that this study faced with.

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Authors' contribution

Conceptualization: Ghassan Salah Ahmed.
Data curation: Ghassan Salah Ahmed and Rasha K. J. Ali.
Formal analysis: Rawsan Sabri Ali.
Investigation: Rawsan Sabri Ali and Rasha K. J. Ali.
Methodology: Rawsan Sabri Ali.
Project management: Ghassan Salah Ahmed.
Resources: All authors.
Supervision: All authors.
Validation: Rasha K. J. Ali.
Writing–original draft: All authors
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. Informed written consent was taken from all participants. This study was conducted at Al-Basrah Teaching Hospital, in Basrah, Iraq and approved by the University of Basrah. (EC134 at 10/01/2025). Accordingly, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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