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FREQUENCY OF ACUTE KIDNEY INJURY IN PATIENTS OF CHRONIC KIDNEY DISEASE STAGE III/IV WITH TYPE 2 DIABETES MELLITUS USING SGLT2 INHIBITORS

Original Research

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ABSTRACT

Background: Chronic kidney disease (CKD) is a major global health burden, often exacerbated by type 2 diabetes mellitus (T2DM). Sodium-glucose cotransporter 2 (SGLT2) inhibitors, though primarily prescribed for glycemic control, have demonstrated renal protective effects. However, concerns remain regarding their potential to precipitate acute kidney injury (AKI), particularly in patients with moderate-to-severe CKD. This study was conducted to evaluate the frequency of AKI among patients with CKD stage III/IV and T2DM receiving SGLT2 inhibitors.

Objective: To determine the frequency of acute kidney injury in patients with chronic kidney disease and type 2 diabetes mellitus undergoing treatment with SGLT2 inhibitors.

Methods: This descriptive cross-sectional study was conducted in the Department of Nephrology, Sheikh Zayed Hospital, Lahore, over six months. A total of 160 patients with CKD stages G3 and G4 and diagnosed with T2DM, who had been taking SGLT2 inhibitors for at least four weeks, were enrolled through non-probability consecutive sampling. Serum creatinine and eGFR were assessed to identify AKI based on KDIGO criteria. Data were analyzed using SPSS version 27.0. Means and standard deviations were calculated for continuous variables, while frequencies and percentages were presented for categorical variables. Chi-square tests were applied post-stratification with a significance threshold of ≤ 0.05.

Results: The mean age was 59.3 ± 8.6 years, with 58.8% male and 41.2% female participants. Mean serum creatinine was 2.1 ± 0.6 mg/dL, and mean eGFR was 38.4 ± 7.9 mL/min/1.73 m². AKI was observed in 12 patients (7.5%), while 148 patients (92.5%) did not develop AKI. Empagliflozin was the most commonly used SGLT2 inhibitor (45.0%).

Conclusion: AKI occurred in a manageable proportion of CKD stage III/IV patients with T2DM receiving SGLT2 inhibitors. These findings support the cautious yet beneficial use of SGLT2 inhibitors in this high-risk population, with emphasis on routine renal function monitoring.

Keywords: Acute Kidney Injury, Chronic Kidney Disease, Diabetes Mellitus Type 2, Empagliflozin, Glomerular Filtration Rate, Renal Insufficiency, SGLT2 Inhibitors

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INTRODUCTION

Chronic kidney disease (CKD) has emerged as a significant global public health burden, with an estimated 700 million people affected worldwide, accounting for approximately 9.1% of the population in 2017 (1). This rising prevalence is closely intertwined with the increasing incidence of type 2 diabetes mellitus (T2DM), a major contributor to the development and progression of CKD. As a result, the global burden of end-stage kidney disease (ESKD) is accelerating, with projections indicating that the number of individuals requiring renal replacement therapy will surpass 5 million by 2035 (2,3). CKD, particularly in individuals with poorly controlled diabetes, leads not only to progressive renal dysfunction but also increases the risk of cardiovascular events, infections, and mortality, thereby intensifying the need for effective preventive and therapeutic strategies. In recent years, sodium-glucose cotransporter-2 (SGLT2) inhibitors have garnered attention for their multifaceted role in managing type 2 diabetes and related renal and cardiovascular complications. Originally developed as glucose-lowering agents, these drugs have demonstrated a capacity to reduce proteinuria, slow the progression of diabetic nephropathy, and mitigate the risk of heart failure and major adverse cardiovascular events (4-6). Notably, large-scale trials and observational studies have investigated their renal safety profile, with several findings suggesting a potential nephroprotective effect. Perkovic et al. observed an acute kidney injury (AKI) incidence of 3.9% among patients with CKD and T2DM using Canagliflozin, highlighting the need to further explore this association (3). Similarly, a comprehensive meta-analysis by Menne et al. encompassing 30 randomized trials indicated that SGLT2 inhibitors were associated with a lower risk of AKI across both clinical trials and real-world settings, despite an increased incidence of volume depletion-related adverse events (6). Zhou et al. also reported a reduced incidence of AKI in older patients initiating SGLT2 inhibitors compared to those receiving DPP-4 inhibitors or GLP-1 receptor agonists (7), while Chu et al. emphasized the drugs' ability to prevent AKI and reduce macroalbuminuria in three major randomized controlled trials (5).

Despite these encouraging findings, a clear understanding of frequency and clinical implications of AKI in patients with advanced stages of CKD (Stage III/IV) who are concurrently on SGLT2 inhibitor therapy remains limited. The heterogeneity in patient profiles, comorbid conditions, and clinical practice across studies further underscores the need for focused research to evaluate real-world outcomes in this high-risk population. In particular, the concern persists that SGLT2 inhibitors, due to their osmotic diuretic effect and potential for volume depletion, may paradoxically precipitate AKI in susceptible individuals, particularly those with preexisting renal impairment (8,9). Given this clinical dilemma, the present study aims to determine the frequency of acute kidney injury in patients with CKD Stage III or IV and T2DM who are being treated with SGLT2 inhibitors. Understanding the occurrence of AKI in this specific cohort will provide valuable insight into the renal safety profile of SGLT2 inhibitors, aiding clinicians in making informed decisions for personalized treatment. This investigation is intended to contribute meaningful data to the ongoing discourse surrounding the nephroprotective versus nephrotoxic potential of SGLT2 inhibitors in patients with dual burdens of diabetes and chronic kidney disease (10).

METHODS

This descriptive cross-sectional study was conducted in Department of Nephrology at Sheikh Zayed Hospital, Lahore, over a period of six months following approval of the research synopsis by the institutional ethics committee. Ethical clearance was obtained, and informed written consent was taken from all participants prior to inclusion in study. The objective was to determine frequency of acute kidney injury (AKI) in patients diagnosed with chronic kidney disease (CKD) Stage III or IV and type 2 diabetes mellitus (T2DM) who were on sodium-glucose co-transporter 2 (SGLT2) inhibitors for glycemic control (11). A sample size of 160 participants was calculated using the WHO sample size calculator, based on an anticipated proportion of 3.909% for AKI in this population (3), with a 3% margin of error and a 95% confidence level. A non-probability consecutive sampling technique was employed for participant recruitment. The study population included both male and female patients aged between 30 and 80 years, with a confirmed diagnosis of type 2 diabetes mellitus and proteinuria. All included individuals had been using SGLT2 inhibitors (Empagliflozin, Dapagliflozin, Canagliflozin, or others) for at least four weeks and were classified as CKD Stage G3 or G4 based on the CKD-EPI Creatinine Equation (12).

Patients were excluded if they had a history of dialysis, kidney transplantation, eGFR < 20 mL/min/1.73 m², AKI due to any etiology other than diabetes and CKD, CKD caused by non-diabetic conditions, or were receiving immunosuppressive therapy for renal disease. All exclusions were verified through patients' medical records to ensure the accuracy of clinical history (13). After enrollment, comprehensive demographic and clinical data were collected using a structured data collection form. Parameters included age, gender, duration of diabetes, HbA1c levels, the specific type of SGLT2 inhibitor used, serum creatinine levels, and calculated eGFR. Patients were monitored and classified as having AKI based on the KDIGO criteria, which includes: an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, an increase to ≥ 1.5 times the baseline within the previous seven days, or urine output of less than 0.5 mL/kg/h for six hours. Only one of these criteria was required to confirm AKI (14). All collected data were entered and analyzed using SPSS version 27.0. Numerical variables such as age, HbA1c, duration of diabetes, serum creatinine, and eGFR were presented as means with standard deviations, while categorical variables including gender, CKD stage, type of SGLT2 inhibitor used, and incidence of AKI were summarized using frequencies and percentages. Stratification was performed for age groups, gender, duration of drug use, and CKD

classification to assess their potential association with the development of AKI. Post-stratification Chi-square tests were applied, with a p-value ≤ 0.05 considered statistically significant (15).

RESULTS

The study included a total of 160 patients diagnosed with chronic kidney disease stage III or IV and type 2 diabetes mellitus who were undergoing treatment with SGLT2 inhibitors. The mean age of the participants was 59.3 ± 8.6 years. Among them, 94 (58.8%) were male and 66 (41.2%) were female. The average HbA1c level recorded was 8.4 ± 1.1%, while the mean duration of diabetes was 132.5 ± 49.7 months. The average duration of SGLT2 inhibitor usage among the participants was 22.4 ± 10.3 weeks. Regarding the renal parameters, the mean serum creatinine level was 2.1 ± 0.6 mg/dL, and the average estimated glomerular filtration rate (eGFR) was 38.4 ± 7.9 mL/min/1.73 m². Classification of CKD showed that 104 patients (65.0%) were in stage G3, whereas 56 patients (35.0%) were in stage G4. Empagliflozin was the most frequently used SGLT2 inhibitor, administered to 72 patients (45.0%), followed by Dapagliflozin in 54 patients (33.8%), Canagliflozin in 23 patients (14.4%), and other agents in 11 patients (6.9%). The frequency of acute kidney injury (AKI) among the study population was found to be 12 out of 160 patients, corresponding to 7.5%, while 148 patients (92.5%) did not experience AKI during the study period. These results provide a quantitative overview of AKI occurrence in a real-world cohort of diabetic CKD patients treated with SGLT2 inhibitors.

Table: Descriptive Statistics of Study Population (n = 160)

Variable	**Mean ± SD**
Age (years)	59.3 ± 8.6
HbA1c Levels (%)	8.4 ± 1.1
Duration of Diabetes (months)	132.5 ± 49.7
Duration of SGLT2 Inhibitor Use (weeks)	22.4 ± 10.3

Table: Frequency and Percentage Distribution of Study Population (n = 160)

Variable	**Frequency (n)**	**Percentage (%)**
Gender		
Male	94	58.8%
Female	66	41.2%
SGLT2 Inhibitor Used		
Empagliflozin	72	45.0%
Dapagliflozin	54	33.8%
Canagliflozin	23	14.4%
Others (e.g., Ertugliflozin)	11	6.9%
CKD Classification		
G3	104	65.0%
G4	56	35.0%

Table: Descriptive Statistics of Renal Function Parameters (n = 160)

Variable	**Mean ± SD**
Serum Creatinine (mg/dL)	2.1 ± 0.6
GFR (mL/min/1.73 m²)	38.4 ± 7.9

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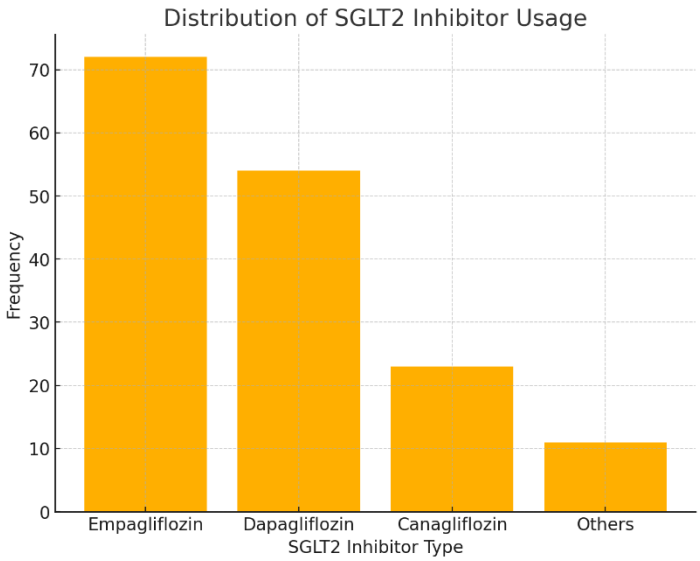
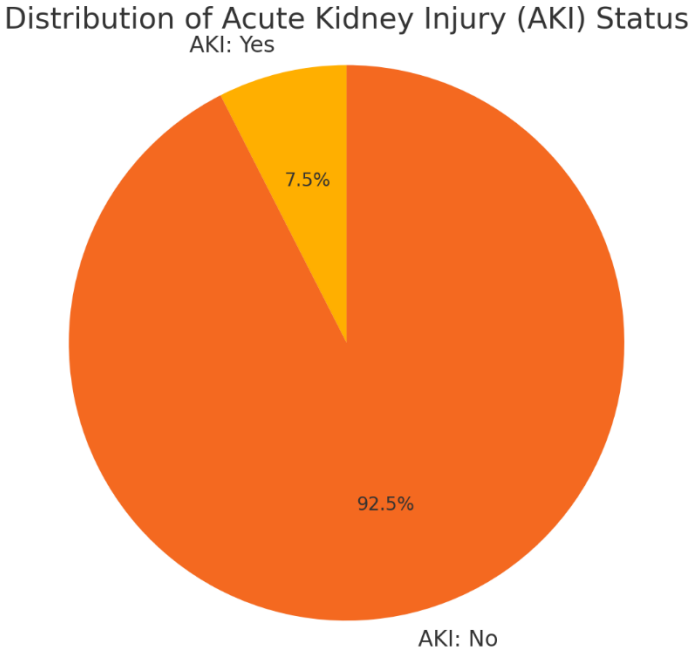
Table: Frequency and Percentage of Acute Kidney Injury (n = 160)

AKI Status	Frequency (n)	Percentage (%)
Yes	12	7.5%
No	148	92.5%





DISCUSSION

The present study aimed to assess the frequency of acute kidney injury (AKI) in patients with chronic kidney disease (CKD) stages III and IV who were concurrently diagnosed with type 2 diabetes mellitus and undergoing treatment with SGLT2 inhibitors. The findings revealed that 7.5% of the participants experienced AKI, a figure moderately higher than that reported in prior international studies. For instance, Perkovic et al. documented an AKI incidence of 3.9% in a large cohort receiving Canagliflozin (3), while Menne et al. observed overall reduced odds of AKI with SGLT2 inhibitors across multiple trials (6). This discrepancy may be attributable to regional variations in healthcare access, comorbidity burden, hydration practices, and medication adherence, particularly in developing countries like Pakistan where earlier-stage CKD may often go undiagnosed or undertreated (16). Empagliflozin emerged as the most commonly prescribed SGLT2 inhibitor in this cohort, aligning with global prescription trends that favor agents with a robust cardiovascular and renal safety profile. The predominance of CKD stage G3 patients in the study mirrors common nephrology referral patterns, where stage G4 patients represent a relatively smaller subset due to progression toward dialysis or transplantation. The mean serum creatinine and GFR values corroborated the classification distribution and further emphasized the moderate-to-severe renal impairment profile of the included patients (17).

While several large randomized controlled trials have demonstrated the renoprotective properties of SGLT2 inhibitors—including reduction in proteinuria, stabilization of eGFR, and prevention of adverse renal outcomes—real-world data, particularly from low- and middle-income countries, remain scarce. The current study adds to this body of evidence by highlighting a modestly elevated risk of AKI, suggesting that patient selection, baseline renal function, and monitoring protocols may significantly influence outcomes. This nuanced risk, though not alarmingly high, reinforces the importance of regular renal function monitoring and cautious volume management in patients initiating or continuing SGLT2 therapy (18,19). One of the key strengths of this study was the inclusion of a clinically relevant population reflective of real-world nephrology practice, where comorbid diabetes and CKD frequently coexist. Additionally, the focus on a specific pharmacologic class allowed for targeted analysis without confounding from broader antihyperglycemic regimens. The use of standardized definitions for both CKD and AKI enhanced the internal validity of the findings (12,20).

However, the study was not without limitations. Its cross-sectional design precluded causal inference or temporal assessment of AKI in relation to drug initiation. The reliance on medical records and single-point laboratory assessments may have led to underestimation or

misclassification of transient AKI episodes. Furthermore, confounders such as volume status, concurrent nephrotoxic drugs, and baseline albuminuria were not controlled, which could have influenced the observed outcomes. The absence of long-term follow-up also limited evaluation of renal recovery or progression following AKI episodes (8,13). Future research should adopt prospective designs with larger sample sizes and longer follow-up to assess not only the incidence but also the predictors and outcomes of AKI in this population. Incorporating markers such as albuminuria, fractional excretion of sodium, and biomarkers of tubular injury could provide mechanistic insights into the pathophysiology of SGLT2-associated AKI. Comparative analyses between individual agents within the SGLT2 class may further delineate differential safety profiles. Emphasis should also be placed on evaluating adherence patterns, hydration practices, and patient education strategies, particularly in resource-constrained settings where the balance between benefit and harm can be influenced by contextual factors (14). Overall, the study underscores the importance of cautious optimism regarding SGLT2 inhibitor use in diabetic CKD patients. While the therapeutic potential of this class remains substantial, vigilance in monitoring renal function and tailoring therapy to individual risk profiles remains crucial for optimizing outcomes in diverse patient populations.

CONCLUSION

This study concluded that acute kidney injury does occur in a proportion of patients with chronic kidney disease and type 2 diabetes mellitus who are treated with SGLT2 inhibitors, though the frequency remained within a clinically manageable range. These findings highlight the importance of cautious patient selection, vigilant renal monitoring, and individualized therapy in clinical practice. By contributing region-specific data, this research adds meaningful insight into the safety profile of SGLT2 inhibitors in a high-risk population, reinforcing their role as a beneficial therapeutic option when used with appropriate safeguards in place.

AUTHOR CONTRIBUTIONS

Author	Contribution
Sana Fiyyaz	Conceptualization, Methodology, Formal Analysis, Writing - Original Draft, Validation, Supervision
Mateen Akram	Methodology, Investigation, Data Curation, Writing - Review & Editing
Rana Muhammad Umar	Investigation, Data Curation, Formal Analysis, Software
Akmal Zaib	Software, Validation, Writing - Original Draft

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