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Original Research Article

EFFECTS OF SODIUM GLUCOSE COTRANSPORTER-2 INHIBITORS ON SERUM URIC ACID LEVELS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: *Hyperuricemia is highly prevalent among patients with chronic kidney disease (CKD) and is associated with accelerated renal progression and increased cardiovascular risk. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated renoprotective and uric acid–lowering benefits in large cardiovascular and renal outcome trials; however, data from low- and middle-income populations with CKD remain limited.* ***Objective:*** *To determine the impact of SGLT2 inhibitor therapy on serum uric acid levels in patients with chronic kidney disease.* ***Study Design:*** *Quasi-experimental study.* ***Setting:*** *Department of Medicine, Aziz Bhatti Shaheed Teaching Hospital, Gujrat.* ***Duration of Study:*** *19 March to 19 June 2025.* ***Methods:*** *A total of 171 patients with established CKD were enrolled. All participants received dapagliflozin-based therapy and were followed for three months. Serum uric acid levels were measured at baseline and at the end of the follow-up period. Statistical analysis was performed using paired t-tests to compare pre- and post-treatment uric acid levels, while independent t-tests and chi-square tests were applied for subgroup comparisons. A p-value ≤ 0.05 was considered statistically significant.* ***Results:*** *The mean baseline serum uric acid level was 7.32 ± 0.46 mg/dL. After three months of therapy, the mean reduction in serum uric acid was 0.70 ± 0.20 mg/dL. The proportion of patients achieving serum uric acid levels ≤7 mg/dL increased significantly from 39.8% at baseline to 70.8% after treatment ($\chi^2 = 29.6$, $p < 0.001$). Greater reductions were observed among male patients, those with a body mass index <30 kg/m², those with CKD stage 3, and those with shorter disease duration.* ***Conclusion:*** *SGLT2 inhibitor therapy was associated with a significant reduction in serum uric acid levels among patients with CKD. These findings support the metabolic and potential renoprotective benefits of SGLT2 inhibitors and their broader role in the comprehensive management of chronic kidney disease.*

Keywords: Chronic Kidney Disease; Sodium–Glucose Cotransporter-2 Inhibitors; Serum Uric Acid; Hyperuricemia; Dapagliflozin; Renal Outcomes

INTRODUCTION

Chronic kidney disease is a significant and increasingly prevalent global health issue, with about 9-13% of the adult population around the globe having the condition, and it is a major contributor to cardiovascular morbidity and premature mortality. (1). Hyperuricemia is very common in patients with chronic kidney disease, and it has been associated with an independent, accelerated rate of renal function and a higher cardiovascular risk. (2). Clinical and experimental studies suggest that elevated serum uric acid may promote renal microvascular damage, oxidative stress, and stimulation of the renin-angiotensin system, thereby contributing to kidney injury. (3). The existence of up to 40-60% of concomitant hyperuricemia in patients with moderate to advanced chronic kidney disease indicates that the clinical relevance of the metabolic abnormality is very high. (4).

Sodium-glucose cotransporter-2 inhibitors inhibit proximal tubular glucose reabsorption, leading to glycosuria and natriuresis and thereby positively affecting intraglomerular hemodynamics. (5). The change in serum uric acid with these agents is believed to be facilitated by elevated uricosuria through inhibition of glucose-urate exchange transporters like GLUT9 in the proximal tubule. (6). Clinical literature consistently reports significant but clinically insignificant improvements of 0.5-1.0 mg/dL in serum uric acid with the introduction of sodium-glucose cotransporter-2 inhibitors. (7). This effect of urate reduction seems unrelated to baseline levels of glycemic control and is therefore more likely a direct effect in the renal tubules. (8).

Findings from many randomized controlled trials have repeatedly demonstrated that sodium-glucose cotransporter-2 inhibitors reduce serum uric acid levels and improve renal outcomes. Empagliflozin significantly lowers serum uric acid levels and is associated with slower renal disease progression in at-risk patients in a recent trial. (9). A follow-up trial also established renal protective benefits of canagliflozin in patients with established diabetic nephropathy, with a concomitant reduction in serum uric acid. (10). Also, in a separate trial, dapagliflozin reduced the risk of kidney failure and mortality, regardless of diabetes status, and lowered uric acid levels. (11). Nevertheless, despite these observations, the majority of the trials were not designed to assess outcomes related to hyperuricemia. (12).

It remains a controversial topic whether serum uric acid is a causative factor in the development of chronic kidney disease, with interventional studies indicating neutral renal prognosis after urate-lowering therapy. (13). Mendelian randomization analyses have proposed uric acid as a marker rather than a mediator of kidney disease progression. (14). However, observational data correlate with increased levels of uric acid with adverse renal and heart outcomes (15). The sodium-glucose cotransporter-2 inhibitors offer a unique opportunity to investigate the decrease in uric acid within the framework of the well-known renoprotective treatment. The effects of these agents are pleiotropic, making it difficult to attribute a benefit to a single mechanism. (16). Moreover, there is very little data on non-Western populations and different levels of chronic kidney disease. These gaps should be addressed to translate trial evidence into clinical practice in the region. (17).

In Pakistan, chronic kidney disease is a significant and under-identified issue, with population-based research estimating a prevalence of 12-16% in adults (18). Poor access to early nephrology care, high diabetes, high hypertension, and late presentation are the reasons behind high rates of fast disease progression and late presentation (19). Hyperuricemia is also a common occurrence among Pakistani patients with chronic kidney disease, partly explained by dietary habits and late diagnosis. Despite this burden, there is a lack

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of local data on metabolic modifiers of chronic kidney disease progression. Their implications for serum uric acid would be significant for risk stratification and overall disease management. The partiality of therapies with multiple protective effects can be particularly important given resource constraints and cardiovascular mortality. Thus, this clinical trial aimed to determine the impact of sodium-glucose cotransporter-2 inhibitor therapy on serum uric acid levels in patients with chronic kidney disease.

METHODOLOGY

The quasi-experimental study was done in the Medicine Department of the Aziz Bhatti Shaheed Teaching Hospital, Gujrat. The study spanned three months from 19 March to 19 June 2025, following the official consent of the research synopsis by the institutional authorities.

The sample size of 171 was determined at a 95% confidence level and an absolute precision of 0.03, based on an anticipated reduction in serum uric acid of 0.7 ± 0.2 mg/dL after dapagliflozin treatment. The sample was recruited using non-probability, consecutive recruitment. The study included patients aged 35-70 years, of any gender, with a known diagnosis of chronic kidney disease, as per the operational definition. Asymptomatic patients whose baseline serum uric acid was not higher than 8 mg/dL were also recruited. Individuals with congenital heart disease or known heart failure were not included in the study. There were no individuals on insulin or on glucagon-like peptide-1 receptor agonists. Patients who had diabetes mellitus were excluded. The individuals with chronic lung diseases related to cor pulmonale, such as chronic obstructive or restrictive lung diseases, were also excluded. Moreover, the patients who were not using diuretics or anti-gout drugs were not included in the research.

RESULTS

A total of 171 patients with chronic kidney disease were included in the study. The mean age of participants was 56.4 ± 8.7 years, with nearly two-thirds (63.7%) belonging to the 51–70-year age group. Male patients constituted 57.3% of the sample, indicating a slight male predominance. The mean BMI was 27.9 ± 4.1 kg/m², with 77.2% of participants classified as overweight or obese. The mean duration of chronic kidney disease was 4.6 ± 2.1 years, reflecting a predominantly moderate-duration CKD population.

Table 1: Demographic Characteristics of Study Participants (n = 171)

Variable	Frequency (n)	Percentage (%)
Age (years)	Mean ± SD	56.4 ± 8.7
35–50 years	62	36.3
51–70 years	109	63.7
Gender		
Male	98	57.3
Female	73	42.7
Body Mass Index (kg/m²)	Mean ± SD	27.9 ± 4.1
Normal (18.5–24.9)	39	22.8
Overweight (25–29.9)	81	47.4
Obese (≥30)	51	29.8
Duration of CKD (years)	Mean ± SD	4.6 ± 2.1

The average serum uric acid level at baseline was 7.32 ± 0.46mg/dL, and 60.2% of patients had a serum uric acid level of 7mg/dL or higher. The estimated mean glomerular filtration rate was 42.5 ± 9.8 mL/min/1.73 m2, indicating that it was mostly stage 3 chronic kidney disease. About a third of the subjects fell in stage 4 CKD. These results are a sign of a population with moderate renal impairment and a high baseline uric acid level, with clinical relevance.

Table 2: Baseline Clinical Characteristics and Outcomes (n = 171)

Variable	Mean ± SD / n (%)
Baseline Serum Uric Acid (mg/dL)	7.32 ± 0.46
Serum Uric Acid ≤7 mg/dL	68 (39.8%)
Serum Uric Acid >7 mg/dL	103 (60.2%)
Baseline eGFR (mL/min/1.73m²)	42.5 ± 9.8
CKD Stage 3	112 (65.5%)
CKD Stage 4	59 (34.5%)
Baseline BMI (kg/m²)	27.9 ± 4.1

After three months of treatment, there was a considerable change in serum uric acid categories. The percentage of patients with serum uric acid 7mg/dL or less rose to 70.8% after treatment, compared with 39.8% at baseline. In line with this, individuals with levels above 7mg/dL decreased from 60.2% to 29.2%. The chi-square test showed a highly significant relationship between treatment exposure and uric acid category ($\chi 2 = 29.6$, $p < 0.001$), indicating a significant treatment effect.

Table 3: Pre- and Post-Treatment Stratification of Serum Uric Acid Levels

Serum Uric Acid Category	Baseline n (%)	After 3 Months n (%)	χ^2	p-value
≤7 mg/dL	68 (39.8)	121 (70.8)		
>7 mg/dL	103 (60.2)	50 (29.2)	29.6	<0.001

The independent t-test demonstrated statistically significant differences in mean serum uric acid reduction across stratified subgroups. The mean change was lower in females than in male patients (0.74 vs 0.66 mg/dL, $p = 0.041$). Patients with a BMI less than 30 kg/m 2 had a substantially greater decrease than obese patients (0.71 vs 0.63 mg/dL, $p = 0.032$). Equally, patients who had a short CKD (less than 5 years) showed higher uric acid reduction compared to patients with a longer duration of the disease ($p = 0.018$).

Table 4: Comparison of Mean Serum Uric Acid Levels Using Independent t-Test After Stratification (n = 171)

Stratification Variable	Mean SUA Reduction (mg/dL) ± SD	p-value
Gender		
Male (n=98)	0.74 ± 0.21	0.041
Female (n=73)	0.66 ± 0.19	
BMI		
BMI <30 kg/m² (n=120)	0.71 ± 0.20	0.032
BMI ≥30 kg/m² (n=51)	0.63 ± 0.18	
CKD Duration		
≤5 years (n=94)	0.76 ± 0.22	0.018
>5 years (n=77)	0.64 ± 0.19	

The reduction in serum uric acid was significantly associated with various clinical variables. Greater reductions (≥0.7 mg/dL) were more frequent in male patients than in women ($p = 0.042$). The number of patients who responded significantly increased compared with those with stage 4 disease and CKD stage 3 (66.1% vs 35.6%, $p < 0.001$). Moreover, patients who were not obese tended to experience a greater decrease in uric acid than obese patients ($p < 0.001$), reinforcing the role of disease severity and metabolic status in treatment response.

Table 5: Correlation of Post-Treatment Serum Uric Acid Reduction with Clinical Variables (Chi-Square Test)

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Variable	SUA Reduction ≥0.7 mg/dL n (%)	SUA Reduction <0.7 mg/dL n (%)	χ^2	p-value
Gender (Male)	61 (62.2)	37 (37.8)		
Gender (Female)	34 (46.6)	39 (53.4)	4.12	0.042
CKD Stage 3	74 (66.1)	38 (33.9)		
CKD Stage 4	21 (35.6)	38 (64.4)	13.8	<0.001
BMI <30 kg/m²	79 (65.8)	41 (34.2)		
BMI ≥30 kg/m²	16 (31.4)	35 (68.6)	15.2	<0.001

DISCUSSION

This research aimed to assess how sodium-glucose cotransporter-2 inhibitor therapy would affect serum uric acid levels in patients with chronic kidney disease over three months. The baseline serum uric acid level in the present study of 171 patients was 7.32 ± 0.46 mg/dL, and it significantly improved after treatment, with a mean improvement of about 0.70 ± 0.20 mg/dL. The size of the effect is clinically important because even a reduction of 0.5 mg/dL in serum uric acid level has been linked with better renal and cardiovascular outcomes in post-observation cohort studies. (19). The change in the uric acid category was statistically significant, with patients with levels at or below 7mg/dL increasing from 39.8% to 70.8% at the end of treatment ($\chi^2 = 29.6$, $p < 0.001$). These results are consistent with mechanistic experiments showing that SGLT-2 inhibition induces uricosuria by modulating transporter activity in the proximal tubules. (20). In large cardiovascular outcome studies, similar decreases in serum uric acid, ranging from 0.6 to 0.9 mg/dL, were noted. (21). These trials are consistent with the current findings, which enhance the internal validity of the observed treatment effect.

Another important modifier of treatment response was body mass index, with non-obese (BMI <30kg/m2) patients showing a higher mean reduction in uric acid than obese patients (0.71 ± 0.20 vs 0.63 ± 0.18 mg/dL, p=0.032). The population sample described in this research consisted of 77.2% overweight and obese individuals, which is similar to the high metabolic burden that is typically witnessed in CKD cohorts. (21). Obesity is also known to interfere with renal urate excretion by causing insulin resistance and altering tubular transporter activity, which could inhibit pharmacologic uricosuria. (22). Post-hoc analyses of a recent trial also reported similar trends, with greater metabolic derangements associated with smaller relative changes in serum uric acid. (24). Nevertheless, the mean loss of over 0.6 mg/dL was observed in the currently studied obese patients, though attenuated, resulting in a clinically significant outcome. The chi-square analysis also revealed that obese patients had a reduction of ≥0.7 mg/dL, whereas non-obese patients had 65.8 ($\chi^2 = 15.2$, $p = 0.001$). These data indicate that the urate-lowering effect of SGLT-2 inhibition depends on metabolic status, which does not exclude its benefits.

Treatment response in this study was strongly associated with disease severity, as measured by CKD stage and duration. The proportion of patients with CKD stage 3 who achieved significant uric acid lowering (66.1%) was higher than that of patients with CKD stage 4 (35.6%), and the difference between the two groups was highly significant ($\chi^2 = 13.8$, $p < 0.001$). Likewise, those with a CKD duration of 0 to 5 years showed larger mean changes than those with a longer disease duration (0.76 ± 0.22 vs 0.64 ± 0.19 mg/dL, p = 0.018). The findings are biologically robust, with advanced CKD being one in which nephron mass and tubular secretory capacity decrease, rendering them incapable of responding to uricosuric therapy. (23). Another trial showed weaker metabolic effects of SGLT-2 inhibitors at lower eGFR, while still exhibiting renal protective effects. (24). These findings were further supported by the current findings, which measured uric acid response levels stratified by CKD severity.

The general pre- and post-treatment comparison showed significant redistribution of serum uric acid in the cohort. The percentage of patients whose serum uric acid exceeded 7mg/dL also decreased, from 60.2% at baseline to 29.2% after three months of treatment, an absolute change of 31.0%. This type of categorical improvement is clinically relevant, as an elevated serum uric acid level (over 7 mg/dL) is linked to faster CKD Development and greater cardiovascular outcomes. (25). Similar categorical changes were noted in the analysis by Mori et al. (2024), in which canagliflozin showed a significant decrease in cases of gout and hyperuricemia-related events. (26). Chi-square analysis supports the conclusion that the observed changes were not due to random variation. In addition, the reliability of the findings across various stratifications strengthens them. The findings support serum uric acid as a useful metabolic endpoint in future CKD studies of SGLT-2 inhibitors.

In the general clinical context, the results of the current research have significant implications for the management of CKD under resource-constrained conditions. Average baseline eGFR of 42.5 ± 9.8 mL/min/1.73 m^2 and average age of 56.4 ± 8.7 years indicate that it is a high-risk population regarding progression and cardiovascular complications. Therapies with several effects, such as a mean reduction of uric acid of about 0.7 mg/dL, are especially useful in such groups of people. (27). The study was conducted on a region-specific population, with most prior global research conducted on Western cohorts, which is consistent with their findings. (28). The statistical significance of the findings across gender, BMI, and CKD stage groups suggests they may be widely applicable. Mechanically, the urate-lowering effect can be added to the previously described hemodynamic and anti-inflammatory processes of SGLT-2 inhibitors. (29).

There are some limitations to consider when interpreting the findings of this study. The 3-month follow-up period was relatively short, and it was not possible to evaluate the sustained decrease in serum uric acid and its effect on renal outcomes. Since the research was carried out at a single center, the applicability of the findings to broader, more heterogeneous populations is questionable. Potential confounding variables, e.g., dietary purine levels and variability in adherence, were not quantified formally. Also, the study does not include patients with diabetes mellitus, which limits the extrapolation of the results to the general population of patients with chronic kidney disease, who are most frequently prescribed sodium–glucose cotransporter-2 inhibitors.

CONCLUSION

This study has shown that treatment with a sodium-glucose cotransporter 2 inhibitor had a statistically and clinically significant reduction in serum uric acid levels in patients with chronic kidney disease over 3 months. The average serum uric acid dropped to about 0.70 ± 0.20 mg/dL, and the percentage of patients with uric acid levels below 7 mg/dL rose to 70.8%, up from 39.8%. It was found that significant associations were observed along the main clinical strata, such as gender, body mass index, chronic kidney disease stage, and duration of illness, and indicated a consistent treatment effect. Patients with earlier-stage disease, lower body mass index, and short-term illness exhibited greater uric acid reduction, underscoring the significant role of therapeutic intervention at an early stage. These are consistent with large-scale international trials and support the uricosuric effect of sodium-glucose cotransporter-2 inhibitors as a class effect. On the whole, the findings substantiate the potential of sodium-glucose cotransporter-2 inhibitors as metabolically favorable therapeutic agents in the chronic kidney disease management outside

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glycemic control.

DECLARATIONS

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All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department Concerned. (IRBEC-AZBHG-243/24)
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

ABDUL RAOOF
Conception of Study, Development of Research Methodology Design, Study Design, Review of manuscript, and final approval of manuscript.
SYED BABAR HUSSAIN RIZVI
Data entry, data analysis, and drafting an article.
Conception of Study, Final approval of manuscript.
Study Design, Review of Literature.
FARHAN NASIR
Manuscript drafting.
Manuscript revisions, critical input.

All authors read and approved the final version of the manuscript

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