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Effect of Glomerular Filtration Rate on Uric Acid Metabolism in a Retrospective Cohort of Type-2 Diabetes Mellitus Patients on SGLT-2 Inhibitor Therapy

Emre Vuraloglu,[1] Altug Kut,[2] Özlem Turhan İyidir[2]

[1]Department of Family Medicine, Başkent University Faculty of Medicine, Ankara, Türkiye
[2]Department of Endocrinology and Metabolism, Başkent University Faculty of Medicine, Ankara, Türkiye

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Address for correspondence:
Altug Kut.
Department of Family Medicine, Başkent University Faculty of Medicine, Ankara, Türkiye
Phone: +90 532 560 80 45
E-mail: altugkut@gmail.com

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ABSTRACT

Objective: This study aimed to investigate the effects of different glomerular filtration rates (GFRs) on serum uric acid (SUA) levels in patients with type 2 diabetes mellitus receiving sodium-glucose transporter 2 (SGLT-2) inhibitor therapy.

Materials and Methods: A total of 3,004 patients with type 2 diabetes mellitus treated with SGLT-2 inhibitors between January 2017 and September 2022 were analyzed. Patients who did not attend follow-up visits, had missing data, discontinued SGLT-2 inhibitors, were taking medications that affect SUA levels, or were being treated for gout were excluded. The final study group consisted of 410 patients. Biochemical parameters were retrospectively compared before treatment and at the 3rd and 12th months of drug therapy. To evaluate the effect of GFR on uric acid levels during SGLT-2 inhibitor treatment, patients were analyzed with and without grouping based on GFR levels.

Results: The study showed that glycated hemoglobin, fasting plasma glucose, creatinine, low-density lipoprotein, triglycerides, and SUA levels decreased with SGLT-2 inhibitor treatment, while high-density lipoprotein and urine glucose levels increased. The efficacy of SGLT-2 inhibitors in reducing SUA levels was found to correlate closely with changes in GFR, with a notable reduction observed at GFR levels below 60 mL/min/1.73 m^2. Moreover, the effect was independent of the specific active substance used.

Conclusion: SGLT-2 inhibitors not only regulate blood glucose levels and lipid profiles but also have a significant impact on uric acid levels. However, this study found that this effect is considerably diminished in patients with extremely low GFR.

Keywords: Diabetes mellitus, glomerular filtration rate, sodium-glucose transporter 2 inhibitors, uric acid, chronic kidney diseases.

INTRODUCTION

The prognosis and course of type 2 diabetes mellitus (T2DM) are closely associated with elevated uric acid levels, along with many other contributing factors. In particular, chronic renal failure (CRF) and cardiovascular diseases are among the primary complications linked to hyperuricemia.[1]

Laboratory studies have demonstrated that uric acid impairs endothelial function, reduces nitric oxide production, induces oxidative stress, and stimulates vascular smooth muscle proliferation.[2]

Sodium-glucose transporter 2 (SGLT-2) inhibitors in patients with T2DM improve long-term outcomes in major cardiovascular events and renal function, which progressively deteriorate due to diabetes.[2,3–5] Studies have shown that these benefits are partly independent of the glucose-lowering effects of SGLT-2 inhibitors.[2] Although direct evidence is limited, one widely accepted potential mechanism for their renoprotective effects is the reduction of elevated uric acid levels in the bloodstream.[6,7]

While there is a consensus that the primary mechanism by which SGLT-2 inhibitors lower serum uric acid (SUA) levels involves increased urinary excretion of uric acid, the precise mechanism is unclear.[8] Human urate transporter 1 (URAT-1) and facilitative glucose transporter 9 (GLUT-9) are the primary transporters responsible for urate reabsorption. Organic anion transporters 4 and 10 (OAT-4 and OAT-10) also contribute to this process. The reuptake of uric acid from circulation into epithelial cells is mediated by OAT-1 and OAT-3, while its secretion into the nephron lumen is mediated by multidrug resistance-associated protein 4 (MRP-4) and ATP-binding cassette subfamily G member 2 (ABCG-2).[2] *In vitro* experiments have shown that uric acid is not directly transported by SGLT-2, and SGLT-2 inhibitors have no effect on the activity of URAT-1, OAT-4, or OAT-10.[9] However, uric acid reabsorption was found to be inhibited following treatment with SGLT-2 inhibitors. This effect was attributed to reduced glucose reabsorption and decreased activity of GLUT-9 isoform 2.[9] Novikov A. et al.[10] reported that two specific transporters, urate transporter-1 and glucose transporter-9, play crucial roles in the efficient excretion of uric acid. Their research further highlighted that SGLT-2 inhibitor, a protein involved in glucose reabsorption in the kidney, can decrease GLUT-9 activity. This reduction in GLUT-9 activity could diminish uric acid reabsorption in a specific variant of GLUT-9 found in the kidney's collecting ducts, thereby increasing the amount of uric acid excreted in urine. Consequently, the effectiveness of SGLT-2 inhibitors in enhancing uric acid excretion is closely linked to kidney function, which may explain why their ability to lower uric acid levels diminishes as kidney function declines.

Consistent with the literature, previous meta-analyses of randomized controlled trials (RCTs) have suggested that the degree of reduction in SUA levels decreases as GFR becomes restricted.[6,11] Therefore, the effects of SGLT-2 inhibition seem to be attenuated in patients with chronic kidney disease (CKD).[6,11] However, some RCTs examining the relationship between SUA levels and GFR have yielded conflicting results.[12–14] While RCTs have predicted reductions in SUA levels relative to GFR and presented these findings in meta-analyses, the presence of contradictory reports and limited real-world data support indicate that this issue requires further investigation.

KEY MESSAGES

- This study focuses on the effect of different GFR on SUA metabolism in diabetic patients, a point that has not yet been sufficiently clarified by research on SGLT-2 inhibitors, which are widely used for their cardiorenal protective effects as well as in diabetes.
- The results showed that SGLT-2 inhibitor treatment had no effect on SUA levels in patients with low GFR.
- Regardless of the active substance, SGLT-2 inhibitors significantly reduce SUA levels as treatment duration is prolonged and GFR increases.

This study aimed to evaluate how uric acid excretion varies with different GFR levels in a cohort of diabetic patients who had been receiving continuous SGLT-2 inhibitor therapy for at least 12 months (52 weeks) and were monitored in real time at a university hospital. Additionally, the study sought to assess the efficacy of the active substance in patients with impaired renal function.

The preprint of this article was previously posted to the Research Square server on March 21, 2024.[15]

MATERIALS AND METHODS

Study Design

This retrospective cohort study was conducted with approval from the Başkent University Medical and Health Sciences Research Board (Institutional Review Board; IRB) under IRB number KA 22/494 (ethics committee date: December 20, 2022). In 2017, the clinical use of SGLT-2 inhibitors began in Türkiye, starting with dapagliflozin and subsequently empagliflozin. No other SGLT-2 inhibitors became available in Türkiye during the study period. The study population was recruited from patients diagnosed with T2DM who attended the Endocrinology and Metabolic Diseases Outpatient Clinics of Başkent University, Türkiye, between January 1, 2017 and September 30, 2022. Patient recruitment was non-randomized, and data were collected from all individuals meeting the inclusion criteria during the study period. A total of 83,295 patients with T2DM were evaluated and registered in the database. After removing duplicate entries, 25,112 unique patients with T2DM remained. Among these, 3,004 individuals who initiated treatment with an SGLT-2 inhibitor and adhered to the prescribed therapy formed the study population. The study flowchart is presented in Figure 1.

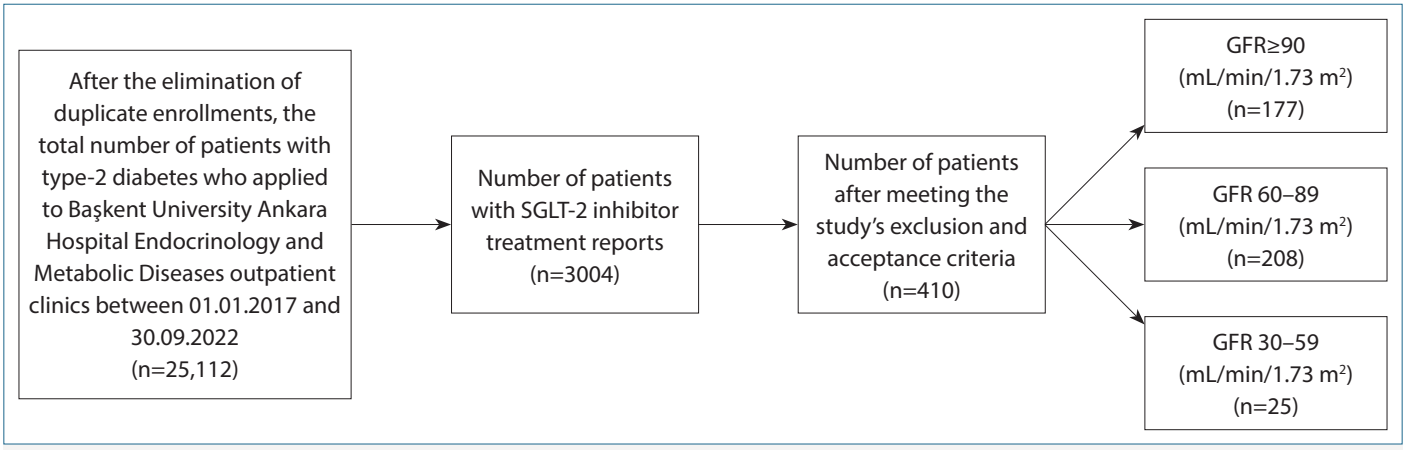

Figure 1. Flowchart of the study.

Exclusion and Inclusion Criteria

Exclusion criteria for the study population included the following:

- Discontinuation of SGLT-2 inhibitor therapy.
- Failure to attend follow-up visits at the third month and/or twelfth month.
- Use of medications that lower serum uric acid levels, including:
  - Drugs that inhibit uric acid production (e.g., allopurinol and febuxostat).
  - Uricolytic drugs (e.g., pegloticase).
  - Uricosuric drugs (e.g., probenecid, sulphinpyrazone, fenofibrate, and losartan).
- Use of medications that increase serum uric acid levels, including:
  - Diuretics, cyclosporine, tacrolimus, levodopa, pyrazinamide, and ethambutol.
- Treatment for acute gout.

On the other hand, the inclusion criteria for this study were as follows:

- Patients must have attended Başkent University Endocrinology and Metabolic Diseases Outpatient Clinic between January 1, 2017 and September 30, 2022.
- Patients must have received an SGLT-2 inhibitor drug use report or prescription.
- Patients must have used the prescribed SGLT-2 inhibitor continuously for at least 12 months without interruption.
- The following laboratory parameters must have been measured and recorded during each visit:
  - Serum glycated hemoglobin (HbA1c).
  - Fasting plasma glucose (FBG).
  - Creatinine.
  - Glomerular filtration rate (GFR).
  - High-density lipoprotein cholesterol (HDL-C).
  - Low-density lipoprotein cholesterol (LDL-C).
  - Triglycerides.
  - Uric acid.
  - Urine glucose.

After applying these inclusion criteria and corresponding exclusion criteria, 410 patients constituted the final study cohort. As the study utilized retrospective data derived from routine follow-ups, there were no instances of exclusion or data loss during the analytical process for the patients included in the study group. The study cohort was initiated retrospectively with 410 patients, and the same number of patients was included in the final analysis.

Variables

The parameters assessed in this study included age, sex, duration of diabetes, body mass index, type of SGLT-2 inhibitor active substance used (empagliflozin or dapagliflozin), and laboratory measurements such as serum HbA1c, FBG, creatinine, GFR, HDL-C, LDL-C, triglycerides, uric acid, microalbuminuria, and urine glucose levels. The independent variable of the study was SGLT-2 inhibitor treatment. The modulatory variable of the study was GFR, measured using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) 2021 technique. The dependent variable of the study was the SUA level. The GFR, considered a regulatory variable in this study, was analyzed in three groups according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[16] The groups were categorized as follows:

- GFR ≥90 mL/min/1.73 m^2: Normal or high.
- GFR = 60–89 mL/min/1.73 m^2: Mildly decreased.
- GFR = 30–59 mL/min/1.73 m^2: Moderately decreased.

Additionally, the relationship between SUA and GFR was examined by treating GFR as a continuous variable, without dividing the patients into groups.

We utilized data extracted from the hospital's electronic medical information system to obtain laboratory values measured prior to initiating SGLT-2 inhibitor treatment, as well as laboratory values measured at the third and twelfth months of treatment, for patients who met the inclusion criteria. To prevent bias, the investigators did not interfere with the file information during the data collection or patient evaluation process.

Statistical Methods

We presented continuous data as means, standard deviations, medians, minimums, and maximums, and discrete data as numbers and percentages in descriptive statistics. The Kolmogorov-Smirnov test was used to assess the conformity of continuous data to a normal distribution. Missing and marginal data were excluded from the analysis.

To compare serum HbA1c, FBG, creatinine, HDL-C, LDL-C, triglycerides, uric acid, microalbuminuria, and urine glucose levels measured before SGLT-2 inhibitor treatment, at 3 months, and at 12 months after treatment, we used the Friedman test. Friedman's multiple comparison test was applied to determine which measurements showed differences. Patients were grouped according to their GFR prior to SGLT-2 inhibitor treatment. Changes in SUA levels among these groups before treatment, after 3 months, and after 12 months of treatment were analyzed using the Mann-Whitney U test. To examine the relationship between GFR and SUA levels without grouping patients, we used the Pearson correlation coefficient. A modelled association plot with 95% confidence intervals (CI) illustrated the range of GFR values studied, the error margin around estimates at each continuous GFR level, and the linearity of the relationship. All statistical evaluations were performed using IBM SPSS, version 20 (IBM Corp., released 2011; Armonk, NY, USA). A p value of <0.05 was considered the threshold for statistical significance at the 95% confidence interval.

RESULTS

Out of the 3,004 patients in the initial study population, 2,594 were excluded based on various inclusion and exclusion criteria. During the exclusion process, 2,119 patients were excluded for failing to attend the 3rd and/or 12th month follow-up visits regularly, and 2,119 patients were excluded due to missing data for one or more of the following parameters: HbA1c, FBG, creatinine, GFR, HDL-C, LDL-C, triglycerides, uric acid, and urine glucose levels. This reduced the sample size to 885 patients. Further exclusions were made as follows: 206 (7.9%) patients were receiving diuretics; 137 (5.3%) patients were on allopurinol; 70 (2.7%) patients were on losartan; and 58 (2.6%) patients were on fenofibrate. Additionally, 3 patients (0.1%) were excluded due to non-continuous use of SGLT-2 inhibitors, and 1 patient (0.03%) was excluded for an acute gout attack. The final sample size for analysis was 410 patients. Baseline characteristics are summarized in Table 1.

Among the included patients, 55.4% (n=227) were male and 44.6% (n=183) were female, yielding a male-to-female ratio of 1:0.8. The mean age was 59.1±11.55 years (range: 20–87 years; males: 59.30±11.16; females: 58.79±12.03; p=0.680). All patients received SGLT-2 inhibitors during the study period, with 54.9% (n=225) taking dapagliflozin and 45.1% (n=185) taking empagliflozin. Regardless of whether the drugs were used alone or in combination, the distribution of additional active substances used by the patients alongside SGLT-2 inhibitors was as follows:

- Metformin: 88.5% (n=363),
- Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors): 43.2% (n=177),
- Insulin: 18.5% (n=76),
- Sulfonylureas: 18.1% (n=74),
- Thiazolidinediones (TZD): 15.1% (n=62),
- Glucagon-like peptide-1 agonists (GLP-1) agonists: 4.9% (n=20), and
- Glinides: 0.5% (n=2).

Regarding GFR values, 43.2% (n=177) of patients had a GFR of ≥90 mL/min/1.73 m^2, 50.7% (n=208) had a GFR of 60–89 mL/min/1.73 m^2, and 6.1% (n=25) had a GFR of 30–59 mL/min/1.73 m^2.

Table 2 presents the comparison of serum and urine findings for the 410 patients included in the study across three time points: before initiating SGLT-2 inhibitor therapy, at the 3rd month, and at the 12th month of treatment, analyzed using the Friedman one-way repeated measures analysis of variance by ranks test. Statistically significant differences were observed in the study group's serum HbA1c, FBG, creatinine, HDL-C, LDL-C, triglyceride, uric acid, and urine glucose levels measured before initiating SGLT-2 inhibitor therapy and at months 3 and 12 of therapy. Under SGLT-2 inhibitor treatment, HDL-C and urine glucose levels increased, while all other values decreased.

Table 1. Baseline characteristics of the patients in the study (n=410)

	Mean±SD	Median (Min–Max)	n	%
Age (years)	59.10±11.55	59 (20–87)		
Diabetes duration (years)	9.91±7.68	9 (1–40)		
Body mass index (kg/m^2)	30.74±4.99	30.2 (19.1–46.9)		
Gender				
Male			227	55.4
Female			183	44.6
SGLT-2 inhibitor active substance				
Dapagliflozin			225	54.9
Empagliflozin			185	45.1
Presence of complications related to diabetes				
Retinopathy			41	10.0
Nephropathy			59	14.4
Polyneuropathy			61	14.9
Glomerular filtration rate				
≥90 (mL/min/1.73 m^2)			177	43.2
60–89 (mL/min/1.73 m^2)			208	50.7
30–59 (mL/min/1.73 m^2)			25	6.1

SD: Standard deviation; Min: Minimum; Max: Maximum.

Table 2. Comparison of serum and urine findings of patients before, and at 3 and 12 months of sodium-glucose cotransporter 2 (SGLT-2) inhibitor treatment

SGLT-2 Use (n=410)	Predrug Median (Min–Max)	3rd month of therapy Median (Min–Max)	12th month of therapy Median (Min–Max)	p*
HbA_1C	6.9 (4.5–14.6)	6.4 (4.5–12.6)	6.2 (4.0–12.6)	<0.001[a]
FBG	140 (77–441)	121.5 (61–376)	112 (70–360)	<0.001[a]
Creatinine	0.86 (0.54–1.88)	0.84 (0.51–1.79)	0.82 (0.40–2.03)	0.002[a]
Uric acid	5.7 (2.7–9.2)	5 (2.3–8.3)	4.8 (2.1–8.2)	<0.001[a]
HDL-C	44 (18–94)	46.2 (22–93)	48 (27–91)	<0.001[a]
LDL-C	134 (52–357)	116 (42–216)	114 (34–222)	<0.001[a]
Triglyceride	152 (37–1342)	135 (30–745)	125 (35–769)	<0.001[a]
Urine glucose	0 (0–2000)	1000 (0–2000)	1000 (0–2000)	<0.001[a]

HbA_1C: Glycated hemoglobin; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; *: P<0.05 was accepted as the threshold for statistical significance at a 95% confidence interval; a: The Friedman one-way repeated measures analysis of variance by ranks test results.

The Friedman multiple comparison test was applied to identify specific time intervals with statistically significant differences for each variable (HbA1c, FBG, creatinine, uric acid, HDL-C, LDL-C, triglycerides, and urine glucose). The results are presented in Table 3. According to multiple comparison analyses, the effect of SGLT-2 inhibitors on SUA levels increased at each time interval compared to the previous interval, with a continued and significant decrease. Accordingly, as the duration of SGLT-2 inhibitor use in a patient's treatment is extended, the reduction in SUA levels is expected to continue increasing.

Table 3. Comparison of differences in serum and urine findings at specific time intervals for each variable

Variables	Time intervals	p*
HbA_1C	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.000[a]
FBG	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.000[a]
Creatinine	Predrug - 3rd month of therapy	0.002[a]
	Predrug - 12th month of therapy	0.152[a]
	3rd month of therapy - 12th month of therapy	0.413[a]
Uric acid	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.000[a]
HDL-C	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.000[a]
LDL-C	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	1.000[a]
Triglyceride	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.006[a]
Urine glucose	Predrug - 3rd month of therapy	0.000[a]
	Predrug - 12th month of therapy	0.000[a]
	3rd month of therapy - 12th month of therapy	0.606[a]

HbA_1C: Glycated hemoglobin; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; *: P value of <0.05 was considered statistically significant at a 95% confidence interval; a: The Friedman's multiple comparison test results.

The study also analyzed microalbuminuria levels, which were measured at least three times: before treatment, and at 3 and 12 months of therapy. The mean microalbuminuria levels were 5.08±22.84 mg/dL, 4.35±20.85 mg/dL, and 3.34±13.66 mg/dL, respectively. No statistically significant differences were observed between these values (p=0.430).

We also analyzed the effects of SGLT-2 inhibitors on reducing SUA levels at different GFR categories (Table 4) using the Friedman one-way repeated measures analysis of variance by ranks test. Based on the information in Table 4, when the GFR is within normal limits or mildly reduced, and the duration of SGLT-2 inhibitor treatment is prolonged, the reduction in uric acid levels progressively increases, and this effect is statistically significant. However, when the GFR falls below 60 mL/min/1.73 m^2, SUA levels still decrease to a certain extent, but the strength of this effect becomes statistically insignificant. The findings of our study indicate that SGLT-2 inhibitors had no statistically significant impact on SUA levels in the cohort with a GFR of 30–59 mL/min/1.73 m^2 (p=0.368). The relatively small number of patients in this GFR range introduced a type II statistical margin of error and, as a result, this subgroup was excluded from the tables.

The effect of treatment duration on SUA reduction was also analyzed at normal (≥90 mL/min/1.73 m^2) and mildly decreased (60–89 mL/min/1.73 m^2) GFR levels using the Mann-Whitney U test (Table 5). The results showed that the uric acid-lowering effect was more pronounced at higher GFR levels and that prolonged treatment with SGLT-2 inhibitors significantly enhanced this effect. The significant impact of SGLT-2 inhibitors on SUA levels was observed as early as month 3 and continued to gradually increase over time.

Table 4. Effect of sodium-glucose cotransporter 2 inhibitor therapy on serum uric acid levels at different glomerular filtration rates

GFR levels (mL/min/1.73 m²)	Uric acid levels (mg/dL)			p*
	Predrug Median (Min–Max)	3rd month of therapy Median (Min–Max)	12th month of therapy Median (Min–Max)	
≥90	5.5 (2.7–9.0)	4.7 (2.5–8.3)	4.3 (2.1–8.2)	<0.001[a]
60–89	5.8 (3.0–9.1)	5.2 (2.3–8.0)	5 (2.7–7.4)	<0.001[a]

GFR: Glomerular filtration rate; Min: Minimum; Max: Maximum; *: P<0.05 was accepted as the threshold for statistical significance at a 95% confidence interval; a: The Friedman one-way repeated measures analysis of variance by ranks test results.

Table 5. Comparison of serum uric acid-lowering effect of sodium glucose cotransporter-2 inhibitors at normal and mildly decreased GFR levels

Treatment status	Uric acid levels (mg/dL)		p*
	GFR ≥90 (mL/min/1.73 m²) Median (Min–Max)	GFR 60–89 (mL/min/1.73 m²) Median (Min–Max)	
Difference between pre-drug and 3rd month of therapy	-0.60 (-4.80–2.0)	-0.45 (-3.70–2.40)	0.063[a]
Difference between pre-drug and 12th month of therapy	-1.0 (-4.60–1.40)	-0.70 (-4.10–2.50)	0.007[a]
Difference between 3rd month and 12th month of therapy	-0.3 (-3.60–2.40)	-0.3 (-2.30–2.0)	0.069[a]

GFR: Glomerular filtration rate; Min: Minimum; Max: Maximum; *: P value of <0.05 was accepted as the threshold for statistical significance at a 95% confidence interval; a: Mann-Whitney U test results.

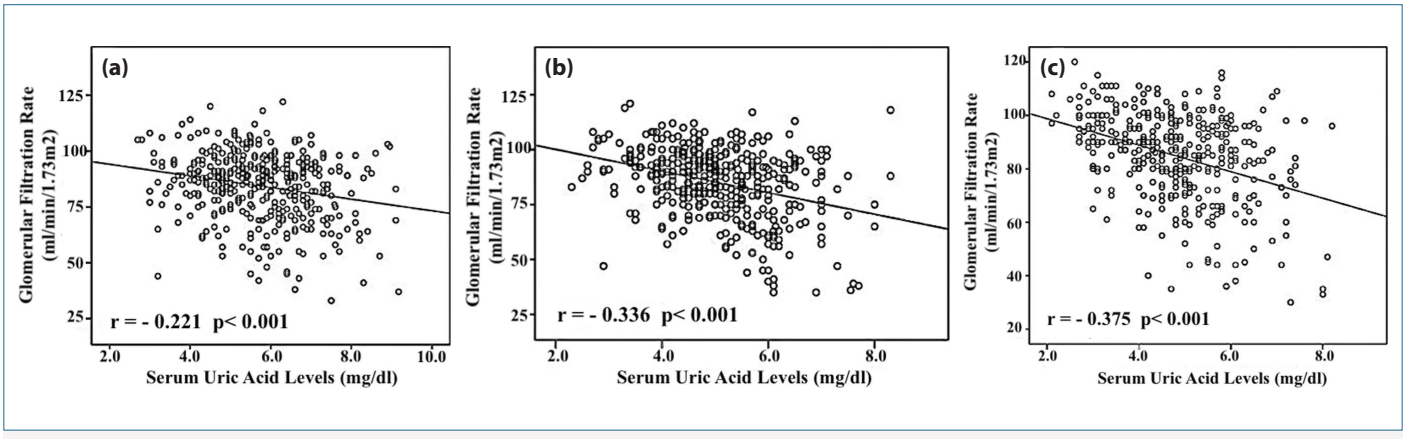

Figure 2. Correlation between glomerular filtration rate and serum uric acid levels at various stages of treatment: **(a)** Before the initiation of sodium-glucose transporter 2 (SGLT-2) inhibitor treatment. **(b)** At the 3rd month of treatment. **(c)** At the 12th month of treatment (Pearson Correlation Test).

We also examined the association between SUA levels and GFR by treating GFR as a continuous variable in our study. A plot of the modeled association with a 95% CI revealed the range of GFR values examined, the estimated margin of error around each continuous GFR level, and the linearity of the relationship (Fig. 2) (Pearson Correlation Test). Our results showed a linear negative correlation between GFR and SUA levels (p<0.001).

Additionally, we investigated whether the effects of different SGLT-2 inhibitors on lowering SUA levels varied (Table 6) using the Friedman one-way repeated measures analysis of variance by ranks test. The analysis showed that different active substances had similar effects across varying treatment durations and GFR levels, resulting in a significant decrease in SUA levels.

Table 6. Effect of different active substances on serum uric acid levels according to different glomerular filtration rates

GFR levels (mL/min/1.73 m²)	AS	Uric acid levels (mg/dL)			p*
		Predrug Median (Min–Max)	3rd month of therapy Median (Min–Max)	12th month of therapy Median (Min-Max)	
≥90	DAPA (n=103)	5.8 (3.0–9.0)	4.9 (2.7–8.3)	4.4 (2.5–8.2)	<0.001[a]
	EMPA (n=74)	5.2 (2.7–8.6)	4.5 (2.5–8.3)	4.0 (2.1–7.6)	<0.001[a]
60–89	DAPA (n=112)	5.81 (3.0–8.4)	5.1 (2.3–8.0)	5 (2.7–7.4)	<0.001[a]
	EMPA (n=96)	5.77 (3.2–9.1)	5.30 (2.9–8.0)	5.0 (3.0–7.4)	<0.001[a]

GFR: Glomerular filtration rate; AS: Active substance; Min: Minimum; Max: Maximum; DAPA: Dapagliflozin; EMPA: Empagliflozin; *: P<0.05 was accepted as the threshold for statistical significance at a 95% confidence interval; a: The Friedman one-way repeated measures analysis of variance by ranks test results.

DISCUSSION

Our study demonstrated that SGLT-2 inhibitors not only lower blood glucose levels but also significantly reduce uric acid levels, although this reduction is diminished in patients with lower GFR levels.

Patients with T2DM generally exhibit higher uric acid concentrations than individuals without the disease. While these levels often fall within the normal laboratory range, they serve as independent risk factors for cardiovascular (CV) and renal diseases. SGLT-2 inhibitor therapy has been widely utilized in large RCTs to lower CV risk and enhance renal function in T2DM patients.[5] Similarly, two meta-analyses encompassing 62 and 43 clinical trials, respectively, demonstrated that SGLT-2 inhibitors reduced SUA concentrations, even when baseline uric acid levels were within the normal range. This effect persisted over two years.[6,11] Our study showed that SUA levels were mostly within the normal range, particularly in patients with normal GFRs. A decline in uric acid levels was observed throughout the treatment period and remained significant at the 12th month of therapy.

There remains uncertainty regarding the effects and optimal doses of different SGLT-2 inhibitors on SUA levels in patients with CKD. A recent meta-analysis demonstrated that SGLT-2 inhibitors significantly reduced SUA levels in participants with CKD stages 1–2 but had no significant effect on those with CKD stages 3–4.[17] In contrast to these findings, the DERIVE study (Dapagliflozin Efficacy in Patients with Moderate Renal Impairment) conducted by Fioretto et al.[14] in 2018 in patients with stage 3a chronic kidney disease with a GFR between 45–59 mL/min/1.73 m² reported a statistically significant decrease in SUA levels at the end of week 24 in the dapagliflozin group compared with the placebo group. Similarly, a study by Pollock et al.[13] in 2019 compared baseline SUA levels in patients with T2DM and a GFR range of 25–75 mL/min/1.73 m² to SUA levels after 24 weeks of dapagliflozin treatment versus placebo. This study reported an increase in SUA levels in the SGLT-2 inhibitor group, though the difference was not statistically significant.[13] Conversely, Yale et al.[12] reported findings consistent with our study, indicating that serum uric acid levels did not change significantly at the end of the 52nd week in patients with T2DM and CKD receiving canagliflozin. Based on these results, the reduction in SUA levels may vary across different studies in patients with glomerular filtration rates below 60 mL/min/1.73 m², but it generally remains at the same level. This suggests the possibility of a group effect rather than being influenced by the specific type of SGLT-2 inhibitor active substance used in the studies.

At first glance, the literature on this topic appears contradictory. However, closer examination reveals that studies with differing conclusions often have variations in design. We conclude that these conflicting results in the literature may stem from differences in the characteristics of the patient populations studies. Cohorts with differing characteristics may have contributed to variations in the effects of SGLT-2 inhibitors on uric acid levels. This may be because the serum uric acid-lowering effect of SGLT-2 inhibitors is more pronounced in patients with higher uric acid levels and/or those without diabetes.[18,19]

Our study found that SGLT-2 inhibitors had no significant effect on SUA levels in the group with a GFR of 30–59 mL/min/1.73 m². Unfortunately, the number of patients analyzed in this group was smaller than in the other GFR groups. It was necessary to determine whether the results were influenced by the small number of patients in this group. Therefore, we conducted a correlation analysis to assess the effect of individual GFRs on SUA levels. Our results revealed a significant linear negative correlation between GFR and SUA levels, regardless of group. We believe that the reduction in SUA levels in the 30–59 mL/min/1.73 m² GFR group was not influenced by the sample size.

In our study, no difference was observed between empagliflozin and dapagliflozin regarding their SUA-lowering effects in patients with lower GFR rates. The EMPEROR study (Empagliflozin

Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) reported that the magnitude of the uric acid-lowering effect of empagliflozin remained consistent in patients with impaired renal function.[18] Although no study has directly compared empagliflozin and dapagliflozin, Zhang et al.[17] reported that a 10 mg dose of dapagliflozin may be optimal for patients with chronic renal failure.

With respect to the glucose- and lipid-lowering effects of SGLT-2 inhibitors, this study demonstrated that after one year, these medications were still beneficial for glucose control and lipid reduction in all patients included in the study. In particular, there is growing evidence of the advantages of SGLT-2 inhibitors in people with diabetes. Our study provides valuable insights in this context, as it is based on real-life data.

While this study has many strengths, it also has several limitations. One strength is that the study included all patients who met the inclusion and exclusion criteria listed in our database, rather than a randomized sample, ensuring a rigorously restricted cohort. However, these restrictions resulted in a smaller and non-homogeneously distributed sample size, necessitating the use of nonparametric tests. Another strength is that, unlike much of the literature, we were able to test this hypothesis using both SGLT-2 inhibitor active substances available in Türkiye. However, the fact that the patients were drawn from a single center specializing in high-prevalence medicine and reflecting tertiary health care services (university outpatient clinics) somewhat limits the generalizability of the clinical implications of the active substances.

CONCLUSION

The effects of SGLT-2 inhibitors, which are currently among the most popular therapies for their use in diabetes treatment and their cardio- and renoprotective properties, clearly require further exploration through randomized controlled trials or additional studies based on real-life data, such as this one. However, the antihyperuricemic effect of SGLT-2 inhibitors, which has been well-documented in several meta-analyses and is believed to enhance their role in diabetes management, appears to be dependent on GFR. Specifically, our findings demonstrate that this expected effect is not observed in patients with very low GFRs, such as those with end-stage renal disease.

While the antidiabetic efficacy of SGLT-2 inhibitors persists even at low GFR values, their reduced impact on hyperuricemia and the limitations of their renoprotective properties in such cases require further investigation. Additionally, our study raises the question of whether SGLT-2 inhibitors may serve as effective treatments for hyperuricemia and related conditions in nondiabetic patients, which may be another issue that should be investigated in the future.

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