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Original Article

Renal and Hemodynamic Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Patients with Type 2 Diabetes and Chronic Kidney Disease Receiving Varying Doses of Renin-Angiotensin System Blockade

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Abstract

Background: Chronic kidney disease (CKD) in the context of type 2 diabetes mellitus (T2DM) remains a significant global health challenge. Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have emerged as a renoprotective therapy, often co-administered with renin–angiotensin system inhibitors (RASi). However, the clinical impact of background RASi intensity on SGLT2i-associated renal and hemodynamic outcomes remains unclear.

Methods: This retrospective study included 67 patients with T2DM and CKD initiated on SGLT2i therapy and followed for 12 months. Patients were stratified into three groups based on background RASi use: no RASi, moderate-dose RASi, and full-dose RASi. Clinical, biochemical, and hemodynamic parameters—including blood pressure, eGFR, proteinuria, and glycemic/metabolic markers—were evaluated at baseline, 3 months, and 12 months. Adverse events including acute kidney injury (AKI) and urinary tract infections (UTIs) were recorded.

Results: All groups exhibited significant reductions in systolic blood pressure (SBP), with the greatest decline observed in the full-dose RASi group (–13 mmHg at 12 months). A transient significant dip in eGFR was noted at month 3 in the full-dose group, with partial recovery by month 12. Proteinuria decreased significantly in both the moderate-dose and full-dose RASi groups, with the greatest absolute reduction in the moderate-dose group. Glycemic control improved across all groups, with the non-RASi group showing the most pronounced decline in fasting glucose and HbA1c. No significant differences in AKI or UTI incidence were observed among groups.

Conclusion: SGLT2i therapy is safe and effective across all RASi backgrounds. However, co-administration with RASi—particularly at full doses—appears to enhance antihypertensive, renal function, and antiproteinuric outcomes. These findings underscore the potential synergistic role of full-dose RAS blockade in optimizing the renoprotective benefits of SGLT2i in diabetic CKD.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Renin-Angiotensin System, Diabetic Nephropathies, Glomerular Filtration Rate, Proteinuria

INTRODUCTION

Chronic kidney disease (CKD) is a major global health concern, affecting approximately 850 million individuals worldwide. The increasing prevalence of aging, obesity, and diabetes mellitus are key drivers of this growing burden (1,2). In response to this challenge, landmark studies published over the past five years have reignited hope for the nephrology community, which has awaited more effective treatment options since the introduction of renin–angiotensin system inhibitors (RASi) nearly two decades ago. Based on accumulating evidence of their renoprotective effects, sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and nonsteroidal mineralocorticoid receptor antagonists (MRAs) have emerged as promising therapeutic options for patients with CKD (3).

The renin–angiotensin system (RAS) regulates fundamental physiological processes, including

fluid balance, blood pressure, vascular responses to inflammation, and tissue repair (4). Inappropriate RAS activation leads to elevated angiotensin II levels, resulting in direct vascular, renal, and cardiac damage. Consequently, RAS inhibition remains a cornerstone in the treatment of systemic hypertension, heart failure, and kidney disease (5). Among commonly used RAS blockers, angiotensin-converting enzyme inhibitors (ACEis) reduce the conversion of angiotensin I to angiotensin II, whereas angiotensin receptor blockers (ARBs) prevent angiotensin II from binding to the angiotensin type 1 receptor (6).

SGLT2i act by blocking glucose reabsorption in the proximal tubule, where approximately 90% of filtered glucose is reabsorbed. This mechanism promotes urinary glucose excretion and simultaneously increases sodium excretion, thereby activating tubuloglomerular feedback. The resulting reduction in intraglomerular pressure helps mitigate hyperfiltration. In addition, SGLT2i have been shown to improve tubular oxygenation and reduce renal fibrosis, offering further renoprotective benefits (7). Unlike RASi, which induce efferent arteriolar vasodilation, SGLT2i exert afferent vasoconstriction via tubuloglomerular feedback, producing a distinct hemodynamic effect. This occurs despite elevated plasma aldosterone and angiotensin II levels. A study evaluating the impact of SGLT2i on intrarenal RAS activity observed modest increases in systemic and urinary RAS components, likely reflecting volume contraction secondary to osmotic diuresis (8,9).

SGLT2 inhibitors and RAS blockers operate at different sites within the kidney, and their combination has been hypothesized to produce synergistic effects (10,11). In patients with type 1 diabetes, empagliflozin was found to increase circulating angiotensin I levels more than angiotensin II, suggesting a shift in RAS balance. Despite RAS upregulation, afferent arteriolar constriction due to tubuloglomerular feedback emerged as the dominant hemodynamic effect, contributing to reduced glomerular hypertension. The "alternative" RAS axis, characterized by angiotensin-(1–7), is considered a beneficial counter-regulatory pathway to the "classical" RAS. Evidence suggests that combining an ACEi with an SGLT2i may activate this alternative axis (4). Thus, the natriuretic effects of SGLT2i and the vasodilatory actions of RASi may complement each other, potentially reducing systemic oxidative stress and inflammation and thereby lowering the incidence of cardiovascular and renal events (12). Indeed, various clinical trials have demonstrated that the combination of SGLT2i with ACEi/ARBs results in superior cardiorenal protection, with improvements in glycemic parameters, blood pressure, and body weight, while maintaining a favorable safety profile (10,11,13). Supporting this, some studies have shown that the addition of SGLT2i to RASi therapy yields better renal and cardiovascular outcomes compared to the addition of MRAs (14).

Although several pivotal trials comparing SGLT2 inhibitors to placebo have reported outcomes in patient subgroups with and without background RAS inhibition, the findings remain inconclusive. To address this gap, researchers recently conducted a meta-analysis incorporating subgroup data from major trials. The results demonstrated that SGLT2i therapy provides comparable clinical efficacy and safety in patients with or without RAS inhibition. However, they also noted that the combination of SGLT2i and RASi may lead to greater improvements in select renal parameters, including reductions in blood pressure and body weight, compared to SGLT2i monotherapy. Further investigation is warranted to confirm and expand upon these observations (15,16).

This study aims to investigate the potential synergistic effects of SGLT2i and varying doses of RASi on kidney outcomes in patients with DM and CKD.

METHODS

Study Design

The study included patients with DM and CKD who were followed up in the nephrology outpatient clinic between 2022 and 2024 and who were started on SGLT2i for the purpose of treating DM and providing cardiorenal protection. Patients treated with SGLT2 inhibitors were stratified into three groups based on their RASi usage (none, low–moderate dose, and full dose), and evaluated over a one-year follow-up period using biochemical and demographic data. By analyzing these subgroups, the study seeks to contribute to the ongoing debate regarding the clinical benefits and optimization of combination therapy involving SGLT2i and RASi. The clinical and biochemical findings of the patients were subjected to retrospective analysis, resulting in the preparation of a data set. The clinical findings, comorbidities, medications, and current blood and urine tests (urea, creatinine, C-reactive protein (CRP), albumin, hemogram, lipid levels, HbA1c, CRP, proteinuria and albuminuria) were recorded, as were the demographic characteristics of the patients. The laboratuary values of all patients at the 3th and 12th month after the commencement of treatment were analysed and recorded. Furthermore, all hospital admissions within one year from the start of treatment were analysed retrospectively.

The exclusion criteria comprised the following: receiving kidney replacement therapy, eGFR < 25 ml/min/1.73m^2, previous use of SGLT2i treatment, diagnosis of type 1 DM, presence of active urinary tract infection, dehydration, hypovolemia, sepsis, or urinary catheterisation, complication-free interruption of SGLT-2i treatment after initiation, insufficient data available

RASi intensity definition

Patients were stratified into groups based on the intensity of renin–angiotensin system inhibitor (RASi) therapy. Those in the low-moderate dose group were receiving less than the maximum recommended daily dose of an ACE inhibitor or ARB, whereas the full dose group was treated with target or maximum approved doses commonly used in clinical trials for kidney and cardiovascular protection.

For reference, the following dose ranges were used to define low-moderate versus RASi intensity:

ACE Inhibitors:
- Enalapril: 2.5–10 mg/day (low-moderate), 20 mg/day (full)
- Ramipril: 1.25–5 mg/day (low-moderate), 10 mg/day (full)
- Lisinopril: 5–10 mg/day (low-moderate), 20 mg/day (full)
- Perindopril: 2.5–5 mg/day (low-moderate), 10 mg/day (full)
- Trandolapril: 1–2 mg/day (low-moderate), 4 mg/day (full)

Angiotensin Receptor Blockers:
- Losartan: 25–50 mg/day (moderate), 100 mg/day (full)
- Valsartan: 40–160 mg/day (moderate), 320 mg/day (full)
- Irbesartan: 75–150 mg/day (moderate), 300 mg/day (full)
- Telmisartan: 20–40 mg/day (moderate), 80 mg/day (full)
- Olmesartan: 10–20 mg/day (moderate), 40 mg/day (full)
- Candesartan: 4–8 mg/day (moderate), 16–32 mg/day (full)

This classification was based on therapeutic ranges commonly accepted in nephrology and cardiology guidelines (e.g., KDIGO, ESC, ADA), and reflects real-world prescribing patterns in patients with diabetic kidney disease.

Complication Definition

Acute kidney injury (AKI) was characterized by an elevation in serum creatinine of at least 0.5 mg/dL. Due to the retrospective design and fixed laboratory assessment intervals (baseline, 3rd, and 12th months), AKI was defined as ≥0.5 mg/dL increase in serum creatinine, in line with previous studies, to ensure consistency and optimize the balance between sensitivity and specificity for detecting clinically relevant renal events (17,18). Acute cystitis and uncomplicated urinary tract infection (UTI) were identified based on the presence of cystitis symptoms, along with a urinalysis showing ≥10 white blood cells per microliter and positive leukocyte esterase and nitrite results on the dipstick test.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS software (version 23.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics included the presentation of continuous variables as mean ± standard deviation, regardless of distribution, and categorical variables as frequency and percentage. For comparisons between groups, the Independent Samples T-test was used for normally distributed numerical data, whereas the Mann-Whitney U test was employed for non-normally distributed data. The chi-square test was utilized to analyse categorical variables. Blood pressure and laboratory findings were evaluated at three time points: baseline, 3 months, and 12 months. For parameters showing normal distribution across these repeated measures, repeated measures ANOVA (Greenhouse-Geisser correction) was applied. For parameters not normally distributed, the Friedman test was used for comparisons involving three time points, and the Wilcoxon test for pairwise comparisons. Bonferroni correction was applied for multiple comparisons. Additionally, patients were stratified into two groups based on the presence or absence of SGLT2i-related side effects, and group differences were assessed. A p-value below 0.05 was considered to indicate statistical significance.

RESULTS

A A total of 67 patients were included in the study. The mean age of the participants was 64.5 ± 8.6 years, and 53% (36) of them were female.

The patients were categorized into three groups based on RAS blockade intensity: no RASi (n=18), moderate-dose RASi (n=27), and full-dose RASi (n=22). The mean age was slightly higher in the non-RASi group (67.8 ± 8.7 years) compared to the moderate (64.1 ± 7.6) and full-dose groups (62.2 ± 9.2). Female representation ranged from 44.4% to 59.1%. 31 of the 49 patients (64%) receiving antihypertensive treatment were using thiazide or thiazide-like diuretics.

There were no significant differences between the groups in terms of comorbidities, duration of diabetes, prevalence of end-organ damage, or the use of glucose-lowering agents other than metformin.

All groups experienced a reduction in systolic blood pressure over time. At 12 months, the decline was statistically significant in all groups ($p<0.05$), with the most pronounced decrease observed in the full-dose RASi group (from 130 ± 17 to 117 ± 10 mmHg). Diastolic blood pressure also decreased slightly in all groups, reaching significance only in the full-dose RASi group (from 76 ± 10 to 71 ± 9 mmHg, $p<0.05$) (**Table 1a and 1b**). These trends are numerically supported in **Table 2**, where the 0–12-month mean change in systolic pressure reached –13 mmHg in the full-dose group.

A significant transient decrease in eGFR was noted in

Table 1a. Table 1. Demographic, Clinical, and Laboratory Characteristics and Their Changes Over 12 Months According to RAS Inhibitor Dosage Groups in Patients Receiving SGLT2 Inhibitor Therapy initiation.

Parameters	Non-RASi (n=18)	Low-Moderate Dose RASi (n=27)	Full Dose RASi (n=22)
Gender, Female n (%)	8 (44.4)	15 (55.6)	13 (59.1)
Age (years)	67.8 ± 8.7	64.1 ± 7.6	62.2 ± 9.2
Duration of diabetes (years)	15.1 ± 10.5	13.3 ± 9.7	13 ± 8.4
Duration of hypertension (years)	15.8 ± 11.1	13.5 ± 9.7	13 ± 9.2
Proteinuria n (%)	12 (66.7)	19 (70.4)	15 (68.2)
Coronary artery disease n (%)	8 (44.4)	12 (44.4)	8 (36.4)
Diabetic Retinopathy/Neuropathy n (%)	6 (33.3)	10 (37)	7 (31)
Metformin n (%)	5 (27)	17 (63)	13 (59)
Sulfonylurea n (%)	4 (22.2)	4 (14.8)	4 (18.2)
DPP-4 inhibitor n (%)	4 (22.2)	10 (37)	8 (36.4)
Insulin n (%)	8 (44.4)	11 (40.7)	10 (45.5)
SGLT2i (dapagliflozin/empagliflozin %)	44/56	37/63	59/31
SGLT2i associated Adverse Effect n (%)	2 (11.1)	6 (22.2)	2 (9.1)

RASi, renin–angiotensin system inhibitor; **DPP-4** inhibitor, dipeptidyl peptidase-4 inhibitor; **SGLT2i**, sodium-glucose cotransporter-2 inhibitor

the full-dose RASi group at month 3 (from 58.0 ± 12.6 to 53.8 ± 14.4 mL/min/1.73 m², p=0.009), but this value recovered to 56.5 ± 15.8 by 12 months. This is also reflected in Table 2, where the GFR decline from baseline to month 3 was greatest in the full-dose RASi group (–8.4 vs –6.1 and –3). Serum creatinine increased slightly across all groups, reaching statistical significance only in the full-dose RASi group at month 3 (p=0.003).

Figure 1 illustrates the trajectory of eGFR across the three groups. Despite an early drop at month 3, renal function remained largely preserved at month 12, particularly in the full-dose RASi group.

Proteinuria significantly decreased at 12 months in both the moderate-dose (from 1034 ± 608 to 608 ± 630 mg/day, p=0.002) and full-dose RASi (1278 ± 1114 to 916 ± 1058 mg/day, p=0.024) groups, with the greatest absolute reduction observed in the moderate-dose RASi group (–426 mg/day). The non-RASi group exhibited a smaller, non-significant reduction (–159 mg/day).

Fasting glucose levels declined significantly across all groups at both 3 and 12 months (p<0.05 for each), with the most notable early reduction in the non-RASi group (209 → 127 mg/dL at month 3). HbA1c also improved significantly in all groups over 12 months, with the greatest reduction observed in the non-RASi group (from 8.9 ± 1.7% to 7.2 ± 1.1%, p<0.05).

There were no statistically significant changes or differences between groups in serum sodium, potassium, calcium, magnesium, phosphorus, albumin, or hemoglobin over the 12-month period. Similarly, CRP values remained stable across all groups. Lipid profiles (total cholesterol, LDL, HDL) showed minor fluctuations but no statistically significant trends. Ferritin and uric acid levels did not demonstrate meaningful variation.

Regarding SGLT2 inhibitor–associated adverse events (including acute kidney injury in 4 patients and urinary tract infections in 6 patients), no statistically significant differences were observed among the groups. In the patients who developed urinary tract infections (UTIs) or acute kidney injury (AKI), the treatment was temporarily interrupted and then reinitiated after resolution of the complication. However, in none of the cases was permanent discontinuation of the medication required.

DISCUSSION

This study investigated the clinical outcomes of initiating SGLT-2i in patients with diabetes and CKD, stratified by background RAS blockade intensity: no RASi, moderate-dose RASi, and full-dose RASi. Our findings reveal meaningful differences in hemodynamic, renal, and metabolic responses depending on the degree of background RAS blockade at the time of SGLT-2i initiation.

Reductions in systolic blood pressure (SBP) were observed across all groups, aligning with the well-established antihypertensive properties of SGLT-2i (18). Notably, the most significant SBP decline occurred in the group receiving full-dose RAS blockade, suggesting a synergistic interaction between maximal RAS inhibition and SGLT-2i-induced natriuresis. This finding supports previous data from the DAPA-CKD and EMPA-KIDNEY trials, which demonstrated superior hemodynamic control with combination therapy (19,20).

Renal function, as assessed by estimated glomerular filtration rate (eGFR), exhibited a transient significant dip at 3 months in the full-dose RASi group—an expected early hemodynamic response associated with both SGLT-2i and RASi therapies (21). Importantly, eGFR partially recovered by month 12, highlighting the reversibility and likely benign nature of this

Table 1b. Table 1. Demographic, Clinical, and Laboratory Characteristics and Their Changes Over 12 Months According to RAS Inhibitor Dosage Groups in Patients Receiving SGLT2 Inhibitor Therapy initiation.

Parameters	Time	Non-RASi (n=18)	Low-Moderate Dose RASi (n=27)	Full Dose RASi (n=22)
Systolic Blood Pressure (mmHg)	0 month	130 ± 20	133 ± 17	130 ± 17
	3 months	129 ± 19	124 ± 13*	119 ± 10*
	12 months	124 ± 17*,+	122 ± 12*	117 ± 10*
Diastolic Blood Pressure (mmHg)	0 month	74 ± 9	76 ± 8	76 ± 10
	3 months	72 ± 10	72 ± 9	74 ± 7
	12 months	71 ± 12	72 ± 10	71 ± 9*
Glucose (mg/dL)	0 month	209 ± 131	162 ± 69	156 ± 64
	3 months	127 ± 34*	148 ± 54*	134 ± 59*
	12 months	151 ± 59*	152 ± 61*	127 ± 42*
Creatinine (mg/dL)	0 month	1.41 ± 0.4	1.28 ± 0.2	1.25 ± 0.3
	3 months	1.49 ± 0.4	1.37 ± 0.3	1.35 ± 0.4*(p:0.003)
	12 months	1.46 ± 0.4	1.33 ± 0.3	1.31 ± 0.4
Urea (mg/dL)	0 month	56.7 ± 24.3	47 ± 11.4	47.1 ± 13.6
	3 months	64.3 ± 24.2	53.1 ± 22.1	56.5 ± 26.6
	12 months	62.8 ± 23.3	51.8 ± 20.8	49.7 ± 15.8
eGFR (mL/min/1.73 m²)	0 month	52.2 ± 14.9	56.7 ± 14.9	58 ± 12.6
	3 months	49.2 ± 14.6	52.9 ± 15.7	53.8 ± 14.4*(p:0.009)
	12 months	49.3 ± 13.3	54.1 ± 14.3	56.5 ± 15.8
Sodium (mEq/L)	0 month	139.7 ± 3	139 ± 3.2	139.9 ± 2.1
	3 months	140.5 ± 2.2	140.4 ± 2	139.4 ± 4.5
	12 months	139.3 ± 2.9	139.8 ± 2.5	140.2 ± 2.3
Potassium (mEq/L)	0 month	4.8 ± 0.4	4.6 ± 0.4	4.8 ± 0.3
	3 months	4.8 ± 0.5	4.72 ± 0.5	4.9 ± 0.5
	12 months	4.9 ± 0.3	4.7 ± 0.4	4.7 ± 0.5
Calcium (mg/dL)	0 month	9.6 ± 0.3	9.7 ± 0.3	9.7 ± 0.4
	3 months	9.8 ± 0.5	9.6 ± 0.4	9.7 ± 0.5
	12 months	9.7 ± 0.5	9.3 ± 1.4	9.7 ± 0.5
Magnesium (mg/dL)	0 month	2 ± 0.2	2 ± 0.2	1.8 ± 0.3
	3 months	2.1 ± 0.2	2 ± 0.19	2.1 ± 0.4
	12 months	2.1 ± 0.2	2.1 ± 0.3	2 ± 0.3
Phosphorus (mg/dL)	0 month	3.5 ± 0.4	3.7 ± 0.5	3.7 ± 0.6
	3 months	3.8 ± 0.6	3.7 ± 0.5	3.8 ± 0.6
	12 months	4 ± 0.6	3.7 ± 0.5	3.9 ± 0.4
Serum Albumin (g/dL)	0 month	4.5 ± 0.3	4.4 ± 0.2	4.3 ± 0.4
	3 months	4.5 ± 0.2	4.3 ± 0.3	4.6 ± 0.4
	12 months	4.4 ± 0.3	4.2 ± 0.2	4.4 ± 0.4
Hemoglobin (g/dL)	0 month	13 ± 2.3	13 ± 1.7	13 ± 1.8
	3 months	13.1 ± 1.9	13.7 ± 3	13 ± 1.5
	12 months	13.3 ± 2.3	12.9 ± 2.1	13 ± 1.3
Total Cholesterol (mg/dL)	0 month	188 ± 39	183 ± 45	193 ± 45
	3 months	174 ± 35	176 ± 46	195 ± 46
	12 months	177 ± 31	178 ± 51	175 ± 27
LDL (mg/dL)	0 month	104 ± 35	106 ± 41	110 ± 38
	3 months	95 ± 26	92 ± 34	116 ± 39
	12 months	100 ± 26	103 ± 42	96 ± 24
HDL (mg/dL)	0 month	46 ± 12	44 ± 10	45 ± 15
	3 months	49 ± 12	43 ± 11	46 ± 14
	12 months	47 ± 13	43 ± 12	43 ± 14
Ferritin (mg/dL)	0 month	94 ± 103	74 ± 64	48 ± 37
	12 months	116 ± 109	81 ± 68	44 ± 33
Uric Acid (mg/dL)	0 month	6 ± 1.8	6.2 ± 1.8	6 ± 1.1
	12 months	5.9 ± 1.9	6.1 ± 1.5	5.8 ± 1.1
Proteinuria (g/day)	0 month	966 ± 1061	1034 ± 608	1278 ± 1114
	12 months	771 ± 842	608 ± 630 (p=0.002)	916 ± 1058 (p=0.024)
HbA1c (%)	0 month	8.9 ± 1.7	8.1 ± 1.6	8.1 ± 1.5
	12 months	7.2 ± 1.1*	7.3 ± 1.1*	7.3 ± 1.3*
CRP (mg/L)	0 month	4 ± 4.3	4.5 ± 3.7	5.6 ± 4.2
	12 months	5.1 ± 4.6	5.1 ± 4.9	4.2 ± 3.2

RASi, renin–angiotensin system inhibitor; **eGFR**, estimated glomerular filtration rate; **LDL**, low-density lipoprotein; **HDL**, high-density lipoprotein; **CRP**, C-reactive protein; **HbA1c**, glycated hemoglobin

initial decline, especially in patients with preserved autoregulation. These results reinforce current clinical guidance that early eGFR reductions following SGLT-2i initiation should not prompt treatment discontinuation unless other clinical concerns are present (22). Notably, the percentage reduction in eGFR from baseline to month 12 was smallest in the full-dose RASi group. As shown in Figure 1, this group demonstrated a more favorable

Table 2. Changes and percentage reduction in key clinical parameters over time according to RAS inhibitor dosage in patients initiating SGLT2 inhibitor therapy

	Non-RASi (n:18)	Low-Moderate Dose RASi (n:27)	Full Dose RASi (n:22)
Systolic Blood Pressure (mmHg)			
Δ(0-3 month)	-1	-9	-11
Δ(0-12 month)	-6	-11	-13
Diastolic Blood Pressure (mmHg)			
Δ(0-3 month)	-2	-4	-2
Δ(0-12 month)	-3	-4	-5
Creatinine (mg/dl)			
Δ(0-3 month)	0.08	0.09	0.1
Δ(0-12 month)	0.05	0.05	0.06
Urea (mg/dl)			
Δ(0-3 month)	7.6	6.1	9.4
Δ(0-12 month)	6.1	4.8	2.6
eGFR (CKD-EPI 2021)			
Δ(0-3 month)	-3	-6.1	-8.4
Δ(0-12 month)	-2.9	-4.8	-2.6
Potassium (mEq /L)			
Δ(0-3 month)	0	0.12	0.1
Δ(0-12 month)	0.1	0.1	-0.1
Proteinuria (gr/day)			
Δ(0-12 month)	-159	-426	-362

Δ indicates absolute change from baseline (0 month) to 3rd and 12th months. eGFR: Estimated glomerular filtration rate, RASi : Renin angiotensinogen inhibitors.

eGFR trajectory by the end of follow-up, suggesting that long-term kidney outcomes may benefit most from combined full-dose RAS blockade and SGLT-2i therapy.

Proteinuria decreased significantly in both the moderate and full-dose RASi groups, highlighting the additive antiproteinuric effect of SGLT-2i when layered onto existing RAS blockade. This is consistent with the known complementary mechanisms: SGLT-2i reduce intraglomerular pressure via afferent arteriole vasoconstriction, while RASi act via efferent arteriole dilation (23). The largest absolute reduction in proteinuria occurred in the moderate-dose RASi group, potentially reflecting a plateauing effect at maximal RAS inhibition or better tolerability at intermediate dosing.

Glycemic control improved across all groups, with the most pronounced reduction in HbA1c and fasting glucose levels observed in the group not receiving RAS blockade. While SGLT-2 inhibitors primarily exert their glycemic effect through glucosuria, RAS blockers have also been associated with positive or neutral effects on glucose metabolism, improving insulin sensitivity and offering protection against diabetes development (24). The unexpectedly greater glycemic response in the non-RASi group may reflect unmeasured factors such as differences in insulin regimens, dietary adherence, or baseline glycemic burden.

Finally, SGLT-2i therapy was well tolerated across all groups, with no significant differences in adverse event rates, including acute kidney injury or urinary tract infections, further supporting its safety in real-world settings (25).

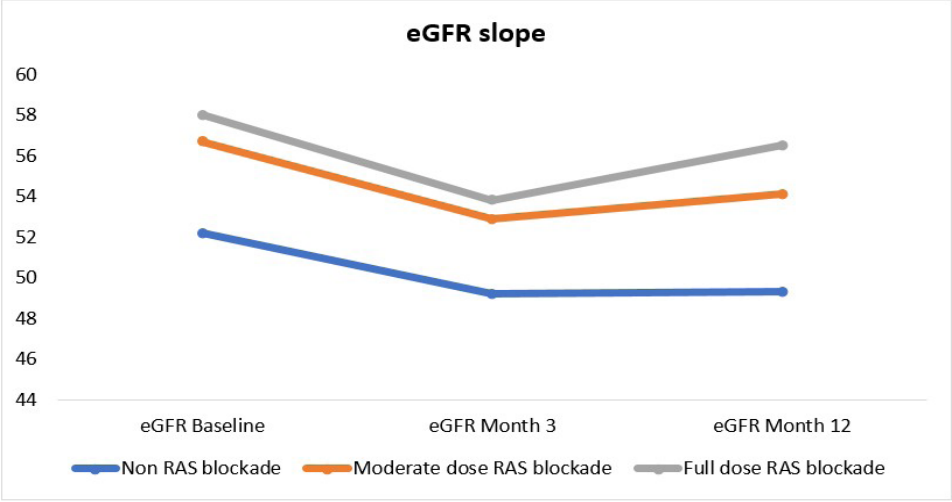

Figure 1. Trajectory of Estimated Glomerular Filtration Rate (eGFR) Over 12 Months According to RAS Inhibitor Use and Dosage. eGFR: Estimated glomerular filtration rate, RASi :Renin angiotensinogen inhibitors

Limitations of the Study

The limitations of this study include a relatively small sample size, which may have reduced the statistical power to detect subtle differences, particularly in safety outcomes. Moreover, factors such as medication adherence, dietary intake, and insulin usage were neither standardized nor prospectively monitored, introducing potential bias—especially in the interpretation of glycemic endpoints.

CONCLUSION

The findings of this study suggest that initiating SGLT2i in patients with diabetes and CKD is generally safe and associated with favorable renal and metabolic outcomes, regardless of background RAS blockade. However, the combination of SGLT2i with RAS inhibitors—particularly at full doses—appears to confer additional benefits in terms of blood pressure control and eGFR preservation. Moderate-dose RAS blockade may represent an optimal balance between efficacy and tolerability when layering SGLT2i therapy, especially in proteinuric diabetic CKD. These results support the complementary roles of SGLT2i and RASi in renal protection and reinforce current clinical recommendations favoring their co-administration when tolerated. Future studies with longer follow-up are warranted to evaluate whether the more favorable eGFR slope seen in the full-dose RASi group translates into sustained long-term kidney protection..

DECLARATIONS

Ethics committee approval: All procedures performed in the study were conducted in accordance with the ethical standards set forth by the Clinical Research Ethics Committee of Kırklareli University Faculty of Medicine. The protocols in this study (Protocol No. P202300036/02) were approved by the aforementioned committee and are in alignment with the ethical principles set forth in the 1964 Declaration of Helsinki.

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Author contributions: Author declares that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

Conflicts of interest: Author declares none.

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AI: None

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