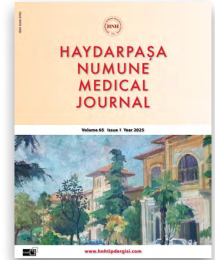
HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2025.67864
Haydarpasa Numune Med J 2025;65(4):302–312



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ORIGINAL ARTICLE

The Effects of SGLT-2 Inhibitors on Biochemical Parameters, Kidney Function, and Adverse Events in Elderly Patients with Diabetes Mellitus and Chronic Kidney Disease: A Retrospective Single-Center Study

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Abstract

Introduction: SGLT2 inhibitors (SGLT2i) have multiple metabolic benefits, including reducing glycated hemoglobin, weight, and blood pressure. Additionally, there are strong renoprotective effects in selected populations. The aim of our study was to investigate changes in biochemical parameters, incidence of complications, and associated factors following SGLT2i use in elderly patients.

Methods: The study population comprised patients aged 60 years and older who were treated with SGLT2i. The clinical and biochemical data were subjected to analysis at the baseline, six-month, and twelve-month marks following the commencement of treatment. The incidence of complications was evaluated.

Results: A total of 64 patients were included in the analysis, with 54.7% of them being female and an average age of 66.8±5.6 years. Significant reductions in blood pressure, HbA1c, estimated glomerular filtration rate (eGFR), and proteinuria were observed after treatment. Conversely, there was a notable increase in serum magnesium and phosphorus levels. The eGFR exhibited a decline of 3.7 mL/min at the six-month mark, which subsequently slowed to a decrease of 2.4 mL/min at the twelve-month interval. Four patients developed acute kidney injury (AKI), and seven patients experienced urinary tract infections (UTIs) after treatment. The most significant factor associated with the occurrence of side effects was identified as high CRP levels (OR: 1.261; p=0.024).

Discussion and Conclusion: The findings of our study indicate that SGLT2i are effective in improving glycemic control, blood pressure, and proteinuria in elderly patients. It is noteworthy that patients with elevated CRP levels prior to treatment experienced a higher incidence of side effects, indicating that such patients may require closer monitoring.

Keywords: Acute kidney injury; C-reactive protein; chronic kidney disease; diabetes mellitus; sodium-glucose co-transporter 2 inhibitors; urinary tract infections.

Diabetic kidney disease is a serious complication of Type 2 Diabetes mellitus (T2DM). It is the leading cause of end-stage kidney disease (ESRD) and therefore represents a major challenge in clinical practice and public health [1]. In order to overcome this problem, studies published in the last 5 years have been groundbreaking for the nephrology community, which has been waiting for a new and effective treatment for about 20–25 years

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Submitted Date: 20.04.2025 **Revised Date:** 28.04.2025 **Accepted Date:** 02.07.2025
Haydarpaşa Numune Medical Journal
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after the understanding of the nephroprotective effects of renin-angiotensin blockers and the start of their clinical use [2]. Sodium glucose transporter-2 inhibitors (SGLT2i), Glucagon-like peptide-1 (GLP-1) agonists, and nonsteroidal mineralocorticoid receptor antagonists (nMRA) have shown promise for patients with diabetic nephropathy, with studies supporting their renoprotective effects [3]. SGLT2i, which is more commonly used among these drugs, shows its effect by inhibiting glucose reabsorption in the proximal tubules where 90% of glucose is reabsorbed. Thus, sodium excretion increases along with urinary glucose excretion. By changing tubuloglomerular feedback, it has been found to have positive effects such as decreasing intra-glomerular pressure and preventing hyperfiltration, as well as improving tubular oxygenation and reducing fibrosis [4]. There are six Food and Drug Administration (FDA) approved SGLT2i; empagliflozin and dapagliflozin are available for use in Türkiye.

In patients with T2DM enrolled in the EMPA-REG OUTCOME study, empagliflozin was associated with a reduced incidence of new-onset overt albuminuria, new-onset or worsening nephropathy, kidney replacement therapy initiation, and kidney disease-related mortality (HR: 0.61, 95% CI: 0.53–0.70; p<0.0001) [5]. In the DECLARE-TIMI 58 study (dapagliflozin vs. placebo) in patients with T2DM, a 1.3% absolute and 24% relative risk reduction (HR: 0.76; 95% CI: 0.67–0.87) was observed in secondary kidney outcomes (eGFR decline of 40% or more below 60 ml/min, new-onset ESRD, and death from kidney/cardiovascular causes) [6]. In accordance with the evidence of cardiorenal protection, the Kidney Disease Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease recommends the use of SGLT2i for all patients with Type 2 DM and CKD (eGFR 20 mL/min/1.73 m^2 or higher), irrespective of glycemic level. The treatment may be continued until the point at which kidney replacement therapy is required, provided that the patient is able to tolerate this [7]. Although SGLT2i is an effective method of managing blood glucose levels and providing cardiovascular and kidney benefits, it is associated with a number of side effects. Such adverse effects include an elevated risk of diabetic ketoacidosis, genital and urinary tract infections (UTIs), and acute kidney injury (AKI). Further research is being conducted with the aim of enhancing our understanding of these risks and of reducing them while simultaneously optimizing the therapeutic benefits of SGLT2i [8].

The prevalence of Type 2 diabetes mellitus (T2DM) in older patients is increasing as the population ages and life expectancy increases. In 2021, 25% of the 530 million people with diabetes worldwide were older adults. By 2045, the number of older adults with diabetes is expected to double [9]. The older adult population is characterized by considerable heterogeneity, with notable variability in self-care, sarcopenia, and mobility [10]. It remains unclear whether diabetes contributes to the development of frailty or whether it is a consequence of the presence of multiple chronic conditions. The provision of diabetes care to frail older adults is a challenging endeavor, compounded by the presence of multiple comorbidities, polypharmacy, hypoglycemia, and the increasing detrimental effects of other adverse events [11]. Previous studies have highlighted potential concerns regarding the use of SGLT2i in elderly populations, particularly in light of the known side effects associated with this medication, including candidiasis and UTIs. However, SGLT2i have been demonstrated to confer a range of clinical benefits beyond their glucose-lowering effect, including a reduced risk of cardiovascular death, all-cause mortality, heart failure, kidney disease, and improvements in weight and blood pressure [12,13]. In light of these multiple beneficial effects, ease of administration, good tolerability, and negligible hypoglycemia, SGLT2i appear to be an ideal therapeutic option for older adults. Post hoc analyses of drug trials also demonstrate the clinical value of SGLT2i in this population. The study of dapagliflozin in patients over the age of 65 demonstrated that the drug was efficacious in this age group and that it was safe in terms of side effects [14]. A similar outcome was observed with empagliflozin [15]. Nevertheless, a meta-analysis of data from elderly patients revealed an increased incidence of acute kidney injury, genital mycotic infections, and diabetic ketoacidosis, while the renoprotective effects observed in patients with eGFR below 60 ml/min were found to be diminished in comparison to those observed in the placebo group [16]. In light of the existing literature, it is unclear whether SGLT2i has beneficial or adverse effects on elderly patients. In practice, clinicians are often reluctant to prescribe SGLT2 inhibitors to older people with diabetes because of safety concerns. This is because the expected cardiovascular and kidney benefits are likely to occur in the distant future, while dehydration and genital infections can cause immediate discomfort [17]. Consequently, our study aimed to investigate the impact of SGLT2i on biochemical parameters, the incidence of complications, and the potential associated factors in elderly patients with diabetes and CKD at 6 and 12 months following drug administration.

Materials and Methods

Data Management

The study included patients over 60 years of age with DM 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. 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, parathormone, HbA1c, CRP, proteinuria, and albuminuria) were recorded, as were the demographic characteristics of the patients. The creatinine values of all patients at the 6^{th} and 12^{th} month after the commencement of treatment were analyzed and recorded. Furthermore, all hospital admissions within one year from the start of treatment were analyzed retrospectively.

The exclusion criteria comprised the following: age below 60 years, receiving kidney replacement therapy, eGFR < 25 ml/min/1.73 m^2, previous use of SGLT-2i treatment, diagnosis of type 1 DM, presence of active urinary tract infection, dehydration, hypovolemia, sepsis, or urinary catheterization, complication-free interruption of SGLT-2i treatment after initiation, insufficient data available.

Complication Definition

In accordance with the existing literature, acute kidney injury (AKI) was defined as an increase in creatinine levels of 0.5 mg/dL [18]. In addition to the symptoms of cystitis, a urinalysis with ≥10 WBC/µL and positive results for leukocyte esterase and nitrite on the dipstick test were interpreted as indicative of acute cystitis and an uncomplicated urinary tract infection (UTI). The occurrence of two or more UTIs within a month or three or more UTIs within a year was defined as recurrent UTI [19].

Statistical Analysis

The statistical analyses were conducted using the SPSS (version 23.0, SPSS, Chicago, IL, USA) software. Descriptive statistical methods were employed to analyze the data, with mean±standard deviation used for continuous numerical variables with and without normal distribution, and number and percentage used for categorical variables. The blood pressure measurements and results of patients who were initiated on SGLT-2 inhibitors were analyzed according to three categories: baseline, six months, and 12 months. A repeated measures analysis of variance (Greenhouse-Geisser) was conducted on the repeated measurements of normally distributed parameters to facilitate a comparison of the three time periods. In the case of non-normally distributed parameters, a Friedman analysis was conducted when three parameters were compared, while a Wilcoxon analysis was employed when two parameters were compared (non-parametric tests). Finally, a Bonferroni correction was applied. A two-group comparison was conducted between patients with and without side effects of SGLT2i. For normally distributed numerical variables, an Independent Sample T-test was employed; for non-normally distributed variables, a Mann-Whitney U-test was used; and for categorical variables, a chi-square test was applied. The parameters that were significant in the univariate analysis and did not show multicollinearity were included in the binary logistic regression analysis. The backward LR strategy was applied in the multivariate analysis. The risk estimates were presented as unadjusted (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI). The Hosmer-Lemeshow statistic was used to determine the fit of the model in the logistic regression analysis. A p-value of less than 0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

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.

Written informed consent was obtained from all patients/authors participating in the study.

Results

A total of 64 patients were included in the study, of whom 35 were female (54.7%) and the mean age was 66.8±5.9 years. A total of 53 patients (83.8%) had an estimated glomerular filtration rate (eGFR) below 60 ml/min, while 44 patients (68.8%) exhibited proteinuria. The mean duration of diabetes diagnosis was 13.5±9 years. In the group of 44 patients with proteinuria, the mean duration of diagnosis was 2±1.8 years. Hypertension was present in 58 patients (90.6%), coronary artery disease (CAD) in 27 (42.5%), heart failure in 12 (18.8%), and diabetic retinopathy/neuropathy in 24 (37.5%). Of the patients, 33 (51.6%) were administered dapagliflozin, while 31

Table 1. Patient demographics and data analysis

Parameters	Results n=64		Parameters	Results n=64	
	n	%		n	%
Categorical variables			Diuretic	36	56.3
Female	35	54.7	ACEi /ARB	46	71.4
Dapagliflozin	33	51.6	Statin	31	48.4
Empagliflozin	31	48.4	Adverse effects after SGLT-2	11	17.2
eGFR <60 ml/ min	53	82.8	AKI	4	6.3
Proteinuria	44	68.8	UTIs	7	10.9
Coronary artery disease	27	42.5		Mean±SD	
Heart failure	12	18.8	Numerical variables		
Hypertension	58	90.6	Age	66.8±5.9	
Diabetic Retinupathy/Neuropathy	24	37.5	Duration of CKD diagnosis (years)	3.1±2.3	
Metformin	34	53.1	CAD, duration of diagnosis (years)	2.4±2	
Sulfanilurea	2	3.1	HF, duration of diagnosis (years)	1.9±0.9	
DPP-4i	20	31.3	Proteinuria, duration of diagnosis (years)	2±1.8	
Insulin	28	43.8	Duration of diabetes diagnosis (years)	13.5±9	
GLP-1 Agonist	3	4.7	Duration of hypertension diagnosis (years)	13.1±10.1	
Acetylsalicylic acid	37	57.8			

CKD: Chronic kidney disease; CAD: Coronary artery disease; HF: Heart failure; eGFR: Estimated glomerular filtration rate; SD: Standard deviation; AKI: Acute kidney injury; UTIs: Urinary tract infection; SGLT-2i: Sodium glucose transporter 2 inhibitor; DPP-4i: Dipeptidyl peptidase-4 inhibitor; ACEi : Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; GLP -1: Glucagon -like peptide-1.

(48.4%) were administered empagliflozin. The remaining parameters are presented in Table 1.

A comparison of blood pressure measurements, urine, and blood tests of the patients before and 6–12 months after treatment revealed a statistically significant reduction in systolic (p = 0.0001) and diastolic blood pressure (p=0.001), fasting blood glucose (p=0.015), HbA1c value (p=0.0001), eGFR level (p=0.001), proteinuria (p=0.013), and albuminuria (p=0.0001) values compared to the pretreatment period. Significant increases were observed in serum creatinine (p=0.001), urea (p=0.039), magnesium (p=0.005), and phosphorus (p=0.048) values between the groups. No significant differences were observed in serum albumin, potassium, sodium, calcium, bicarbonate, hemoglobin, lipid levels, vitamin D, parathormone, ferritin, uric acid, and CRP values between the groups. The results are presented in Table 2.

When patients were divided into two groups according to eGFR values, stage 1–2 and stage 3–4, there was no significant difference in the change in eGFR between the two groups at 0 and 12 months (p=0.075) (Fig. 1).

A total of 11 patients (17.1%) experienced side effects potentially associated with SGLT2i. Of the aforementioned patients, four developed acute kidney injury (AKI) and seven developed urinary tract infection (UTI). Of the patients diagnosed with UTI, six presented with acute cystitis/uncomplicated UTI, while one presented with recurrent cystitis. A urine culture was requested from patients presenting with symptoms of urinary tract infection. Systemic antibiotic therapy was initiated in patients exhibiting both clinical and laboratory findings (positive urine culture) indicative of infection. No patients developed a UTI that necessitated hospitalization or a complicated UTI, such as pyelonephritis. In six of the seven patients diagnosed with UTI, SGLT2i treatment was reinitiated following treatment, and UTI did not recur. Consequently, the treatment could be continued. However, as a single patient developed recurrent UTIs (more than three in a twelve-month period) and no other identifiable cause was identified, SGLT2i treatment was discontinued at the thirteenth month of treatment. All patients diagnosed with a UTI were female, and no underlying facilitating factor was identified.

Kidney dysfunction was identified in three of the four patients with AKI during the initial month of treatment. Given that prerenal causes were postulated to be the etiology in two of these patients, SGLT2i was discontinued, and they were monitored with regard to oral hydration. At the outpatient clinic follow-up, the creatinine values of

Table 2. Presentation of the parameters measured before and 6 and 12 months after the start of SGLT-2i and the results of the analysis between months

Parameter (mean±SD), n=64	Pretreatment	Month 6	Month 12	p
Systolic blood pressure (mm Hg)	133.9±17.9	125±14.7***	122±13.5***,X	**0.0001**
Diastolic blood pressure (mm Hg)	78.1±9.4	73.7±8.6*	72.5±10.3*	**0.001**
Glucose (mg/dl)	177±93.3	140±54.9*	147.6±57.2	**0.015**
Creatinine (mg/dl)	1.27±0.4	1.36±0.46**	1.32±0.44*	**0.001**
eGFR (CKD-EPI 2021) (ml/min/1.72 m^2)	58.4±18.9	54.7±19.8*	56±19.3	**0.001**
Urea (mg/dl)	50.9±21	56.4±23.8*	53.8±19.1	**0.039**
Sodium (mEq /L)	139.5±2.8	140.3±3.2	139.8±2.6	0.124
Potassium (mEq /L)	4.7±0.4	4.7±0.5	4.7±0.4	0.77
Calcium (mg/dl)	9.7±0.4	9.7±0.5	9.5±1	0.25
Magnesium (mg/dl) n=55	1.9±0.3	N/A	2.1±0.3	**0.005**
Phosphorus (mg/dl) n=61	3.6±0.5	3.8±0.5	3.8±0.5	**0.048**
Albumin (g/dl) n=62	4.4±0.3	4.3±0.3	4.3±0.3	0.07
Bicarbonate (mEq /L) n=37	24.6±3	N/A	25.6±3	0.132
Hemoglobin (g/dl)	12.9±1.8	12.9±1.8	13±1.9	0.35
Cholesterol (mg/dl)	186±42	179±44	175±38	0.22
LDL (mg/dl)	105±36	99.4±35.3	99.5±32	0.36
HDL (mg/dl)	46±13	46.6±13.1	44.8±13.2	0.46
Triglyceride (mg/dl)	183±89	163±75	158±90	0.09
Vitamin D (ng/mL) n=49	22.8±12.8	N/A	25.7±9.2	0.43
Parathyroid hormone (pg/mL) n=40	71±40	N/A	64.2±36.6	0.91
Ferritin (ml/ng)	76±76	69±66	80±79.8	0.55
Uric acid (mg/dl) n=51	6.1±2	N/A	5.6±1.5	0.83
Proteinuria (gr/day) n=44	894±956	418±631,*n=30	477±657	**0.013**
Albuminuria (gr/day) n=33	615±817	N/A	250±485	**0.0001**
HbA1c (%)	8.6±2.3	7.6±1.6*	7.4±1.2***	**0.0001**
CRP (mg/L)	4.7±4	5.3±6.4	4.3±3.8	0.51

*: $p<0.05$ vs 0.month; **: $p<0.001$ vs 0.month; ***: $p<0.0001$ vs 0.month, ^{X}: $p<0.05$ vs 6th month. SD: Standard deviation; LDL: Low density lipoprotein; HDL: High density lipoprotein; CRP: C reactive protein; HbA1c: glycosylated hemoglobin; eGFR: Estimated glomerular filtration rate.

these two patients were found to have decreased to the basal level, and SGLT2i was restarted. Examination of the emergency department applications of the remaining two patients revealed elevated creatinine levels. They were admitted to the hospital and monitored for AKI. One patient developed AKI in the third month of treatment, which was attributed to gastroenteritis-related prerenal causes and was managed with intravenous hydration. The final patient was diagnosed with cardiorenal syndrome type 2 and was undergoing treatment with diuretics. Despite a reduction in the diuretic dose following the initiation of SGLT2i treatment, the patient was hospitalized with AKI secondary to diuretic excess and decreased oral intake. However, kidney functions and the patient's condition improved with hydration and a reduction in the diuretic treatment. SGLT2i was restarted in both patients at the outpatient clinic control. There were no cases of AKI following the restart of SGLT2i.

A comparison of the two groups, defined as those with and without side effects within a one-year period, revealed that female gender (p=0.047) and high pre-treatment CRP level

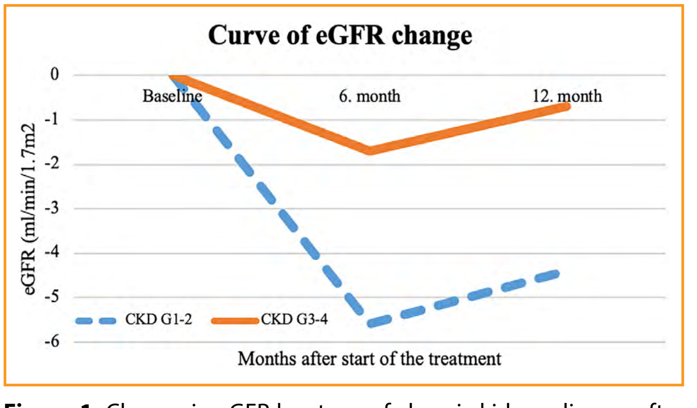

Figure 1. Change in eGFR by stage of chronic kidney disease after treatment initiation.

CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate.

Table 3. Parameters that were found to differ between the two groups when patients were grouped according to Sglt2 inhibitor-related side effects (univariate analysis)

Parameter	No side effects (n=53)		Side effects (n=11)		p
	n	%	n	%	
Gender					
Female	26	74.3	9	25.7	0.047
Male	27	93.1	2	6.9	
CRP (mg/L)	4±3.9		7.9±3		0.001

CRP: C reactive protein.

Table 4. Parameter found to be associated in multivariate analysis when patients were grouped according to SGLT-2 inhibitor-related side effects (binary logistic regression-forward LR)

Parameter	p	Exp (B)	95% CI (low-high)
CRP (mg/L)	0.024	1.261	1.032–1.573

CI: Confidence interval.

(p=0.001) were significantly more prevalent in the group with side effects (Table 3). No statistical significance was found in the comparison of the type of SGLT-2 inhibitor and the frequency of side effects.

The results of the multivariate analysis indicated that the only factor associated with the occurrence of side effects was the pretreatment CRP level (OR 1.261; 95% CI 1.032–1.573; p=0.024) (Table 4).

Discussion

The global prevalence of diabetes mellitus is increasing, with the condition continuing to cause chronic health problems. Diabetes mellitus is a significant contributor to CKD, with kidney replacement therapy and cardiovascular mortality. Intensive glucose control and blood pressure management are key strategies for slowing the progression of CKD in diabetic patients [20]. Furthermore, due to the complex pathophysiology of DM, it is necessary to implement targeted prevention and treatment strategies to reduce organ damage. In this search for treatments, following the astonishing results shown in randomized controlled trials in terms of prevention of cardiovascular events, the drug group SGLT2i, which has also demonstrated significant efficacy in preventing the progression of CKD regardless of diabetes status, has initiated a paradigm shift in the treatment of patients with kidney disease as well as DM [21,22]. The treatment of diabetes in the elderly presents a number of challenges, including potential drug interactions and the paucity of data from randomized controlled trials. Moreover, the specific guidelines for the treatment of DM in the elderly address the use of the most recently approved therapies, such as SGLT2i, only to a limited extent [23]. Although a post-hoc analysis of the pivotal studies of empagliflozin and dapagliflozin revealed that efficacy and safety in elderly patients were comparable to other populations, the most recent meta-analysis yielded conflicting results [13,15,16]. Accordingly, the objective of this study was to make a contribution to the existing literature by determining the effects of SGLT2i in elderly patients. The objective was to investigate the effects and safety of these drugs in clinical practice in diabetic patients over 60 years of age, as well as the parameters affecting the incidence of side effects over a one-year period. Significant reductions in glycemic parameters, blood pressure, and proteinuria/albuminuria were observed following the administration of SGLT2i, while there was a notable increase in blood magnesium, phosphorus, and urea levels. Although a significant decline in kidney function was observed during the initial six-month period, the eGFR demonstrated a tendency towards improvement over the longer term (one year). With regard to adverse effects, UTI and AKI were moderate and did not necessitate the discontinuation of treatment, except in one patient. The independent parameter in terms of adverse effects was the level of CRP prior to the initiation of treatment.

In individuals with no underlying pathology, all tubular glucose is reabsorbed, and there is no urinary excretion of glucose. SGLT1 and 2 play a role in the renal reabsorption of glucose. SGLT2 is responsible for 90% of glucose reuptake in segment 1 of the proximal tubule, while SGLT1 accounts for the remaining 10% [24]. The selective inhibition of SGLT channels by SGLT2i or phlorizin derivatives, collectively known as gliflozins, has been demonstrated to exert profound metabolic and hemodynamic effects [25]. They function by blocking SGLT2 in the proximal tubule of the kidney, thereby preventing glucose reabsorption, increasing glucose excretion, and osmotic diuresis [26]. In contrast to other antidiabetic drugs, which act by increasing insulin secretion or enhancing insulin sensitivity to receptors, these agents prevent the reuptake of glucose into the bloodstream, thereby improving HbA1c levels and glucose parameters. In addition to reducing glycemia, these agents have been observed to exert additional beneficial effects, including modest reductions in systemic blood pressure (4–6 mmHg) and weight loss [27,28]. The results of our study demonstrated a significant improvement in glycemic parameters in our patients, which is in accordance with the findings reported in the literature. Furthermore, a notable reduction in both systolic and diastolic blood pressure was observed.

The mechanism underlying diabetic kidney disease is the elevation of intraglomerular pressure and hyperfiltration resulting from the overstimulation of the renin-angiotensin-aldosterone system (RAAS), in addition to the direct effects of hyperglycemia. An increase in angiotensin-2 and SGLT1/2 receptor levels has been observed in patients with diabetic CKD [2]. SGLT2i exerts its renoprotective effects by suppressing the RAAS through the stimulation of tubuloglomerular feedback (TGF) and increased transmission to the macula densa, which is a consequence of decreased reabsorption of sodium and glucose. This results in the constriction of the afferent arterioles and a reduction in glomerular hydrostatic pressure. It is hypothesized that this provides kidney protection by reducing hyperfiltration injury [29]. In the study conducted by Kohan et al. [30], it was observed that the mean eGFR change in patients undergoing treatment with SGLT2i (dapagliflozin) exhibited a decrease of 4.8 and 4.4 ml/min, respectively, in the sixth and twelfth months of treatment when compared to the pretreatment period. In another study, the eGFR decreased by 4 mL/min at week 12 in patients with stage 3 CKD who were treated with empagliflozin. However, there was a slight improvement at week 52. It is noteworthy that the eGFR returned to its original baseline values following the cessation of the drug treatment [31]. The longer-term effects of SGLT2i on kidney functions have been investigated in placebo-controlled studies with extended follow-up periods. The results of these clinical trials indicated that SGLT2i typically resulted in an initial reduction in eGFR. In the longer term, evidence indicates that it preserves kidney function and slows the progression of CKD [32–34]. The data indicate that the initial reduction in eGFR in response to SGLT2 inhibition is reversible and thus reflects functional rather than structural changes [32]. It is anticipated that an annual decline in eGFR will occur in patients with CKD. While there is no clear limit to this decline, it is recommended that individuals exhibiting an eGFR decline of more than 3 ml/min/1.73 m^2/year undergo further investigation [35]. In our study, a decrease of 3.7 and 2.4 ml/min was observed at 6 and 12 months, respectively. As observed in previous literature, our study similarly demonstrated that hemodynamic decline in the early phase tended to improve over a longer period of time. In a meta-analysis conducted by Liu et al. [16] on elderly patients, it was reported that the renoprotective effects decreased in patients with eGFR below 60 ml/min, and early-stage eGFR decline did not reach the baseline level. Although our study did not include a longer follow-up period, the mean eGFR of the patient population was 58 ml/min, and GFR changes consistent with the aforementioned study were detected.

SGLT2i has been demonstrated to diminish proteinuria, with multiple proposed mechanisms of action. Firstly, proteinuria is reduced as a consequence of increased TGF and decreased intraglomerular pressure and hyperfiltration [36]. Furthermore, SGLT2 inhibition elevates the concentration of ketones, which suppress mTORC1 hyperactivation. Consequently, podocyte injury and proteinuria are diminished [37]. Additionally, SGLT2i has been demonstrated to contribute to a reduction in both systolic and diastolic blood pressure, which has an indirect effect on the reduction of proteinuria [38]. These effects collectively contribute to a reduction in proteinuria and a slowing of the progression of chronic kidney disease. The results of our study demonstrated a statistically significant reduction in proteinuria levels among the patient cohort. The observed increase in proteinuria at month 12 compared to month 6 appears to be associated with the recovery of the eGFR to its baseline level. Nevertheless, the considerable reduction in proteinuria compared to the baseline continues at month 12.

SGLT2i is a class of drugs that has been demonstrated to exert an influence on serum electrolyte levels, including magnesium and phosphate. A meta-analysis demonstrated an increase in mean magnesium levels of 0.04 to 0.1 mmol/L following treatment [39]. The potential mechanisms underlying this phenomenon include volume depletion and augmented magnesium reabsorption, which may occur in the proximal tubule or thick ascending limb [40]. A study conducted on three patients with refractory hypomagnesemia demonstrated that canagliflozin, empagliflozin, and dapagliflozin were capable of reducing fractional excretion of magnesium and elevating serum magnesium levels. This suggests that SGLT2i may represent a novel therapeutic avenue for conditions characterized by hypomagnesemia [41]. It is possible that SGLT2i may increase tubular reabsorption of phosphate, which could result in elevated serum phosphate levels [42]. In our study, the administration of SGLT2i was found to result in a notable elevation in magnesium and phosphorus levels.

Although SGLT2i has numerous beneficial effects, it has been linked to a number of adverse events, including diabetic ketoacidosis, genital infection, decreased intravascular volume, and an elevated risk of AKI, fractures, amputations, pancreatitis, and UTIs [43,44]. In elderly patients, it was reported that 23.5% of patients discontinued the drug due to adverse effects, with the most common being genitourinary tract infection [34]. This rate was 17.1% in our study. As demonstrated in the aforementioned study, age was identified as a contributing factor to the incidence of side effects. The younger age of the patients in our study may have contributed to a reduction in the incidence of side effects (mean age 75.4±3.9 vs. 66.8±5.9 years).

SGLT2i may contribute to volume depletion and predispose to AKI through its natriuretic properties, effects on TGF, and various other mechanisms. In addition, the volume and intrarenal hemodynamic effects of SGLT2i may be synergistic when combined with RAAS antagonists and conventional diuretics, which are commonly prescribed in this patient population with T2DM [45]. It has also been suggested that it may cause AKI due to its uricosuric effect and medullary hypoxia [46]. The FDA has expressed concerns regarding the potential risk of AKI associated with SGLT2i. In December 2015 and June 2016, the FDA issued two warnings pertaining to the safety of SGLT2i. The aforementioned warnings were issued due to the reporting of 101 confirmed cases of AKI with canagliflozin or dapagliflozin to the FDA adverse event reporting system since 2013 [47]. Nevertheless, a recent randomized, placebo-controlled trial demonstrated that there is no elevated risk of AKI during SGLT2 inhibition [6]. Moreover, meta-analyses have shown that the incidence of AKI is reduced rather than increased compared with the control group [48,49]. In contrast to case reports, placebo-controlled studies and meta-analyses have been more effective in demonstrating the safety of SGLT2i with respect to kidney function [48]. It is important to note that the risk of AKI due to other causes in elderly patients with CKD and DM is not lower than in the general population. The reversible AKI observed in five patients in our study can be interpreted within this framework.

The presence of T2DM has been demonstrated to elevate the risk of developing UTIs and non-sexually transmitted genital infections, a phenomenon that can be attributed to elevated levels of glucose in the urine [50]. The pharmacologically induced urine glucose with SGLT2i may result in an increased growth rate of commensal genital microorganisms. It can be reasonably deduced that the risk of genital infections and UTIs is likely to be further increased in patients treated with SGLT2i [51]. In December 2015, the FDA issued a warning that SGLT2i may cause serious urinary tract infections [52]. A number of systematic reviews and meta-analyses have been conducted to examine this issue, but the findings are inconsistent [28,53]. It has been estimated that between 10 and 15 percent of women taking SGLT2i will develop urinary tract infections and vulvovaginitis [51]. In a study conducted by Lunati and colleagues, the two most common reasons for drug discontinuation in elderly patients were found to be UTI and worsening kidney function [34]. In our study, the prevalence of UTI was 10.9%, with all patients with UTI being female. The findings are consistent with those of previous studies and indicate that, particularly in women with recurrent vulvovaginitis and urinary tract infections, the underlying condition should be addressed before initiating treatment and the drug should be started with greater caution.

Factors that may predict drug side effects have been previously investigated in the literature. In a study investigating the side effect of AKI in patients started on SGLT2i, the frequency was found to be 1.8%. It was shown that the frequency of AKI increased in elderly patients, patients with higher serum potassium, glucose, creatinine, and albuminuria [54]. In another study, a higher incidence of AKI was found in elderly patients, high drug dosages, loop diuretic users, and patients with impaired kidney function [55]. Banerjee et al. [56] showed that duration of DM was the factor that increased the risk of SGLT2i-related genital mycotic infection in men. In our study, elevated CRP was found to be a determinant of adverse events. One explanation for this may be the exacerbation of subclinical inflammation, such as unrecognized genital or asymptomatic urinary tract infections, especially in older patients, after SGLT2i initiation. Moderate elevations in CRP can often be detected, especially in lower urinary tract infections [57]. When the relationship between CRP and AKI, another adverse effect, was reviewed in the literature, it was reported that elevated CRP was identified as a risk factor for AKI [58]. In addition, patients with elevated CRP may be more susceptible to AKI of prerenal origin. It is therefore plausible that elevated CRP is associated with adverse effects. Although SGLT2i is generally well tolerated by most patients, clinicians should consider potential adverse effects and warn patients when prescribing these agents. In older patients with a high potential for adverse effects, such as those with frequent urinary tract infections or predisposing factors for urinary tract infections, patients with inadequate volume status and signs of infection, it may be more rational to delay treatment or to start treatment with close follow-up. The detection of infectious diseases in elderly patients can be difficult because of weak clinical findings. Therefore, patients with elevated CRP should be questioned in detail, and caution should be exercised when starting drugs such as SGLT2i, which have good long-term effects but interfere with compliance in the event of illness.

It should be noted that the present study was not without limitations. As the study was based on data extracted from electronic medical records, we encountered missing data and difficulties in accessing the results of some previous laboratory tests, which are common limitations of retrospective studies. It would be beneficial to corroborate our findings with a longer follow-up period. The sample size was necessarily limited by the fact that the study was conducted in a single center and included a group of elderly patients with chronic kidney disease. A randomized study with a similar group, including patients not using SGLT2i, may provide a more accurate answer to the questions that were the aim of our study. Finally, although comorbidity and polypharmacy are confounding factors in terms of the etiology of AKI, we attempted to avoid overestimating SGLT2i-related side effects by minimizing the impact of these factors as much as possible.

Conclusion

SGLT2i confer substantial benefits with regard to cardiovascular and kidney health in elderly patients with T2DM, thereby representing a highly valuable therapeutic option. The findings of our study demonstrate that treatment with SGLT2i is associated with notable improvements in glycemic parameters, blood pressure, and proteinuria/albuminuria in elderly patients with T2DM. SGLT2i represents an efficacious alternative for the enhancement of metabolic parameters, the conservation of kidney functionality, and the stabilization of electrolytes, including magnesium. In particular, despite a decline in eGFR observed during the initial six-month treatment period, eGFR tends to improve after one year. However, the use of SGLT2i has been linked to a number of adverse effects. These include an increased risk of urinary tract infections, genital mycotic infections, and volume depletion. It is therefore recommended that adverse events such as AKI and UTI be monitored carefully during treatment. The adverse effects observed during the course of this study were mild and infrequent, and in no case did they necessitate the complete cessation of the drug. An elevated CRP level prior to treatment was found to be associated with the occurrence of adverse events. In order to optimize the established beneficial effects of this pharmacological category, which is generally considered safe in this patient population, it is crucial to be aware of the potential adverse effects and their management, and to advocate for the continued use of the drug.

Ethics Committee Approval: The study was approved by Kırklareli University Clinical Research thics Committee (Protocol No. P202300036/02, Date: 15.06.2023).

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declare that there is no conflict of interest.

Financial Disclosure: The author declared that this study has received no financial support.

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