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RESEARCH ARTICLE

Effect of Sglt-2 Inhibitors on Renal Tubular Damage

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Abstract

Introduction: In this study, it was aimed to evaluate the relationship between the use of two different sodium glucose transporter 2 (SGLT-2) inhibitors, dapagliflozin and empagliflozin, and renal tubular injury, with type 2 diabetes mellitus patients obtaining levels of neutrophil gelatinase-associated lipocalin (NGAL) in serum and arylesterase in urine. Methods: Sixty patients diagnosed type 2 diabetes mellitus were enrolled in the study; 30 of these patients used dapagliflozin and 30 patients used empagliflozin. The serum NGAL levels of the patients were measured by sandwich ELISA method while urine arylesterase levels were studied by centrifugation. Results: No significant relationship was found between the considered SGLT-2 inhibitors and the occurrence of acute tubular damage. There was no significant difference in serum NGAL levels or urinary arylesterase levels between the dapagliflozin and empagliflozin groups. The levels of microalbuminuria were significantly decreased in both groups. Conclusion: It can be said that there is no significant relationship between SGLT-2 inhibitors and renal tubular damage, with no significant difference found between dapagliflozin and empagliflozin.

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Introduction

Diabetes mellitus is a metabolic disease that occurs due to the inability to produce enough insulin in the pancreas and/or the ineffective use of the produced insulin.[1] Diabetes mellitus increases mortality by affecting all organ systems, and especially the cardiovascular, renal, and neural systems, with microvascular and macrovascular complications.[2]

Sodium glucose transporter 2 (SGLT-2) inhibitors are promising agents for the treatment of type 2 diabetes and various studies are being conducted on them in terms of side effect profiles. While research has shown that SGLT-2 inhibitors have renoprotective effects,[3] there are also suspicions that they may have toxic effects on renal tubules due to their glycosuric properties and there are currently not enough studies on this subject.

The neutrophil gelatinase-associated lipocalin (NGAL) protein and its lipocalin-2 variant are yielded by the LCN2 gene encoded in humans.Recent studies have shown that NGAL can be used as a new biological marker protein for the early diagnosis of Diabetic Kidney Disease (DKD) and is closely related to the development of DKD. Elevated levels of serum and urine NGAL can be detected in patients with early DKD. It has been shown that in acute kidney injury (AKI) serum NGAL levels increase with the occurrence of kidney damage. Therefore NGAL may play an important role in predicting early kidney disease. In the event of acute kidney injury (AKI) NGAL levels have been associated with the severity of prognosis and are used as a biomarker for AKI.[4]

Arylesterase is an enzyme that requires calcium ions for its activity. It belongs to the PON1 family and its levels decrease in the event of oxidative damage. Arylesterase levels have a potential role for the detoxification of lipid peroxides and suggests that individuals with a low levels may have a greater risk of developing a disease such as atherosclerosis, which may involve lipid peroxidation, than high-activity individuals. Studies of diabetic patients have shown a decrease in their arylesterase levels.[5]

There are a few studies in the literature investigating the relationship between SGLT-2 inhibitors and AKI, with researchers observing that some patients using SGLT-2 inhibitors may develop AKI and offering various hypotheses about the reasons for that occurrence.[6]

In the present study, the effects of SGLT-2 inhibitors on renal tubules were evaluated in groups of patients using dapagliflozin and empagliflozin, as these inhibitors affect proximal tubules of the kidneys.

Material and Methods

This study was conducted in Ankara City Hospital's Internal Medicine Clinic between June 2020 and December 2020 as an observational prospective study. The design and procedures of the study were approved by Ankara City Hospital's Ethics Committee and the Turkish Medicines and Medical Devices Agency in line with the principles of the Declaration of Helsinki and ethical standards for human experiments. Written informed consent was obtained from all participants.

A total of 60 patients comprising a mixture of men and women registered with the diagnosis code of type 2 diabetes mellitus in the general internal medicine outpatient clinic of Ankara City Hospital, aged 18-80 years and using oral antidiabetic drugs or insulin, were included in the study. Thirty of these patients were started on empagliflozin (10 mg) and the other 30 on dapagliflozin (10 mg).

Patients were excluded from the study for the following reasons: known hypertension; usage of ACE inhibitors, angiotensin receptor blockers, or diuretics; the presence of non-diabetic nephrotic syndrome, AKI, or chronic kidney injury with glomerular filtration rate (GFR) of <60; immunosuppressive therapy; diabetes mellitus due to secondary causes or diagnosis of type 1 diabetes mellitus; and the presence of malignancies or infectious diseases.

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Labarotory parameters

Blood samples were taken from the antecubital vein after 10-12 hours of fasting and analyzed within 6 hours. Urine samples were taken after 10-12 hours of fasting and analyzed within 4 hours. The obtained blood samples were analyzed in the Ankara City Hospital Central Laboratory. Complete blood counts were performed with a Mindray BC-6800 device. Lipid parameters and HbA1c levels were examined with an ARCHITECT c16000 device. Spot urine tests were performed with an ARCHITECT c4000 model device. HbA1c was studied by immunoturbidimetric methods. In order to measure serum NGAL levels, venous blood samples of 10 mL were taken into vacu-

um biochemistry serum tubes and centrifuged at 1300 × g for 10 minutes. The separated sera were divided into Eppendorf tubes and stored at -80 °C until analysis. NGAL levels were measured using a quantitative sandwich enzyme immunoassay technique with an ELISA kit (BT Laboratory, Shanghai, China; Catalog Number: E1719Hu, Lot: 202003008). The detection range of the test was 5-600 ng/mL. Intra-study and inter-study precision were <8% and <10%, respectively. To measure urinary arylesterase levels, urine samples collected in disposable non-sterile urine containers were transferred to empty urine tubes of 10 mL. The samples were centrifuged at 1000 × g for 5 minutes and stored at -20 °C. Urine arylesterase levels were measured with an ADVIA 1800 device (Siemens Healthineers, Germany) and a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey).

Statistical Analysis

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The compliance of the variables with normal distribution was examined by histogram graphics and Kolmogorov-Smirnov tests. Mean, standard deviation, and median values were used to present the results of descriptive analyses. Among the numerical variables, those that showed normal distribution were given as mean ± standard deviation and those that did not show normal distribution were given as median (min-max). Categorical variables were compared with Pearson chi-square tests. The Mann-Whitney U test was used when evaluating non-normally distributed (nonparametric) variables between groups. The change in measured values was evaluated by the Wilcoxon test within groups and compared by repeated measures analysis between groups. Values of $p<0.05$ were considered statistically significant.

Results

The study population consisted of patients with type 2 diabetes mellitus, 30 of whom were using empagliflozin and 30 of whom were using dapagliflozin. A total of 60 people, 61.67% (n: 37) male and 38.33% (n: 23) female with a mean age of 52.60±8.78 years, were included in the study. Of these participants, 31 people smoked and 11 people consumed alcohol. There were 35 patients with hyperlipidemia, 10 with thyroid disease, 10 with coronary artery disease, 5 with anaemia, 1 with chronic obstructive pulmonary disease, and 9 with other diseases. There was no statistically significant difference between the groups in terms of demographic or clinical characteristics (Table 1).

Table 1: Clinical and demographic characteristics of the study population

Variables		Population n (60)
Age		52.60±8.78
BMI		28.35±2.39
Sex	Male	37 (61.67)
	Female	23 (3833)
Tobacco		31 (51.67)
Alcohol		11 (18.33)
CHF		0 (0.00)
Thyroid disease		10 (16.67)
Anemia		5 (8.33)
CAD		10 (16.67)
Other diseases		9 (15.00)
Hyperlipidemia		35 (58.33)
Asthma		0 (0.00)
COPD		1 (1.67)

BMI: Body mass index, CHF: Congestive Heart Failure, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease.

The patient groups using dapagliflozin and empagliflozin were compared in terms of other drugs being used. The rate of sulfonylurea use in the dapagliflozin group was significantly higher than that in the empagliflozin group (p=0.037). No significant difference was found in the comparisons made in terms of other drugs used (Table 2).

Table 2: Comparison of Patient Groups Using Dapagliflozin and Empagliflozin Regarding Other Drugs Used

Variables	Dapagliflozinn 30 (%)	Empagliflozin n 30 (%)	p
Metformin (%)	29 (96.67)	29 (96.67)	1.000
Sulfonylurea (%)	11 (36.67)	4 (13.33)	0.037
DPP4 (%)	10 (33.33)	11 (36.67)	0.787
Glitazone (%)	0 (.00)	3 (10.00)	0.076
Glinide (%)	1 (3.33)	1 (3.33)	1.000
Insulin (%)	4 (13.33)	4 (13.33)	1.000
NSAID (%)	4 (13.33)	2 (6.67)	0.389
PPI (%)	6 (20.00)	9 (30.00)	0.371
Statin (%)	17 (56.67)	13 (43.33)	0.302

Patient groups using dapagliflozin and empagliflozin were compared in terms of laboratory values before the use of those SGLT-2 inhibitors. While the median serum NGAL level was 23.5 ng/mL in the patient population using dapagliflozin, it was 22.7 ng/mL in the empagliflozin group, and while the urinary arylesterase level was 28.3 U/L in the dapagliflozin group, it was 26.3 U/L in the empagliflozin group. Total cholesterol (p=0.003), low-density lipoprotein cholesterol (LDL-C) (p<0.001), and Urine protein (p=0.017) values were significantly higher in the patient group using dapagliflozin compared to patients using empagliflozin. No significant difference was found in the comparison of other laboratory findings (Table 3).

In the dapagliflozin group, fasting blood sugar (p=0.008), triglyceride (p=0.015), total cholesterol (p=0.026), LDL-C (p=0.003), gamma-glutamyl transferase (p=0.033), HbA1c (p<0.001), and urinary microalbumin (UMA) (p<0.001) values decreased, while urea (p=0.002), total protein (p=0.042), albumin (p=0.027), phosphorus (p=0.015), haemoglobin (p=0.003), and red blood cell distribution width (RDW) (p=0.017) values increased significantly. No significant difference was found for other laboratory results (Table 4).

In the empagliflozin group, there was a significant decrease in FBS (p<0.001), triglyceride (p=0.027), HbA1c (p<0.001), platelet count (p=0.034), and UMA (p=0.022) values, while haemoglobin (p<0.001) and RDW (p=0.048) levels increased significantly. No significant difference was found for other laboratory results (Table 4).

There was a significant decrease in HbA1c levels in both groups. HbA1c levels before and after treatment are shown in Table 4. Serum NGAL levels and urinary arylesterase levels were compared before and after treatment and no significant difference was found between groups (Table 4).

Table 3: Comparison of Laboratory Findings of Dapagliflozin and Empagliflozin Groups Before SGLT-2 Inhibitors

Variables	Dapagliflozin	Empagliflozin	p
Fasting blood sugar (mg/dL)	180.0 (109.0-353.0)	161.0 (84.0-341.0)	0.391
Urea (mg/dL)	29.43±6.76	33.93±10.11	0.078
Creatinine (mg/dL)	0.80±0.12	0.80±0.13	0.923
GFR (mL/min/1.73 m2)	97.34±10.34	99.23±10.50	0.662
Sodium (mEq/L)	139.47±2.71	139.37±2.28	0.806
Potassium (mEq/L)	4.5 (3.1-5.4)	4.6 (3.0-5.1)	0.608
Total protein (g/L)	7.2 (5.7-8.1)	7.1 (6.3-7.7)	0.537
Albumin (g/L)	4.7 (4.1-4.9)	4.7 (4.3-5.2)	0.130
Triglyceride (mg/dL)	233.0 (46-968)	192.5 (46-638)	0.297
Total cholestero (mg/dL)	l219.57±42.05	188.83±35.22	0.003
HDL-C (mg/dL)	46.47±8.87	43.13±9.31	0.124
LDL-C (mg/dL)	135.68±30.83	100.47±23.92	<0.001
ALT (U/L)	41.07±29.17	32.60±23.22	0.198
AST (U/L)	34.33±57.28	24.03±14.96	0.836
GGT (U/L)	78.57±200.58	44.00±38.14	0.355
ALP (U/L)	98.10±80.26	80.86±27.78	0.282
Phosphorus (mg/dL)	3.54±0.56	3.75±0.59	0.188
Uric acid (mg/dL)	4.72±0.98	5.33±1.24	0.066
Magnesium (mg/dL)	1.89±0.26	1.95±0.25	0.633
Calcium (mg/dL)	9.63±0.32	9.70±0.48	0.600
HbA1c (%)	9.47±1.57	8.88±1.56	0.108
White blood cells (×109/L)	7.84±1.57	7.92±2.21	0.807
Neutrophils (×109/L)	4.28±1.29	4.44±1.52	0.988
Lymphocytes (×109/L)	2.75±0.58	2.68±0.84	0.391
Hemoglobin (g/dL)	14.61±1.45	14.61±1.26	0.900
Platelets (×109/L)	273.83±66.85	264.80±58.57	0.492
MPV (fL)	8.32±0.68	8.21±0.58	0.543
RDW (%)	13.3 (12.2-18.9)	13.5 (12.5-16.4)	0.695
UPR (mg/L)	147.0 (39.3-2098.5)	74.5 (26.5-376.3)	0.017
UKR (mg/dL)	88.3 (11.2-423.4)	85.4 (12.8-288.7)	0.797
UMA (mg/dL)	32.8 (0.59-865.5)	17.5 (1.7-556.2)	0.086
UPR/CR (mg/g CR)	107.5 (44-987)	99.0 (43.0-225.0)	0.793
Arylesterase level (U/L)	28.3 (17.8-54.2)	26.3 (8.5-66.0)	0.301
NGAL level (ng/mL)	23.5 (6.0-150.4)	22.7 (12.7-771.7)	1.000

GFR: Glomerular Filtration Rate; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gamma Glutamyl Transferase; ALP: Alkaline Phosphatase; MPV: Mean Platelet Volume; RDW: Red Blood Cell Distribution Width; UPR:Urine Protein Ratio ; UKR:Urine Creatinine Ratio ;UMA:Urine Microalbuminuria ; UPR/CR:Urine Protein Ratio/Creatinine Ratio.

Table 4.(Continued).

Variables	Dapagliflozin			Empagliflozin			
	Pre	Post	p	Pre	Post	p	Δp
Calcium (mg/dL)	9.63±0.32	9.74±0.47	0.165	9.70±0.48	9.80±0.50	0.508	0.996
HbA1c (%)	9.47±1.57	7.70±0.76	**<0.001**	8.88±1.56	7.51±0.91	**<0.001**	0.255
WBC (×109/L)	7.84±1.57	7.73±1.45	0.636	7.92±2.21	8.05±1.99	0.424	0.502
Neutrophils (×109/L)	4.28±1.29	4.05±1.23	0.369	4.44±1.52	4.77±1.47	0.210	0.074
Lymphocytes (×109/L)	2.75±0.58	2.95±0.98	0.607	2.68±0.84	2.50±0.82	0.116	0.089
Hemoglobin (g/dL)	14.61±1.45	15.13±1.55	**0.003**	14.61±1.26	15.11±1.23	**<0.001**	0.946
Platelet (×109/L)	273.83±66.85	278.23±70.00	0.697	264.80±58.57	256.33±58.41	**0.034**	0.129
MPV (fL)	8.32±0.68	8.16±0.69	0.420	8.21±0.58	8.36±0.61	0.161	0.090
RDW (%)	13.3 (12.2-18.9)	13.8 (12.2-19.7)	**0.017**	13.5 (12.5-16.4)	13.7 (12.7-16.3)	**0.048**	0.505
UPR (mg/L)	147.0 (39.3-2098.5)	119.1 (11.1-686.6)	0.194	74.5 (26.5-376.3)	92.6 (22.4-341.1)	0.524	0.572
UKR (mg/L)	88.3 (11.2-423.4)	100.3 (15.9-197.8)	0.964	85.4 (12.8-288.7)	85.6 (22.4-557.8)	0.719	0.570
UMA (mg/L)	32.8 (0.59-865.5)	4.7 (1.1-390.7)	**<0.001**	17.5 (1.7-556.2)	8.6 (2.0-472.0)	**0.022**	0.396
UPR/CR (mg/g creatine)	107.5 (44-987)	86.5 (37.0-490.0)	0.139	99.0 (43.0-225.0)	122.0 (40.0-156.0)	0.539	0.126
Arylesterase (U/L)	28.3 (17.8-54.2)	27.0 (19.5-39.0)	0.658	26.3 (8.5-66.0)	28.6 (14.5-87.4)	0.229	0.095
NGAL (ng/mL)	23.5 (6.0-150.4)	24.0 (7.3-466.8)	0.734	22.7 (12.7-771.7)	17.4 (0.2-673.4)	0.080	0.269

Please see Table 3 for abbreviations.

Discussion

This study is one of the rare studies to date examining the effects of SGLT-2 inhibitors on the renal tubule patients with type 2 diabetes mellitus. In this study, serum NGAL and urinary arylesterase levels were examined in terms of acute tubular injury in patients using dapagliflozin or empagliflozin at 10 mg.

Although there is no direct relationship between the usage of SGLT-2 inhibitors and AKI established in the literature, some research has stated that these patients may have AKI. Partial hypoxia in the tubules and a decrease in volume due to diuresis are among the main reasons for this. Peritubular hypervascularization due to increased synthesis of tubular apoptosis and vascular endothelial growth factor are also thought to be among the causes.[7]

In the study conducted by Dekkers et al., no significant correlation was found between using of SGLT-2 inhibitors and urinary NGAL levels in terms of acute tubular damage.[8] In the present study, no significant correlation was observed in serum NGAL levels of patients using SGLT-2 inhibitors. No significant difference was observed in either drug group and the obtained results were congruent with the findings of the literature to date.

Studies on urinary arylesterase levels in type 2 diabetes mellitus patients who use SGLT-2 inhibitors couldn't be found in the literature; the present study is thus a first in this regard. There are data in the literature showing that urinary arylesterase levels decrease in patients with type 2 diabetes mellitus, although no significant relationship was found with diabetic nephropathy.[5] In the present study, there are no significant change urinary arylesterase levels between the dapagliflozin and empagliflozin groups. Further research is needed on this subject.

In a study by Yale et al. involving canagliflozin, it was found that there was a 1.6-4 mL/min decrease in GFR levels in patients using SGLT-2 inhibitors.[9] However, no decrease was found in GFR levels in the present study. This may be related to the follow-up period and GFR levels of the patients in the respective studies. In the EMPA-REG OUTCOME study undertaken by Ferrannini et al., the mean follow-up period was 36 months and the GFR level was 74±21 mL/min. In the present study, the mean follow-up period was 12.3 weeks and the GFR level was 98.29±10.37 mL/min, which strengthens our suggestion that the follow-up period may be related to these outcomes.[10]

In this study, it was observed that there was a significant decrease in the level of microalbuminuria in both groups no significant difference was found between the dapagliflozin and empagliflozin groups. It is thought that the decrease in microalbuminuria was due to a decrease in blood sugar regulation and blood pressure in

the afferent arterioles within the proximal tubules of the kidney due to the effects of SGLT-2 inhibitors[11]- [12] Further studies are needed on this subject.

In the meta-analysis undertaken by Feng et al., a decrease of 6-9 mmol/mol (0.49-0.81 SD) in HbA1c level was observed with the use of dapagliflozin at 10 mg during the administration of monotherapy via SGLT-2 inhibitors.[13] In our study, the HbA1c level significantly decreased from 9.18 to 7.61. It was thought that a greater decrease in HbA1c level compared to the literature findings might be due to decreases in blood sugar levels.

A study by Kohan et al., observed that there was an increase in serum blood urea nitrogen (BUN), albumin, and phosphorus levels in patients during follow-up.[14] In the present study, a significant increase was observed in the levels of BUN, albumin, and phosphorus, and this was thought to be due to secondary hypovolemia caused by the diuretic effect of SGLT-2 inhibitors. Similarly, in the study undertaken by Merlin et al., an increase was observed in the levels of BUN, haemoglobin, and albumin.[15] In the present study, an increase in serum haemoglobin levels was also observed, which may have been due to the decrease in volume.[16]

Wu et al. showed that SGLT-2 inhibitors increase the rates of genital and urinary tract infections.[17] While dysuria was detected in 6 patients and urinary tract infection developed in 1 patient using dapagliflozin and 3 patients using empagliflozin, or a total of 4 patients. In this respect, the obtained findings are congruent with those of the literature to date. The reason why the patients in the present study did not have genital infections is likely owing to the low number of patients and the fact that the majority of the patients were male. In this study, there was no significant change in the biomarkers indicated for acute tubular injury via SGLT-2 inhibitors. When both the dapagliflozin and empagliflozin groups were examined comparatively, no difference was found between them in terms of acute tubular damage.Therefore, it is necessary to investigate better diagnostic biomarkers of DN, and in this study, we tested the diagnostic properties of NGAL, which is the most promising tubular biomarker in the diagnostic field of acute renal disease, considering that tubular dysfunction is an important component of diabetic renal disease. NGAL is mostly released in blood and urine from injured tubular cells after various conditions potentially detrimental to the kidney in experimental and human clinical models. NGAL release from renal tubule occurs precociously after damage, sooner than other ‘‘classic’’ parameter such as serum creatinine. Results of this study are thus in accordance with previous studies in literature. In addition, urinary microalbuminuria levels were decreased in both dapagliflozin and empagliflozin groups. This result supports the data that SGLT-2 inhibitors have a protective effect in terms of diabetic kidney disease. There was no significant difference in the reducing effect of microalbuminuria in both groups .[18] This study showed that empagliflozin and dapagliflozin do not increase acute tubular damage, on the contrary, they reduce microalbuminuria and have a protective effect on kidney functions.

There are some limitations of this study. As the research was conducted in the context of thesis research, conducted in a single centre, a placebo control could not be performed. The fact that the patients were not met in more frequent long-term follow-up visits was also among the limiting factors. In addition, the inability to control the optimal fluid intake of the patients in this period, the fact that the patients were not meeting optimal glycemic targets, and the inability to measure creatinine and arylesterase levels in the 24-hour urine of the patients also limited the study. Finally, psychosocial factors such as anxiety, stress, and worry experienced by patients during the time of the COVID-19 pandemic and the inability to monitor the blood pressure of the patients during this period may also affect the obtained results. Multicenter studies with more patients, longer mean follow-up periods with more frequent follow-ups, and placebo controls are needed. However, the effects of these differences on the results should be minimal, as the reduction rates in the results of the patients were calculated.

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