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Evaluating the renoprotective effectiveness of sodium-glucose co-transporter 2 inhibitor therapy in patients with chronic kidney disease: a prospective study

Procena renoprotektivne efikasnosti terapije inhibitorima natrijum-glukoznog kotransportera tipa 2 kod bolesnika sa hroničnom bolešću bubrega: prospektivna studija

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Abstract

Background/Aim. Chronic kidney disease (CKD) is a global health concern associated with increased cardiovascular risks and premature mortality. Proteinuria is a key prognostic indicator for CKD outcome. Sodium-glucose cotransporter 2 (SGLT2) inhibitors show potential for reducing proteinuria and slowing CKD progression. The aim of the study was to determine the impact of SGLT2 inhibitor therapy on CKD patients by evaluating the changes in the level of serum creatinine (sCr), 24-hour (24h) urine protein (UP), estimated glomerular filtration rate (GFR), and blood pressure (BP). **Methods.** This prospective study monitored 79 patients with CKD on therapy with SGLT2 inhibitors, who were followed up for one year. Patients received an SGLT2 inhibitor (dapagliflozin) once daily (10 mg), and assessment of specific parameters was conducted at baseline, 6 months, and 1 year later during the therapy. The study evaluated the levels of sCr, 24h UP, GFR, systolic BP (BPs), diastolic BP (BPd), uric acid (UA), total cholesterol (TC), triglycerides (Tg), low-density lipoprotein (LDL) cholesterol, sodium (Na^+), and potassium (K^+). **Results.** Over the one-year follow-up, significant changes were seen in UA levels (5.36, 4.99, 4.94 mg/dL, respectively; $p = 0.032$), 24h UP (662.60, 574.11, 417.09 mg/dL, respectively; $p = 0.028$), as well as BPs (128.44, 125.64, 126.12 mmHg, respectively; $p = 0.026$). No significant variations were observed in GFR, BPd, sCr, TC, Tg, LDL, and K^+ levels. Na^+ levels displayed a notable decrease (148.21, 147.57, 146.41 mmol/L, respectively; $p = 0.021$). **Conclusion.** The study suggests a potential benefit of SGLT2 inhibitors in managing CKD.

Key words:
drug therapy; proteinuria; renal insufficiency, chronic; sodium-glucose transporter 2 inhibitors; treatment outcome.

Apstrakt

Uvod/Cilj. Hronična bolest bubrega (HBB) predstavlja globalni zdravstveni problem, povezan sa povećanim kardiovaskularnim rizicima i preranom smrtnošću. Proteinurija je ključni prognostički pokazatelj ishoda HBB. Inhibitori natrijum-glukoznog kotransportera tipa 2 (NGKT2) pokazuju potencijal za smanjivanje proteinurije i usporavanje progresije HBB. Cilj rada bio je da se utvrdi uticaj terapije inhibitorima NGKT2 na bolesnike sa HBB procenom promene u nivou serumskog kreatinina (sKr), 24-časovne (24h) proteinurije (PU), brzine glomerularne filtracije (*glomerular filtration rate* – GFR) i krvnog pritiska (KP). **Metode.** U prospektivnu studiju bilo je uključeno 79 bolesnika sa HBB, praćenih tokom godinu dana. Bolesnici su primali inhibitor NGKT2 (dapagliflozin) jednom dnevno (10 mg), a merenja određenih parametara sprovedena su na početku terapije, šest meseci kasnije i godinu dana posle početka terapije. Studijom su procenjivane vrednosti sKr, 24h PU, GFR, sistolnog KP (KPs), dijastolnog KP (KPd), mokraćne kiseline (MK), ukupnog holesterola (UH), triglicerida (Tg), holesterola niske gustine (*low density lipoprotein* – LDL), natrijuma (Na^+) i kalijuma (K^+). **Rezultati.** Tokom godinu dana praćenja, pokazane su značajne promene u nivoima MK (5,36, 4,99, 4,94 mg/dL, redom; $p = 0,032$), 24h PU (662,60, 574,11, 417,09 mg/dL, redom; $p = 0,028$), kao i KPs (128,44, 125,64, 126,12 mmHg, redom; $p = 0,026$). Nisu zapažene značajne varijacije u vrednostima za GFR, KPd, sKr,

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UH, Tg, LDL i K^+. Nivo Na^+ pokazao je primetno smanjenje (148,21, 147,57, 146,41 mmol/L, redom; p = 0,021). **Zaključak.** Studija ukazuje na postojanje potencijalne koristi od inhibitora NGKT2 u lečenju bolesnika sa HBB.

Ključne reči:
lečenje lekovima; proteinurija; bubreg, hronična insuficijencija; natrijum-glukozni transporter 2, inhibitori; lečenje, ishod.

Introduction

Chronic kidney disease (CKD) is a highly prevalent and serious global health condition, affecting a substantial population worldwide [1, 2]. This medical condition is associated with an escalated vulnerability to cardiovascular disease, end-stage renal disease, and premature mortality [3, 4]. A distinguishing hallmark of CKD is proteinuria, which serves as a robust prognostic indicator for adverse outcomes in those afflicted [5–8].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent an innovative class of antidiabetic medications that exhibit encouraging potential in ameliorating proteinuria and decelerating the progression of CKD. Recent investigations have provided compelling evidence of the renoprotective benefits of SGLT2 inhibitor therapy in CKD patients. Heerspink et al. [9] noted that SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared to initiation of other glucose-lowering drugs. The meta-analysis conducted by Kalay et al. [10] provides compelling evidence supporting the likely beneficial role of SGLT2 inhibitors in patients with nephrotic-range proteinuria concerning the reduction of proteinuria and the deceleration of CKD progression. The findings contribute to a deeper understanding of the therapeutic potential of these inhibitors in managing CKD and proteinuria, shedding light on their promise as a treatment strategy for patients with nephrotic-range proteinuria.

In light of the aforementioned knowledge gaps, the primary aim of this study was to conduct an in-depth investigation into the impact of SGLT2 inhibitor therapy on patients suffering from CKD throughout a period of one year (yr). The study assessed the comprehensive changes in several critical parameters, encompassing serum creatinine (sCr), 24-hour (24h) urine protein (UP), estimated glomerular filtration rate (GFR), systolic blood pressure (BP) (BPs), diastolic BP (BPd), lipid profile, uric acid (UA). This research intends to analyze the variations in these parameters before and after the initiation of SGLT2 inhibitor therapy, shedding light on the potential renoprotective effectiveness of this treatment modality.

Methods

Study design and subjects

This prospective investigation involved a cohort of 79 patients who underwent continuous monitoring at the Clinic for Nephrology, University Clinical Center of Serbia, as part of the standard follow-up procedure from June 1, 2022, to August 21, 2023. The research was conducted in accordance with the Helsinki Declaration, and informed consent for participation was obtained from the patients involved. The research was approved by the Ethics Committee of the University Clinical Center of Serbia (No. 341/15, from September 14, 2023).

Inclusion criteria for the patients were the presence of CKD, with various grades (G) of the disease expressed as various levels of GFR (mL/min/1.73m^2) [the number 1.73 denotes the average body surface area (m^2) of an adult weighing 70 kg]: G2 (60–89 mL/min/1.73m^2), G3 (30–59 mL/min/1.73m^2), G4 (15–29 mL/min/1.73m^2), and G5 (< 15 mL/min/1.73m^2), with underlying diseases such as arterial hypertension (AH), glomerulopathies or type 2 diabetes mellitus (T2DM), age between 18 and 75 yrs, and the ability of the patient to follow the therapy. Individuals with contraindications for SGLT2 inhibitors such as allergic reactions to drugs, severe kidney diseases, acute infections, systemic lupus erythematosus, vasculitis, autosomal dominant polycystic kidney disease, hospitalization during the follow-up period, or discontinuation of SGLT2 inhibitor therapy for either medical or non-medical reasons, were excluded from the study.

Measurements

The study assessed mean values of sCr, 24h UP, GFR, BPs, and BPd at baseline (BL) and after 6 months (mos) and 1 yr of SGLT2 inhibitor therapy duration. Additionally, it examined UA, total cholesterol (TC), triglycerides (Tg), low-density lipoprotein (LDL) cholesterol, as well as sodium (Na^+) and potassium (K^+). sCr and 24h UP values were measured using spectrophotometry on an Alinity C device (Abbott, Ravenswood, Chicago), while GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula: $186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times (\text{age})^{-0.203} \times$ (0.742 if female) [11]. Serum values of TC, Tg, LDL, and UA levels were analyzed using the Olympus AU600 chemistry immuno analyzer (Olympus, Japan).

Study protocol

All patients were prescribed oral therapy with SGLT2 inhibitor (dapagliflozin) once daily at a dose of 10 mg according to the patient's condition. There were no changes in the dosage of the therapy during the follow-up period. Measurements were taken on three occasions: initial measurement, first follow-up measurement after 6 mos (± 15 days) of therapy duration, and second follow-up measurement after 1 yr (± 15 days) of therapy duration.

Statistical analysis

Statistical analysis was performed using IBM SPSS (version 26.0, Statistical Package for the Social Sciences, Chicago, Illinois, USA). The normality of the distribution for

the observed variables was assessed using the Kolmogorov-Smirnov test. Nonparametric tests were applied when deviations from the normal distribution were detected. The Chi-square test was used to examine significant differences in categorical variables. To determine whether there were statistically significant differences between BL and control measurements, a Friedman's test was performed. Statistical significance was set at a *p*-value of ≤ 0.05.

Results

The total number of participants was 79, of which 45 (57.0%) were males and 34 (43.0%) were females ($\chi^2 = 1.53$; $p = 0.216$). The mean age of the participants was 56 ± 19.3 yrs (minimum-maximum: 19–88 yrs), and the majority of the participants were over 65 yrs old (40.5%). Among the participants, 39.2% were categorized in CKD stage G2, closely followed by 36.8% of patients in stage G3. A smaller contingent of participants was allocated to the more advanced stages, with 21.5% of patients in stage G4 and a mere 2.5% of patients in the pinnacle stage G5. The patients in stage G5 also had heart failure, for which an SGLT2 inhibitor was introduced, so therapy was continued. Of all the participants, 26.6% had T2DM, 64.6% had AH, and 59.5% had glomerulonephritis (GN). The statistical analysis showed significant differences in age ($\chi^2 = 10.37$; $p = 0.016$), prevalence of T2DM ($\chi^2 = 17.3$; $p < 0.001$), AH ($\chi^2 = 6.70$; $p = 0.010$), and CKD stage ($\chi^2 = 27.076$; $p < 0.001$) among the participants. However, there were no significant differences in gender ($\chi^2 = 1.53$; $p = 0.216$) and prevalence of GN ($\chi^2 = 2.85$; $p = 0.091$). Participants' therapeutic regimens encompassed a range of pharmacological interventions. Notably, angiotensin-converting enzyme inhibitors were prescribed to 34.3% of individuals ($\chi^2 = 7.911$; $p = 0.005$) and angiotensin receptor blockers to 43.0% of individuals ($\chi^2 = 1.532$; $p = 0.216$). Loop diuretics were administered to 35.4% of participants ($\chi^2 = 6.696$; $p = 0.010$), and statins were prescribed to 41.8% of participants ($\chi^2 = 2.139$; $p = 0.144$) (Table 1).

Table 1

Demographic and clinical characteristics of patients

Variable	n (%)	χ^2	*p*-value
Demographic characteristics			
Gender			
male	45 (57.0)	1.53	0.216
female	34 (43.0)		
Age, (years)			
18–35	14 (17.7)	10.37	**0.016**
36–50	17 (21.5)		
51–65	16 (20.3)		
> 65	32 (40.5)		
mean ± SD (min-max)	56 ± 19.3 (19–88)		
CKD (mL/min/1.73m^2)			
G2 (60–89)	31 (39.2)	27.076	**< 0.001**
G3 (59–30)	29 (36.8)		
G4 (29–15)	17 (21.5)		
G5 (< 15)	2 (2.5)		
Comorbidities			
Type 2 diabetes mellitus			
no	58 (73.4)	17.3	**<0.001**
yes	21 (26.6)		
Arterial hypertension			
no	28 (35.4)	6.70	**0.010**
yes	51 (64.6)		
Glomerulonephritis			
no	32 (40.5)	2.85	0.091
yes	47 (59.5)		
Therapy			
ACEi			
no	52 (65.8)	7.911	**0.005**
yes	27 (34.3)		
ARB			
no	45 (57.0)	1.532	0.216
yes	34 (43.0)		
Loop diuretics			
no	51 (64.6)	6.696	**0.010**
yes	28 (35.4)		
Statins			
no	46 (58.2)	2.139	0.144
yes	33 (41.8)		

SD – standard deviation; CKD – chronic kidney disease; G – grade of disease; ACEi – angiotensin-converting enzyme inhibitors; ARB - angiotensin 2 receptor blockers; χ^2 – Friedman's Chi-square coefficient; n – number of patients. Bolded values indicate statistically significant results.

BL and control values of observed variables are shown in Table 2. The mean values of sCr were 136.78 ± 71.97 μmol/L [reference range (RR): 59–104 μmol/L] at BL and 136.21 ± 70.75 μmol/L after 6 mos. After 1 yr, the mean sCr level was 137.27 ± 73.31 μmol/L ($\chi^2 = 5.842$, $p = 0.054$). For 24h UP, the mean values were 662.60 ± 545.33 mg/dL (RR < 150 mg/dL) at BL, 574.11 ± 507.72 mg/dL after 6 mos and 417.09 ± 513.48 mg/dL after 1 yr ($\chi^2 = 7.117$, $p = 0.028$). The GFR showed minimal variation over time. At BL, the mean GFR was 45.01 ± 17.21 mL/min/1.73m² (RR > 90 mL/min/1.73m^2), and it remained relatively stable at 44.97 ± 16.46 mL/min/1.73m² after 6 mos and 45.80 ± 17.98 mL/min/1.73m² after 1 yr ($\chi^2 = 0.320$, $p = 0.572$). Regarding blood pressure, both BPs and BPd levels exhibited some changes. BPs decreased from 128.44 ± 15.54 mmHg at BL to 125.64 ± 10.35 mmHg after 6 mos and 126.12 ± 10.63 mmHg after 1 yr. This reduction was statistically significant (Friedman's $\chi^2 = 7.270$, $p = 0.026$). BPd showed no significant changes over time, with mean values of 80.45 ± 9.91 mmHg at BL, 80.93 ± 7.48 mmHg after 6 mos, and 80.99 ± 7.79 mmHg after 1 yr (Friedman's $\chi^2 = 359.0$, $p = 0.907$). UA levels exhibited a significant decrease, with mean values of 5.36 ± 1.21 mg/dL (RR: 2–7 mg/dL) at BL, 4.99 ± 1.37 mg/dL after 6 mos, and 4.94 ± 1.39 mg/dL after 1 yr follow-up ($\chi^2 = 7.421$, $p = 0.032$). TC remained stable, ranging from 5.34 ± 1.39 mmol/L (RR < 5.2 mmol/L) at BL, 5.38 ± 1.83 mmol/L after 6 mos, to 5.35 ± 1.91 mmol/L after 1 yr ($\chi^2 = 0.105$, $p = 0.974$). Tg showed a trend towards reduction, registering 2.12 ± 1.03 mmol/L (RR < 1.7 mmol/L) at BL, 1.97 ± 0.65 mmol/L after 6 mos, and 1.96 ± 0.67 mmol/L after 1 yr ($\chi^2 = 5.240$, $p = 0.052$). LDL levels remained steady, with mean values of 2.74 ± 1.21 mmol/L (RR < 3.4 mmol/L) at BL, 2.58 ± 1.29 mmol/L after 6 mos, and 2.54 ± 1.36 mmol/L after 1 yr ($\chi^2 = 0.311$, $p = 0.582$). Na^+ levels exhibited a statistically significant change, varying from 148.21 ± 10.24 mmol/L (RR: 135–148 mmol/L) at BL, 147.57 ± 9.44 mmol/L after 6 mos, to 146.41 ± 10.48 mmol/L after 1 yr ($\chi^2 = 7.870$, $p = 0.021$). K^+ levels remained consistent, showing mean values of 4.81 ± 0.47 mmol/L (RR: 3.5–5.0 mmol/L) at BL, 4.82 ± 0.48 mmol/L after 6 mos, and 4.81 ± 0.44 mmol/L after 1 yr ($\chi^2 = 0.059$, $p = 0.987$).

Discussion

The study revealed a statistically significant decrease in 24h UP, UA, BPs, and Na^+ levels, while other monitored parameters, including sCr, GFR, BPd, TC, Tg, LDL, and K^+ exhibited stability with no significant changes observed. The research findings provide compelling evidence in favor of a male predominance over females, diverging from the observations in the study by Kao et al. [12]. Furthermore, a recent investigation conducted by Lewandowski et al. [13] in Austria concluded that women exhibit a higher susceptibility to CKD compared to men. Concerning age distribution, most of our sample consisted of individuals over 65 yrs. Correspondingly, Liu et al. [14] presented data that aligns with our results, asserting that CKD is more prevalent among older individuals, with advancing age correlating to a higher incidence of complications arising from CKD. However, there is a noticeable shift in boundaries, as CKD is increasingly manifesting in younger individuals [15]. The accelerated disease progression observed in the younger cohort is akin to numerous other diseases, entailing a multitude of comorbidities, which, in most cases, share a causal relationship with CKD [16, 17].

The research outcomes underscore GN as the most prevalent comorbidity linked to CKD, signifying a significant association between these two states. This observation is corroborated by Wetmore et al. [18], whose study elucidated that approximately 10–15% of individuals with GN progress to the terminal stage of renal failure. Conversely, Meremo et al. [19] documented a notably lower GN comorbidity among CKD patients. AH emerges as the second most frequent comorbidity, which is to be expected given the established correlation between elevated blood pressure and the development of CKD [20, 21]. Additionally, T2DM constitutes a significant comorbidity within this study. The well-established link between T2DM and CKD stems from diabetes' propensity to inflict kidney damage over time [21, 22]. The three aforementioned factors are the most common comorbidities causally related to CKD, albeit the order of prevalence may fluctuate in other investigations [23, 24].

Table 2

Baseline and follow-up values of the specific observed variables

Variable	Baseline	Follow-up		χ^2	*p*-value
		6 months	1 year		
sCr (μmol/L)	136.78 ± 71.97 (51.0–443.0)	136.21 ± 70.75 (44.0–375.0)	137.27 ± 73.31 (44.21–376.0)	5.842	0.054
24 h UP (mg/dL)	662.60 ± 545.33 (0.02–44,970.0)	574.11 ± 507.72 (0.07–45,139.0)	417.09 ± 513.48 (0.05–44,970.0)	7.117	**0.028**
GFR (mL/min/1.73m^2)	45.01 ± 17.21 (9.0–108.0)	44.97 ± 16.46 (10.0–90.0)	45.80 ± 17.98 (10–91)	0.320	0.572
BPs (mmHg)	128.44 ± 15.54 (90.0–180.0)	125.64 ± 10.35 (100.0–150.0)	126.12 ± 10.63 (100.0–150.0)	7.270	**0.026**
BPd (mmHg)	80.45 ± 9.91 (60.0–100.0)	80.93 ± 7.48 (60.0–90.0)	80.99 ± 7.79 (60–90)	359.0	0.907
UA (mg/dL)	5.36 ± 1.21 (1.49–10.21)	4.99 ± 1.37 (1.58–7.81)	4.94 ± 1.39 (1.59–7.78)	7.421	**0.032**
TC (mmol/L)	5.34 ± 1.39 (3.55–7.49)	5.38 ± 1.83 (3.42–7.57)	5.35 ± 1.91 (3.24–7.44)	0.105	0.974
Tg (mmol/L)	2.12 ± 1.03 (0.35–4.52)	1.97 ± 0.65 (0.41–4.27)	1.96 ± 0.67 (0.54–4.51)	5.240	0.052
LDL (mmol/L)	2.74 ± 1.21 (0.81–3.12)	2.58 ± 1.29 (0.98–3.12)	2.54 ± 1.36 (1.1–3.37)	0.311	0.582
Na^+ (mmol/L)	148.21 ± 10.24 (145.24–154.01)	147.57 ± 9.44 (144.84–152.11)	146.41 ± 10.48 (145.28–154.05)	7.870	**0.021**
K^+ (mmol/L)	4.81 ± 0.47 (4.44–5.57)	4.82 ± 0.48 (4.51–5.68)	4.81 ± 0.44 (4.37–5.68)	0.059	0.987

sCr – serum creatinine; 24 h UP – 24-hour urine protein; GFR – estimated glomerular filtration rate; BPs – systolic blood pressure; BPd – diastolic blood pressure; UA – uric acid; TC – total cholesterol; Tg – triglycerides; LDL – low-density lipoprotein; χ^2 – Friedman's Chi-square coefficient. All results are shown as mean ± standard deviation (minimum-maximum). Bolded values indicate statistically significant results.

Regarding the impact of SGLT2 inhibitors, the study results demonstrate insignificant alterations in sCr and GFR levels and significant alterations when it comes to BPs between BL and control measurements. Notably, mean BPd values remained within the reference range, indicative of compensated hypertension. Additionally, after 1 yr of SGLT2 inhibitor therapy, a substantial reduction in the range and standard deviation of BP was observed, signifying hypertension stabilization. The results of our study align with the findings of Briasoulis et al. [25] and Baker et al. [26]. Regarding sCr values, prior investigations have shown that SGLT2 inhibitors may elevate sCr levels due to the tubuloglomerular feedback mechanism [27]. Although SGLT2 inhibitors hold renoprotective potential, their judicious use is of paramount importance, as they may entail risks, such as increased sCr levels in CKD patients [27, 28].

This study confirmed significantly decreased follow-up values in 24h UP excretion levels, indicative of the SGLT2 inhibitors' impact. As emphasized by Takashima et al. [29], the renoprotective effect encompasses diminished protein secretion, particularly in patients with T2DM. Furthermore, this renoprotective effect is linked to a reduced risk of cardiovascular incidents [30]. Reduction in protein excretion has also been documented in studies exploring nephrotic syndrome as a consequence of CKD, demonstrating marked improvements in hypoalbuminemia following SGLT2 inhibitor therapy [31, 32]. However, to achieve the complete renoprotective effect of SGLT2 inhibitors, a certain duration of action is required [28, 33].

Furthermore, it is noteworthy that there was a statistically significant reduction in UA levels during the follow-up period, which is an expected outcome. Earlier researchers, including Banerjee et al. [34], confirmed such findings in their meta-analysis of randomized controlled trials. The reduction in Na^+ levels has been confirmed, as observed in the study by Tang et al. [35]. The decrease in blood Na^+ concentration was expected due to the direct action of SGLT2 inhibitors on its reabsorption in the kidneys.

It is of great importance to mention the results of a randomized trial conducted by Perkovic et al. [36], which confirms the renoprotective effects of SGLT2 inhibitors in patients with T2DM. The study claims that the use of SGLT2 inhibitors extends the time of CKD onset by 2.62 yrs compared to patients who do not use SGLT2 inhibitors. Heerspink et al. [37] also achieved significant results, elucidating that dapagliflozin, belonging to the SGLT2 inhibitor class, substantially reduces the risk of CKD progression. In a recent study by the EMPA-KIDNEY Collaborative Group [38], it was found that empagliflozin, another SGLT2 inhibitor, reduces the risk of cardiovascular events and death in CKD patients by 27%.

The preceding three studies provide deeper insights into the role of SGLT2 inhibitors concerning CKD and emphasize their renoprotective potential. Our study's results support the existence of the protective effects of SGLT2 inhibitors, given the observed reduction in proteinuria. However, it is essential to consider the limitation of a short follow-up period when evaluating other variables in this study.

Conclusion

The study's conclusion indicates a correlation between CKD and comorbidities, with GN, AH, and T2DM being the most common accompanying conditions. SGLT2 inhibitors demonstrated a statistically significant reduction in proteinuria, suggesting potential renoprotective effects. However, longer-term monitoring is necessary to fully understand the impact on other measured parameters. These findings provide a basis for further research to better elucidate the role of SGLT2 inhibitors in managing CKD.

Conflict of interest

The authors declare no conflict of interest.

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