DOI 10.4149/BLL_2024_116

*Bratisl Med J 2024; 125 (12):*
759–765

CLINICAL STUDY

# The sodium-glucose cotransporter-2 inhibitors in patients with chronic kidney disease with or without kidney transplantation – a single centre study

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**ABSTRACT**
INTRODUCTION: The sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent the first-line treatment for chronic kidney disease. The question remains of their benefit and safety for patients after kidney transplantation. The study aimed to show the renoprotective effect and safety of use in patients with chronic kidney disease with or without kidney transplantation.
MATERIAL: This is a prospective monocentric study of the Transplant-Nephrology Department in Martin in which patients with chronic kidney disease with or without kidney transplant in therapy with dapagliflozin were included (n=79). The changes in glomerular filtration rate, albuminuria and side effects associated with SGLT2i were studied in patients with chronic kidney disease with or without kidney transplantation and in patients with or without diabetes mellitus.
RESULTS: Patients without diabetes mellitus achieved a significantly higher decrease in albuminuria at the time of the third month of follow-up (p=0.0396), with the continuation of the decrease until the average follow-up (10.9 months) (p=0.7866) than patients with diabetes mellitus. During the observed period, we recorded the cessation of the primary decrease in glomerular filtration with a return to the baseline values. In our group, we did not confirm a significant occurrence of adverse effects associated with dapagliflozin.
CONCLUSION: SGLT2i significantly reduces albuminuria and stabilizes glomerular filtration in patients with chronic kidney disease. Based on our analysis, treatment with gliflozins is effective and safe for patients after kidney transplantation *(Tab. 4, Fig. 6, Ref. 16)*. Text in PDF www.elis.sk
KEY WORDS: chronic kidney disease, kidney transplant recipients, side effects, SGLT2i.

**Abbreviations:** AKI – acute kidney injury, CKD – chronic kidney disease, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration Epidemiology Index, CREDENCE – Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, DAPA-CKD – Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease, DKD – diabetic kidney disease, DM – diabetes mellitus, eGFR – estimated glomerular filtration rate, EMPA-REG – The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose, ERA – European Renal Association, ERBP – European Renal Best Practice Guideline Group, EURECA-m – European Renal and Cardiovascular Medicine Working Group, FDA – Food-Drug Administration, FSGS – focal segmental glomerulosclerosis, GFB – glomerular filtration barrier, HF – heart failure, HFmrEF – heart failure mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, KDIGO – Kidney Disease Improving Global Outcome, KTRs – kidney transplant recipients, MPGN – mebranoproliferative glomerulonephritis, PTDM – post-transplant diabetes mellitus, RAAS – renin-angiotensin-aldosterone system, SGLT2i – sodium-glucose co-transporter-2 inhibitors, UACR – urine albumin/creatinine ratio

## Introduction

The sodium-glucose co-transporter-2 inhibitors (SGLT2i), gliflozins, are selective hypoglycaemic drugs that inhibit one of the several members of the SGLT family. The first gliflozin isolated from the root bark of the apple tree was phlorizin in 1835, which was used to treat fever and infections (1). However, it was a non-selective SGLTi that caused severe gastrointestinal side effects, such as diarrhoea, which led to dehydratation. The era of selective SGLT2i started in 2013, and nowadays, we have canagliflozin, dapagliflozin, empagliflozin and ertugliflozin approved by the Food-Drug Administration (FDA). Canagliflozin, as the first gliflozin, is indicated for patients with diabetes mellitus (DM) type II. In May last year, the FDA expanded the

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indication restriction for dapagliflozin. In addition to patients with DM II, a prescription is also possible for patients with heart failure (HF) with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF). The most recently approved SGLT2i from 2017 is ertugliflozin. European Renal and Cardiovascular Medicine Working (EURECA-m) Group and European Renal Best Practice (ERBP) Guideline Group (ERBP) of the European Renal Association (ERA) published in May 2023 a document summarizing guidelines for SGLT2i in patients with CKD (2). Kidney Disease Improving Global Outcome (KDIGO) published an updated Guideline for Evaluation and Management of Chronic Kidney Disease on April 2024, where SGLT2i (dapagliflozin, empagliflozin and canagliflozin) are the first line of treatment for patients with chronic kidney disease (CKD), not only for diabetic kidney disease (DKD) (3, 4, 5). The latest recommendations are based on the results of large studies conducted with gliflozins, where a significant reno-vascular-metabolic effect was proven.

The effects of gliflozins are pleitropic. Renoprotective effects are divided into primary and secondary. Blockade of SGTL2 cotransporters located at the brush border of tubular cells in segments (S1 and S2) of the proximal tubule leads to glycosuria and natriuresis (6). Increasing natriuresis is critical for renal protection. The increasing concentration of sodium in the juxtaglomerular apparatus leads to a reduction and normalization of tubuloglomerular feedback from macula densa. The result is vasoconstriction of afferent arteriole with reduced intraglomerular pressure and temporary dropping of glomerular filtration rate (3, 6). The inhibitory effect on the $Na^+$-$H^+$ exchanger enhances the inhibitory effect on the $Na^+$-$H^+$ exchanger natriuretic effect of SGLT2i. By inhibiting the SLGT2 cotransporters, the activity of Na-K ATPase on the basolateral membrane also decreases. The result is a decrease in the glucose concentration in the cells of the proximal tubules with a decrease in the formation of advanced glycation end products and a reduction in oxidative stress. Improvement in albuminuria is multifactorial and also associated with a reduction in intraglomerular pressure and glycosuria, which reduces the glucotoxic effect on podocytes (6).

Secondary effects of gliflozins include weight loss, reduction of pro-inflammatory cytokines (TNF, IL-6, IFN) and suppression of hepcidin with improving erythropoiesis. Reduction of weight is associated with the use of lipids as an energy source due to glycosuria, which leads to a reduction in lipotoxicity and cellular stress (6). Despite the significant benefits of gliflozin, all large randomized trials excluded kidney transplant recipients (KTRs) because of the risk of developing unexpected complications (7). Gradually, the results of studies performed with KTRs with DM type II or post-transplant diabetes mellitus (PTDM) appears in the professional literature, which confirms the conclusions of randomized trials. Moreover, no evidence exists, there is no evidence of studies exploring SGTL2is as renoprotective agents in KTRs without diabetes mellitus (8, 9).

**Tab. 1. Basic characteristics of the cohort.**

| n=79 | |
|---|---|
| gender – men (%) | 77.2 (n=61) |
| age (years)±SD | 51±14.6 |
| kiedney transplantation (%) | 53.2 (n=42) |
| diabetes mellitus (%) | 43 (n=34) |
| eGFR base line (ml/min)±SD | 45.4±19.5 |
| UACR base line (g/mol)±SD | 95.5±125.6, median 56.6 |
| eGFR 3M (ml/min)±SD | 43.6±19.7 |
| UACR 3M (g/mol)±SD | 67.8±92.3, median 30.2 |
| eGFR follow up (ml/min)±SD | 42.4±20.7 |
| UACR follow up (g/mol)±SD | 65.5±102.6, median 17.9 |
| follow up (months)±SD | 11±4.8, median 11 |

SD – standard deviation, eGFR – estimated glomerular filtration rate, UACR – urine albumin/creatinine ratio, M – month

Our **s**tudy aimed to show the effect of SGLT2i on albuminuria, estimated glomerular filtration rate (eGFR) and use safety in patients with CKD and patients after kidney transplantation.

## Materials and methods

In our prospective monocentric study, patients followed at the Martin Transplant-Nephrology Departement with CKD with or without kidney transplantation, who met the indication criteria for the prescription of SGLT2i were included.

*Inclusion criteria:*

- patient age >18 years,
- eGFR (CKD-EPI 2021) ≥25 to ≤75 ml/min/1,73 $m^2$,
- albuminuria (urine albumin creatinine ratio (UACR) ≥200 and ≤5 000 mg/g),
- CKD caused by a disease other than genetic polycystic kidney disease, systemic lupus, ANCA-associated vasculitis or DM type I,
- treatment with a stable dose of an inhibitor of the renin-angiotensin-aldosterone system (RAAS) or when treatment with RAAS inhibitor is contraindicated.

Patients were taking SGLT2i (dapagliflozin) at a dose of 10 mg daily. The following parameters were determined for all patients: sex, age at the time of SGTL2i prescription and complications associated with using SGL2i. We also recorded dynamic parameters in all participants such as: eGFR and albuminuria at the time of SGLT2i prescription, in the third month of follow-up and at the time of achieved follow-up of SGLT2i use at the evaluation of the results, which varied among patients. We divided the studied sample of patients in the context of transplantation (transplanted, non-transplanted) and according to the development of DM (without DM, with DM – DM type II or PTDM). We investigated the underlying cause of CKD in non-transplanted patients. The sample of patients was also divided according to the length of follow-up with a focus on eGFR dynamics.

The estimated glomerular filtration rate was determined using the Chronic Kidney Disease-Epidemiology Collaboration Index (CKD-EPI) and albuminuria from 24-hour collected urine. In patients where the UACR test was performed, we converted it to albuminuria according to the equates Lamb E. et al. from 2009 (10). We used a certified statistical program, MedCalc version 13.1.2.

(MedCalc Software VAT registration number BE 0809 344,640, Member of International Association of Statistical Computing, Ostend, Belgium). Categorical variables were presented as counts and weighted percentages. Comparisons of continuous variables between groups were carried out using parametric (t-test) or non-parametric (Mann–Whitney) tests; associations between categorical variables were analyzed using the $\chi$ 2 test and Fisher's exact test, as appropriate. A p-value < 0.05 was considered to be statistically significant.

*Ethical approval*

All procedures involving human participants have been approved according to the ethical standards of the ethical committee of University Hospital Martin and Jessenius Faculty of Medicine, including the 1964 Helsinki Declaration and its later amendments of comparable ethical standards. All signed informed consents are archived for at least 20 years after research completion and are available upon request. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

## Results

A total of 79 patients (men: n=61; 77.2%) with an average age of 51 years were included in the study. The average follow-up was 11 months (SD=4.8). The monitored parameters and characteristics of the cohort are shown in Table 1. The development of eGFR and albuminuria in the monitored group, with an average follow-up of 11 months, is shown in Figures 1 and 2. We recorded a decrease in both monitored parameters in the following period, which, however, did not reach statistical significance. Although the values of eGFR decline did not reach statistical significance, eGFR decline stopped in patients with follow-ups longer than three months, and even in patients with follow-ups longer than 12 months, eGFR returned to the baseline (Fig. 3).

The sample of patients was divided in the context of kidney transplantation into two groups: transplanted (n=42; 53.2%) and non-transplanted (n=37; 46.8%). We found out that the baseline value of albuminuria was statistically significantly lower in kidney transplant patients (p=0.0466) than in non-transplanted patients (Tab. 2). In non-transplanted patients, we focused on the etiology of CKD (Fig. 4), where IgA nephropathy (n=13; 35.1%) and diabetic kidney disease (n=5; 13.5%) were dominant. Because IgA nephropathy represents the most common glomerulonephritis and target therapy is still unavailable, the effect of SGLT2i on the outcome of eGFR and albuminuria was monitored. The result was that patients with IgA nephropathy had a significant decrease in albuminuria during the monitored period (average follow-up of 10.8 months) (Tab. 3).

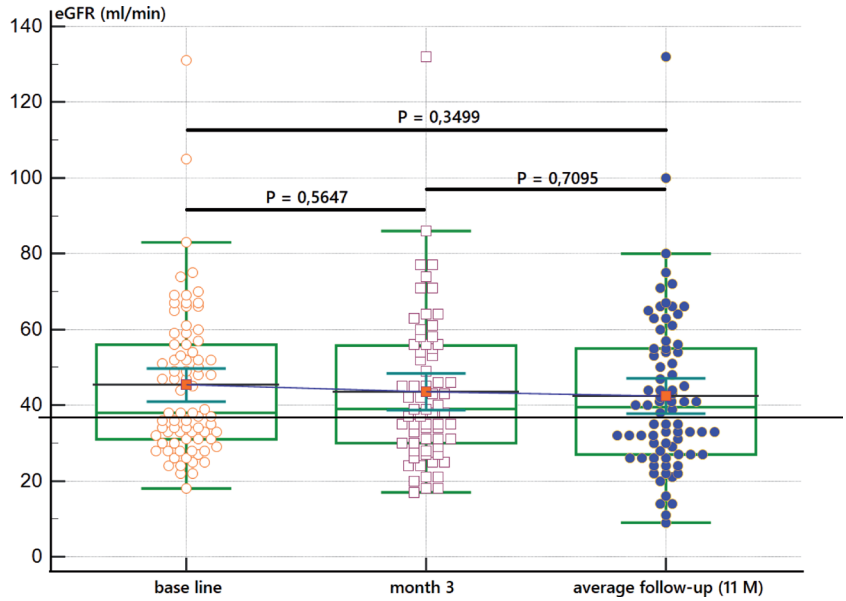


**Fig. 1. Development of eGFR in the cohort. eGFR – estimated glomerular filtration rate, M – month.**

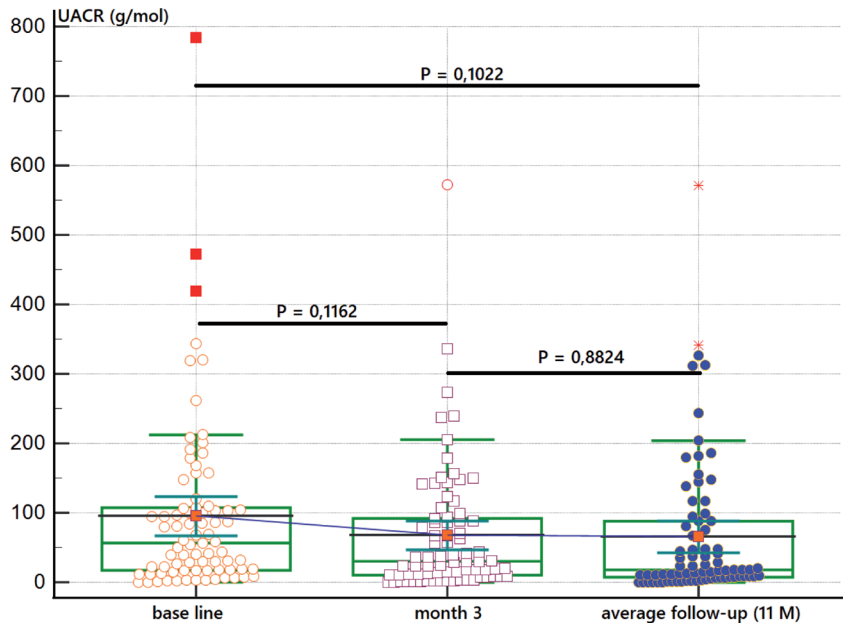


**Fig. 2. Development of albuminuria in the cohort. M – month, UACR – urine albumin/creatinine ratio.**

**Tab. 2. Comparison of monitored parameters in transplanted and non transplanted patients.**

| | Ttransplanted patients n=42 | Non-transplanted patients n=37** | p |
|---|---|---|---|
| Men (%) | 78.6 (n=33) | 75.7 (n=28) | 0.7894 |
| Age (years)±SD | 50.8±12.5 | 50.6±16.9 | 0.9521 |
| Diabetes mellitus (%) | 50 (n=21) | 35.1 (n=13) | 0.4024 |
| eGFR base line (ml/min)±SD | 44.3±15.5 | 46.6±23.4 | 0.6041 |
| UACR base line (g/mol)±SD | 69.1±93.6, median 27.6 | 125.3±150, median 85.9 | **0.0466** |
| eGFR 3M (ml/min)±SD | 41.6±17.3 | 46.3±22.7 | 0.3007 |
| UACR 3M (g/mol)±SD | 56±81, median 18.9 | 82±103.6, median 57.1 | 0.2151 |
| eGFR follow up (ml/min)±SD | 39.7±18.2 | 45.5±23.1 | 0.2163 |
| UACR follow up (g/mol)±SD | 48.8±84.6, median 11 | 85±119, median 45 | 0.1201 |
| follow up (months)±SD | 11.5±4, median 11 | 10.4±5.6, median 11 | 0.3141 |

SD – standard deviation, eGFR – estimated glomerular filtration rate, M – month, UACR – urine albumin/creatinine ratio, *IgA nephropathy: n=13, membranous glomerulonephritis: n=4, membranoproliferative glomerulonephritis: n=3, focal segmental glomerulosclerosis: n=4, nephrosclerosis: n=1, diabetic kidney disease: n=5, others: n=7

Patients were also divided in association with DM into non-diabetics and diabetics (n=34; 43.1%), which included patients with post-transplant diabetes mellitus (n=15; 44.1%) a DM type II (n=19; 55.9%). Patients without DM were significantly younger (p=0.0001) than patients with DM (Tab. 4). They also achieved a statistically significant decrease in albuminuria in the third month of follow-up (p=0.0396), with a continuation of the decrease until the average follow-up (10.9 months) (Fig. 5). In both groups of patients, we noticed decreasing eGFR, but it was not statistically significant (Fig. 6).

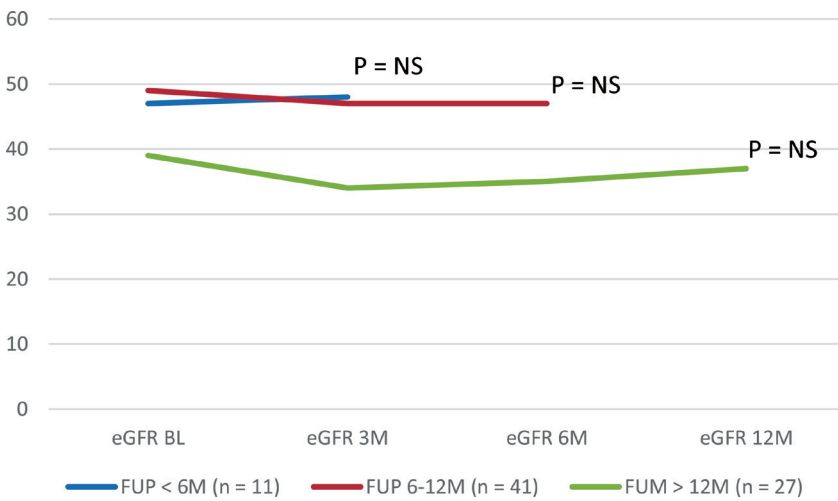


**Fig. 3. Development of eGFR according to duration of SGLT2i use (follow-up. eGFR – estimated glomerular filtration rate, SGLT2i – sodium-glucose co-transporter-2 inhibitors, NS – nonsignificant, M – month, FUP – follow-up.**

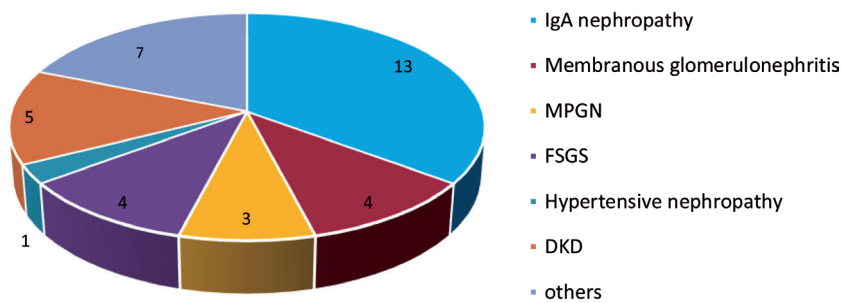


**Fig. 4. The distribution of non-transplanted patients according to CKD aetiology. CKD – chronic kidney disease, MPGN – membranoproliferative glomerulonephritis, FSGS – focal segmental glomerulosclerosis, DKD – diabetic kidney disease.**

In one patient of our cohort after kidney transplantation, a urinary tract infection developed during the use of SGLT2i, however it was managed conservatively, without the need to withdraw the preparation from treatment. Complications associated with SGLT2i treatment were not identified in the other patients.

## Discussion

In our analysis, was confirmed a decreasing trend of eGFR compared to the baseline value during three months of SGLT2i use. The same result was also confirmed by the randomized clinical trials The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG) and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) conducted exclusively in patients with DM type II and the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study, which included also CKD patients (6, 7, 10).

In our group, in patients with follow-up >3 months, the decrease in eGFR gradually stopped, and in patients with follow-up >12 months, eGFR returned to the baseline value. In contrast, in the authors' analysis, Heerspink HJL et al.

(DAPA-CKD) continued to decline in eGFR for 32 months of follow-up with gradual stabilization of eGFR. However, even in the 36th month of randomization, eGFR did not reach baseline (12). However, the DAPA-CKD study was prematurely stopped early by the independent Data Monitoring Committee at a median follow-up of 2.4 years due to the clear benefit of dapagliflozin treatment. An essential outcome of the DAPA-CKD working group was a decrease in the primary composite goal (permanent reduction in eGFR ≥50%, end-stage kidney disease, death from renal causes or cardiovascular death) by 39% compared to the placebo group (12). The results of the named trials and our analysis support that the drop in eGFR is only an initial issue at the beginning of treatment with gliflozins. A sharp drop in eGFR at the beginning of therapy is related to positive hemodynamic changes in the glomeruli (11).

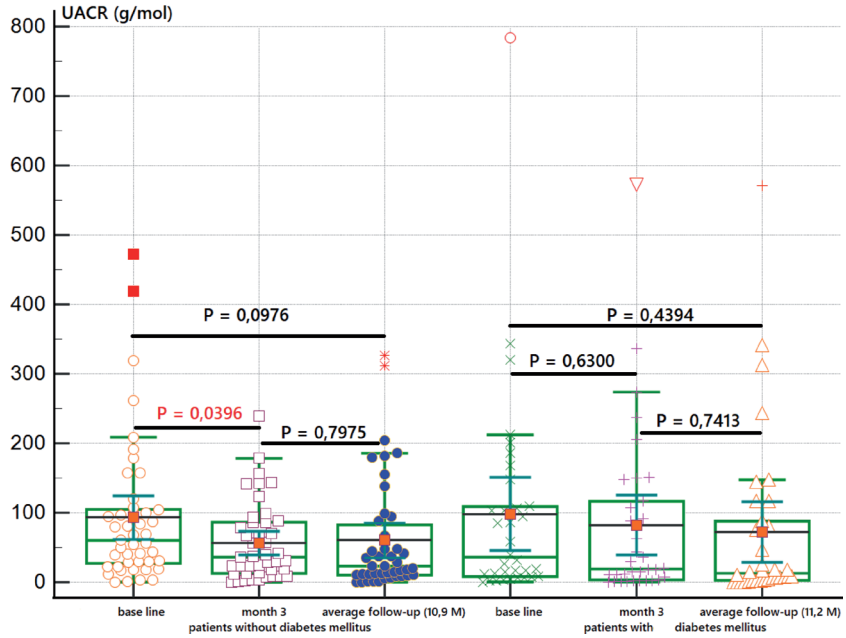


**Fig. 5. The development of albuminuria in patients without and with diabetes mellitus. M – month, UACR – urine albumin/creatinine ratio.**

Wheeler et al performed a pre-specific analysis of the DAPA-CKD study in 2021 with IgA nephropathy patients. The result confirmed an average percentage decrease in UACR of 35% in the SGLT2i group compared to the placebo group in the fourth month of follow-up. At the same time, the downward trend persisted throughout the follow-up period (36 months) (13). We also noted a decrease in albuminuria in patients with IgA nephropathy in our analysis, although with a smaller number of patients and a shorter follow-up. This decrease is related to the protective effect of gliflozins on the cells of the proximal tubules and the structures of the GFB. By blocking SGLT2i, glycosuria occurs with the elimination of the deposition of glucotoxic material in GFB structures, a reduction in the metabolic load of cells of the proximal tubules, and a reduction in the production of pro-inflammatory cytokines acting on podocytes (6).

**Tab. 3. The characteristics of the cohort – IgA nephropathy.**

| **n=13** | |
|---|---|
| Men (%) | 76.9 (n=10) |
| Age (years)±SD | 44.4±12.9 |
| diabetes mellitus (%) | 15.4 (n=2) |
| eGFR base line (ml/min)±SD | 43.7±18.1 |
| UACR base line (g/mol)±SD | 99.3±88.1, median 79.4 |
| eGFR 3M (ml/min)±SD | 49.3±20.5 |
| UACR 3M (g/mol)±SD | 88.9±71.8, median 68.1 |
| eGFR follow up (ml/min)±SD | 44±18.8 |
| **UACR follow up (g/mol)±SD** | 83.6±87, median 47.7 |
| **follow up (mesiace)±SD** | 10.8±6.9, median 11 |

SD – standard deviation, eGFR – estimated glomerular filtration rate, M – month, UACR – urine albumin/creatinine ratio

**Tab. 4. Comparison of monitored parameters in patients without and with diabetes mellitus.**

| | **non-diabetics n=45** | **diabetics* n=34** | **p** |
|---|---|---|---|
| **Men (%)** | 75.6 (n=34) | 79.4 (n=27) | 0.7271 |
| Age (years)±SD | 44.6±14 | 58.7±11.4 | < 0.0001 |
| Kidney transplantation (%) | 46.7 (n=21) | 61.8 (n=21) | 0.3319 |
| eGFR base line (ml/min)±SD | 45.8±22 | 44.9±15.9 | 0.8405 |
| UACR base line (g/mol)±SD | 93.3±104, median 60.2 | 98.3±151.2 , median 36.1 | 0.8623 |
| eGFR 3M (ml/min)±SD | 45.5±22.6 | 41.2±15.5 | 0.3439 |
| UACR 3M (g/mol)±SD | 56.5±56.1, median 36.2 | 82.1±123.4 median 19.2 | 0.2207 |
| eGFR follow up (ml/min)±SD | 42.3±23.2 | 42.6±17.2 | 0.9497 |
| UACR follow up (g/mol)±SD | 60.3±81.6, median 23.3 | 72.1±125.3, median 12.9 | 0.6143 |
| follow up (molnths)±SD | 10.9±5.3, median 13 | 11.2±4.2, median 11 | 0.7866 |

SD – standard deviation, eGFR – estimated glomerular filtration rate, M – month, UACR – urine albumin/creatinine ratio, *diabetes mellitus 2. type: n=19, post-transplant diabetes mellitus: n=15

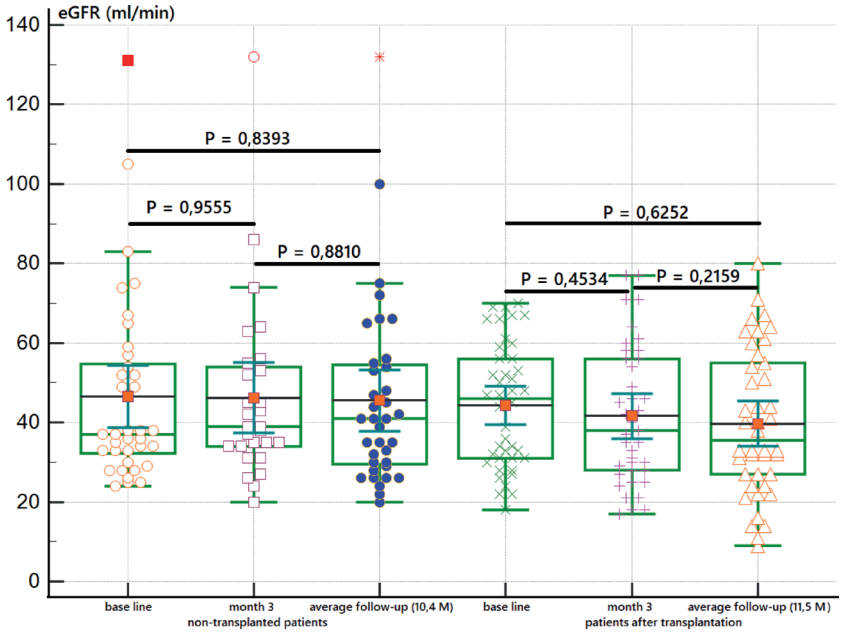


**Fig. 6. The development of eGFR in patients without and with diabetes mellitus. eGFR – estimated glomerular filtration rate, M – month.**

Another important conclusion of our study was a significant decrease in albuminuria in patients without DM. The significantly lower decrease in albuminuria in patients with DM can be explained by insufficient compensation for diabetes mellitus (dietary measures, self-monitoring of blood glucose). Another reason was that 90% of patients with IgA nephropathy has significantly reduced albuminuria were patients without DM. The available studies were conducted exclusively with patients with DM type II. Only the DAPA-CKD study also focused on patients with another cause of CKD. Treatment with dapagliflozin led to a 14.8% decrease in UACR in patients with CKD compared to the placebo group (14). We also noticed that patients without DM were younger than patients with DM. It can be caused by a combination of two factors, such as patients with DM type II typically develops at an older age, and patients who suffer from PTDM, which is linked to transplantation, where the mean age of the patient was 50.8 years.

In our cohort, the patients after kidney transplantation had lower baseline values of albuminuria than non-transplanted patients. It is due to the degree of glomerular filtration barrier (GFB) damage in non-transplanted patients compared to KTRs. In our study, KTRs without DM were betrayed, which made up almost half of patients after kidney transplantation. As far as we know, no study has been conducted with SGLT2i in KTRs without DM.

The observed complications of SGLT2i use included acute kidney injury (AKI), the occurrence of urinary and genital mycotic infections, hypotension, diabetic ketoacidosis, severe hypoglycemia, limb amputations, and bone fractures. Staplin et al. performed a meta-analysis to summarise the named adverse effects in studies conducted with gliflozins (16). The authors of the trial DAPA-CKD from 2020 did not note any adverse effect associated with dapagliflozin. Our analysis confirmed the same result. In the study with canagliflozin, the development of diabetic ketoacidosis was significantly more frequent compared to the placebo group, but the absolute number of cases was low. Differences in the results of the studies may be caused by the representation of patients in some trials, where in the CREDENCE trial (canagliflozin), the authors worked exclusively with patients with DM, where, as is widely known, the overall incidence of infections is higher. Other adverse effects in the context of canagliflozin therapy did not reach statistical significance (13, 16).

## Conclusions

Due to their reno-cardio-metabolic effects, gliflozins are experiencing a renaissance in clinical application. The cardiovascular effect of gliflozins in patients with DM type II has been known for almost ten years. It was necessary to conduct further studies to confirm their renoprotective benefit, the result of which was the extension of prescription restrictions, the inclusion of SGLT2i in the first line of DKD treatment and the creation of an algorithm for patients with CKD. Our analysis confirms the nephroprotective results of randomized trials. In addition, the conclusions of our analysis disprove the feared complications resulting from the drug's mechanism of action, which gives gliflozins an excellent safety profile even in KTRs. Due to the significant benefits of SGLT2i treatment, we should actively search for patients who meet the prescription criteria.

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Received June 11, 2024.
Accepted July 17, 2024.