Use of Empagliflozin in Recipients of Kidney Transplant: A Report of 8 Cases

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ABSTRACT

Transplant teams face increasing challenges to manage diabetes following kidney transplantation. There is an increasing number of diabetics undergoing transplantation and there is an increased incidence of posttransplant diabetes mellitus (PTDM) due to a higher prevalence of obesity, increased use of steroids and calcineurin inhibitors, and the acceptance of older patients as potential candidates.

The options for treating diabetes in the general population are expanding. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors is one of the new modalities of treatment.

We report the cases of 8 patients who underwent kidney transplantation and were treated with the SGLT-2 inhibitor empagliflozin for their pre-existing diabetes or for the development of PTDM. They were followed for an average of 12 months. The average age of the patients was 42.5 years. All 8 patients were taking tacrolimus, mycophenolate, and prednisolone. Although creatinine increased slightly (from 88.5 mmol/L to 99.5 mmol/L) in the month after starting empagliflozin, it stabilized after that. Hemoglobin A_{1c} decreased on average 0.85 g/dL. Urine protein decreased by 0.6 g per day and weight decreased on average 2.4 kg throughout the year. One patient discontinued the medication due to recurrent urinary tract infections.

DIABETES (DM) is a major contributor to end-stage renal disease (ESRD). According to the 2017 United States Renal Disease System Report, DM causes about 50% of new ESRD cases [1]. DM continues to be a major comorbidity after kidney transplantation (whether new onset after transplant or a continuation of a pretransplant process) [2–4]. Studies show the incidence of posttransplant DM (PTDM) after kidney transplantation is increasing [2,3].

International consensus guidelines regarding the definition of PTDM were originally published in 2003 [4,5]. The incidence of PTDM is up to 24% at 3 years after transplant [2,3]. It may predict graft loss and patient survival rate [4,6,7]. This happens mainly because of increasing cardiovascular events and development of chronic kidney disease [8–10]. Jindal et al evaluated 978 transplant recipients and showed that the development of PTDM was associated with a statistically significant decrease in overall survival compared to their nondiabetic counterparts (an overall survival of 11 years without DM and 8.1 years with PTDM) [7]. While Roth et al demonstrated in a retrospective analysis of 314 patients over 4 years that the presence of PTDM may predict increased risk for graft loss [6].

Use of calcineurin inhibitors especially tacrolimus increases risk of development of PTDM. In the Efficacy Limiting Toxicity Elimination (ELiTE-Symphony) trial [11], higher rates of new-onset PTDM developed at 1 year in patients receiving low-dose tacrolimus (8.4%) vs those receiving standard-dose cyclosporine (6%), low-dose cyclosporine (4.2%), and low-dose sirolimus (6.6%) [11].

Prevention and management of PTDM starts with screening and counseling before transplantation [4,5,12]. Treatment of hepatitis C infection, replacement of magnesium, avoidance or early withdrawal or reduction of steroids, and careful and individualized selection of an immunosuppressive regimen will help to lower and control diabetes after transplant [4,12].

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In general, different therapies can be used to manage PTDM [4,12]. Sulfonylureas, especially glipizide and glimepiride, are used frequently [13]. Metformin has been used more recently after changes in labeling allowing use at a lower kidney function [4,12,14]. Meglitinides, specifically repaglinide, may be good alternatives for patients who cannot take sulfonylureas or metformin [15]. Repaglinide is not contraindicated in patients with renal or liver insufficiency and does not have adverse drug interactions [15]. Dipeptidyl peptidase-4 inhibitors have been used to manage PTDM, particularly sitagliptin and vildagliptin [16,17]. Many patients will require institution of insulin, especially those with quite elevated fasting blood sugars [4,12,18].

The sodium-glucose cotransporter 2 (SGLT-2) is expressed in the proximal tubule and mediates reabsorption of approximately 90% of the filtered glucose load. SGLT-2 inhibitors promote the renal excretion of glucose and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes [19,20]. Empagliflozin, an SGLT-2 inhibitor, was shown to help control blood sugar and lower the incidence of cardiovascular death, all-cause mortality, and hospitalizations related to heart failure [21-23]. Other SGLT-2 inhibitors were also shown to have positive cardiovascular and renal effects in patients with type 2 diabetes [24,25]. More recently, canagliflozin was shown to have positive effect on renal outcomes when used with angiotensin II receptor blockers (ARBs) or angiotensin converting enzyme (ACE) inhibitors [26]. At the same time, a group from Norway reported safe use of empagliflozin for 6 months in a randomized prospective study in 44 patients with renal transplant [27].

CASE REPORTS

We report 8 cases of patients who used empagliflozin to manage DM after kidney transplant. We collected data on those patients for 1 year. The average age of the patients was 42.5 years. Four patients were male and 4 had DM before transplantation. The rest developed PTDM. The patients were included on average 21 months after kidney transplant (Table 1). This is a retrospective analysis of those cases and it is not clear why the patients were chosen to receive empagliflozin vs other medications.

Creatinine, at the outset of the data collection, was 88.5 mmol/L on average then increased to 99.5 mmol/L at 1 month and stabilized. Creatinine at the end of 12 months was 96.5 mmol/L on average (Fig 1). All 8 patients were taking tacrolimus (target trough level 4-6 ng/dL), mycophenolate (average dose 750 mg twice daily), and low-dose prednisolone (2.5-5 mg daily). The dose of mycophenolate and prednisolone did not change throughout the study, but tacrolimus dose was increased in 2 patients and decreased in 3 patients to maintain the same target tacrolimus level. There was no reported organ rejection during the study. Also, none of the patients needed a kidney biopsy during the study period. All the patients were either taking an ARB (3 patients) or ACE inhibitor (5 patients). The doses of ARB and ACE inhibitor did not change throughout the study.

Hemoglobin A_{1c} (HbA_{1c}) was checked on average every 3 months during the data collection period. HbA_{1c} levels decreased an average of 0.85 g/dL by the end of the data collection. This decrease occurred in the first 3 months and then was sustained after that (Fig 2). Urine protein was measured in the beginning and at the end of the data collection in the form of urine protein to creatinine ratio (Fig 3); it decreased on average by 0.6 g/day. Information about the weight was collected in the beginning and at the end of the study. Weight decreased on average 2.4 kg throughout the year (Fig 4).

As for adverse reactions, 2 patients developed nausea within the first month but then resolved slowly thereafter. Two female patients developed urinary tract infections (UTIs). The first developed a

Table 1. Patients' Characteristics and Change in Weight and Lab Values Throughout the Data Collection Period

Patient No.	1	2	3	4	5	6	7	8
Age at baseline (y)	34	41	54	49	47	52	39	51
Sex	F	M	M	M	F	F	F	M
ESRD Dx	FSGS	PCKD	DM	DM/HTN	DM	DM	IgA	HTN
PTDM (number of months after transplant)*	11	7	X	X	X	X	21	28
Time after transplant (mo)	11	15	17	18	21	19	27	31
Weight at baseline (kg)	76.5	77	80.3	93.7	74.8	65	79.5	67.6
Weight at the end (kg)	75	75.2	79.5	90.9	72.9	63.6	78.1	64.3
BMI at baseline (kg/m^2)	26.5	25.4	24.8	27.7	27.1	26	27.3	28.6
Cr 0	97	124	89	115	97	73	88	80
Cr 1	115	120	98	122	100	80	90	84
Cr 3	112	118	95	120	93	78	89	82
Cr 6	110	123	93	118	90	80	93	85
Cr 9	113	125	90	120	89	77	85	84
Cr 12	110	120	93	116	88	78	90	83
UP/Cr at baseline	0.9	0.7	0.5	1.2	1.4	1	0.8	1.1
UP/Cr at 6 mo	0.21	0.3	0.2	0.5	0.6	0.3	0.3	0.4
HbA_{1c} at baseline	8.1	8	7.8	8.2	7.9	8.4	8.5	8.1
HbA_{1c} at the end	7.3	6.9	7.1	6.9	7	7	7.4	7.2

Creatinine from 0 to 12 reflects months in the study. Cr 0 is the beginning of the study and Cr 12 is at 12 months of the study.

Abbreviations: BMI, body mass index; Cr, creatinine, DM, diabetes mellitus; Dx, diagnosis; ESRD, end-stage renal disease; F, female; FSGS, focal segmental glomerulosclerosis; HbA_{1c}, hemoglobin A_{1c}; HTN, hypertension; IgA, immunoglobulin A; M, male; PCKD, polycystic kidney disease; PTDM, posttransplant diabetes mellitus; UP/Cr, urinary protein to creatinine ratio.

*The numbers reflect the number of months after transplant PTDM developed. X is used when the patient had DM pre-transplant and not after, but the control got worse after transplant.

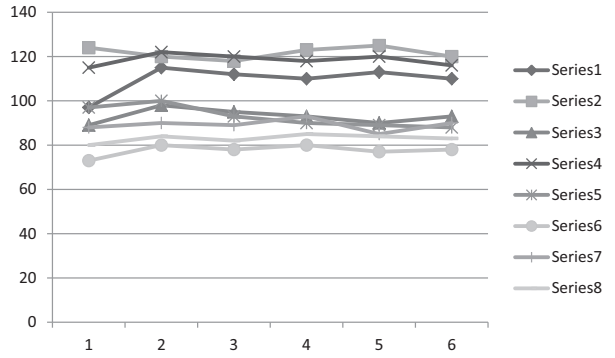

Fig 1. Change in creatinine over time during the data collection period of 1year.

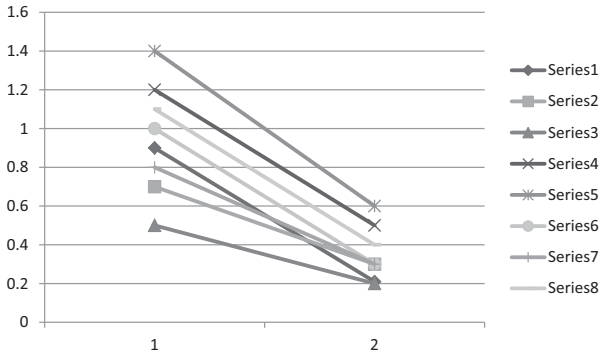

Fig 3. Change in urine protein during the data collection period of 1 year.

UTI after 3 weeks of taking empagliflozin. This episode was treated and resolved. The second patient developed a UTI at 4 weeks and another UTI at 10 months. Both times, the UTI was treated, but empagliflozin was stopped in that patient after the second episode.

DISCUSSION

DM after kidney transplantation complicates management of patients with a history of transplant. PTDM may affect patients and graft survival [4,6,7]. Different strategies have been used to manage this problem [4,12]. SGLT-2 inhibitors promote the renal excretion of glucose and modestly lower elevated blood glucose levels in patients with type 2 diabetes [19,20].

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, 7028 patients with type 2 diabetes (mean HbA_{1c} approximately 8%) and established cardiovascular disease were randomly assigned to empagliflozin or placebo [19]. The majority of patients were taking metformin to control blood glucose. Approximately 48% of patients in each group were taking insulin [21]. After 3 years, the primary outcome (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in fewer patients assigned to empagliflozin than to placebo (10.5% vs 12.1%; hazard ratio [HR] pooled analysis 0.86; 95% confidence interval [CI], 0.74-0.99). The findings were driven by a significant reduction in risk of death from cardiovascular causes (3.7% vs 5.9% with placebo; HR 0.62; 95% CI, 0.49-0.77). The rate of hospitalization for heart failure was lower in the empagliflozin group (2.7% vs 4.1% in the placebo group) [21].

In the same study, microvascular disease was a prespecified secondary outcome. The composite microvascular endpoint occurred in fewer patients in the empagliflozin group (14% vs 20.5%). The reduction was driven entirely by a reduction in incident or worsening nephropathy (defined as progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal replacement therapy, or death from renal disease), which occurred in 12.7% and 18.8% of patients in the empagliflozin and placebo groups, respectively (HR 0.61; 95% CI, 0.53-0.70) [22,23]. There were significant reductions in each component of the outcome, except for death from renal disease. The mechanism behind the reduction in incident or worsening nephropathy with empagliflozin is likely multifactorial but is thought to be largely related to a direct renovascular effect of empagliflozin [19,22,23].

Canagliflozin was also shown to lower cardiovascular events and slow progression of albuminuria in diabetics. There was an increased signal of acute kidney injury, increased bone fractures and amputations in the canagliflozin group [24]. At the same time, in the Dapagliflozin

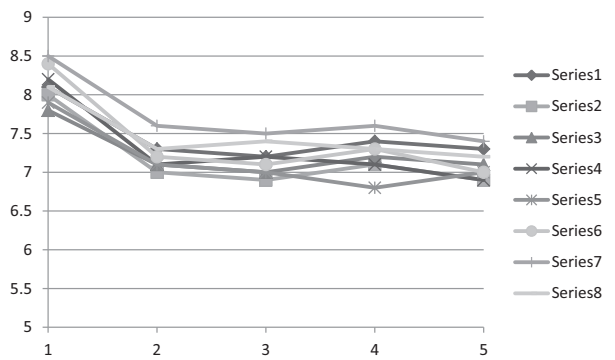

Fig 2. Change in glycated hemoglobin.HbA_{1c}, hemoglobin A_{1c}.

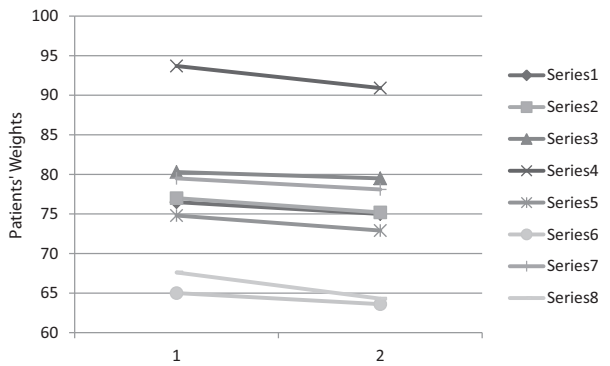

Fig 4. Change in patients' weights during the year.

Effect on Cardiovascular Events (DECLARE) study, 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years, were randomized to dapagliflozin or placebo. A renal event occurred in 4.3% in the dapagliflozin group and in 5.6% in the placebo group (HR 0.76; 95% CI, 0.67 to 0.87), and death from any cause occurred in 6.2% and 6.6%, respectively [25]. Furthermore, in the Canagliflozin and Renal Endpoint in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, 4401 participants with stage 2 or 3 chronic kidney disease and macroalbuminuria were enrolled and received canagliflozin or placebo. All the patients were on a maximally tolerated dose of ACE inhibitor or ARB for at least 4 weeks prior to randomization. Sixty percent of those participants had an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 at enrollment [26]. The CREDENCE trial was prematurely terminated with a median follow-up of 2.62 years. The rate of the primary composite outcome (ESRD, doubling of serum creatinine level, or renal or cardiovascular death) was significantly lower with canagliflozin than with placebo (43 vs 61 per 1000 patient-years) [26].

More recently, empagliflozin was studied in a randomized controlled fashion after kidney transplant [27]. Forty-four recipients of renal transplant (22 empagliflozin, 22 placebo, 34 males) completed the study. HbA_{1c} was significantly reduced with empagliflozin compared with placebo. The magnitude of glucose reduction was dependent on eGFR and baseline HbA_{1c}. The treatment also resulted in a significant reduction in body weight in comparison with the placebo group. There was no significant effect on blood pressure. There were no significant differences between the groups in adverse events, immunosuppressive drug levels, or eGFR [27].

In this case series, we report on 8 patients with kidney transplant who were prescribed empagliflozin for 1 year to help manage PTDM. They all had acceptable eGFR when they were started on the medication (average eGFR was 78.2 mL/min per 1.73 m^2 at baseline). All the patients received 25 mg of empagliflozin daily. They were all taking metformin and 2 patients were on linagliptin before starting empagliflozin. None of the patients were using insulin. In this case series, the kidney function worsened slightly initially then stabilized. This is consistent with what is seen in patients without a transplant who are receiving SGLT-2 inhibitors and is most likely related to a hemodynamic change [19,28]. Urine protein decreased by 0.6 g per day while HbA_{1c} decreased by 0.85 throughout the data collection period. The drop in HbA_{1c} occurred within the first 3 months and this drop was sustainable. The patients' records suggested an increase in urine output after starting the medication but all the patients were encouraged to drink more fluids and there was no evidence (hospitalization or documentation during the office visits) of hypovolemia. Patients' weight decreased on average 2.4 kg. All of these findings are similar to what was found in patients without a history of transplant.

There are several proposed mechanisms in which empagliflozin may improve renal outcomes and slow down proteinuria. Under chronic hyperglycemic conditions (diabetes), SGLT-2 activity is upregulated, and SGLT-2–mediated reabsorption of sodium and glucose is increased [29]. This may impair the tubule-glomerular feedback, less sodium reaches the macula densa, and as a result, arteriolar tone is reduced, which leads to increased renal perfusion, increased glomerular pressure, and increased glomerular filtration [19,28]. Empagliflozin may help restore tubule-glomerular feedback signaling by allowing more sodium to reach the macula densa. As a result, afferent arteriolar tone may increase, reducing renal perfusion and lowering glomerular pressure and filtration rate [28]. At the same time, the use of SGLT-2 inhibitors reduced tubulointerstitial hypoxia and oxidative stress [30] and reduced glucotoxicity, inflammation, and kidney fibrosis [31,32]. Moreover, SGLT-2 inhibitors may improve arterial stiffness, vascular resistance, and cardiac function [29,33]. Combining the use of SGLT-2 inhibitors with an ACE inhibitor or ARB has an additive effect as shown in the CREDENCE study because of hemodynamic effects on both the afferent and efferent arterioles [26].

Another possible mechanism is lowering blood pressure (BP) [29,34]. In different reports, SGLT-2 inhibitors lower systolic BP by 3 to 5 mm Hg. In this series, office-measured systolic BP decreased on average by 4.2 mm Hg mainly within the first 3 months of the data collection and stayed around the same number after that. There was no significant change in BP medications throughout the data collection.

SGLT-2 inhibitors may affect lipid profile. In this case series, low-density lipoprotein and total cholesterol increased (on average 5.3 mg/dL and 4.8 mg/dL, respectively) but there was no significant change in high-density lipoprotein, cholesterol, or triglycerides, which is consistent with previously published reports [35].

Although euglycemic ketoacidosis is a known side effect of SGLT-2 inhibitors [20,34,35], we did not have any reported case of that side effect in this series. This is a rare complication and usually patients with a history of transplant are monitored more carefully than other patients. As for other side effects, 2 patients developed nausea early after starting the medication (patient 1 developed it after 2 weeks and patient 2 developed it after 8 days). In both situations, it was mild and resolved within few days. The medication was not stopped. Patient 5 (who had a history of 2-3 UTIs per year) and patient 6 developed a simple UTI on week 4 and week 3, respectively. They were both treated and the infection resolved within few days. Patient 5 developed another UTI at 10 months and it was subsequently treated, but the patient decided to stop the medication at that point. She was still included in the analysis until the end of the data collection.

During the first month, the serum creatinine increased on average by 12.4% but then stabilized after that. None of the reviewed records indicated that any patient developed acute kidney injury (AKI) or hypovolemia during the data

collection period. No bone fractures or amputations occurred, but the sample was small and the follow-up period was too short to warrant further investigation. Empagliflozin was not shown in other studies to increase risk of bone fractures or amputations [21,27,35].

Pharmacologically, there is no known interaction between empagliflozin and calcineurin inhibitors or mycophenolate. Theoretically, vasoconstriction from calcineurin inhibitors and polyuria induced by empagliflozin in the setting of hypovolemia increases the risk of AKI but that was not observed in this case series.

CONCLUSIONS

In conclusion, in this case series, the use of empagliflozin to manage DM after kidney transplantation was tolerated. The incidence of side effects was small and they were mild in general. There is always a concern of development of AKI especially if the patient does not stay adequately hydrated. The sample in this case series is small and the data was collected retrospectively but empagliflozin could add to the armamentarium of therapies used to manage PTDM. The findings in this case series need to be confirmed in a large prospective study with a longer follow-up period.

REFERENCES

[1] Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US Renal Data System 2017 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2018;71(Suppl 1):A71.

[2] Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003;3:178–85.

[3] Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney Int 2001;59:732–7.

[4] Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, et al. International expert panel - new-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Transplantation 2003;75(10 Suppl):SS3–24.

[5] Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant 2005;19:291–8.

[6] Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J. Posttransplant hyperglycemia. Increased incidence in cyclosporine-treated renal allograft recipients. Transplantation 1989;47:278–81.

[7] Jindal RM, Hjelmesaeth J. Impact and management of posttransplant diabetes mellitus. Transplantation 2000;70(11 Suppl):SS58–63.

[8] Briggs JD. Causes of death after renal transplantation. Nephrol Dial Transplant 2001;16:1545–9.

[9] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.

[10] Karthikeyan V, Karpinski J, Nair R, Knoll G. The burden of chronic kidney disease in renal transplant recipients. Am J Transplant 2003;4:262–9.

[11] Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, et al. ELITE-Symphony Study reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562–75.

[12] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–57.

[13] Kasayama S, Tanaka T, Hashimoto K, Koga M, Kawase I. Efficacy of glimepiride for the treatment of diabetes occurring during glucocorticoid therapy. Diabetes Care 2002;25:2359–60.

[14] Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, et al. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open 2012;2:e001076.

[15] Türk T, Pietruck F, Dolff S, Kribben A, Janssen OE, Mann K, et al. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. Am J Transplant 2006;6:842–6.

[16] Strøm Halden TA, Åsberg A, Vik K, Hartmann A, Jenssen T. Short-term efficacy and safety of sitagliptin treatment in long-term stable renal recipients with new-onset diabetes after transplantation. Nephrol Dial Transplant 2014;29:926–33.

[17] Haidinger M, Werzowa J, Hecking M, Antlanger M, Stemer G, Pleiner J, et al. Efficacy and safety of vildagliptin in new-onset diabetes after kidney transplantation–a randomized, double-blind, placebo-controlled trial. Am J Transplant 2014;14:115–23.

[18] Hecking M, Haidinger M, Döller D, Werzowa J, Tura A, Zhang J, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. J Am Soc Nephrol 2012;23:739–49.

[19] Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010;27:136–42.

[20] Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495–502.

[21] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.

[22] Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752–72.

[23] Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–34.

[24] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.

[25] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.

[26] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306.

[27] Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, et al. Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. Diabetes Care 2019;42:1067–74.

[28] Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium–glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 2014;129:587–97.

[29] Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes Obes Metab 2015;17:1180–93.

[30] Sano M, Takei M, Shiraishi Y, Suzuki Y. Increased hematocrit during sodium-glucose cotransporter 2 inhibitor therapy indicates recovery of tubulointerstitial function in diabetic kidneys. J Clin Med Res 2016;8:844–7.

[31] Oelze M, Kröller-Schön S, Welschof P, Jansen T, Hausding M, Mikhed Y, et al. The sodium-glucose co-transporter 2 inhibitor empagliflozin improves diabetes-induced vascular dysfunction in the streptozotocin diabetes rat model by interfering with oxidative stress and glucotoxicity. PLoS One 2014;9:e112394.

[32] Gallo LA, Ward MS, Fotheringham AK, Zhuang A, Borg DJ, Flemming NB, et al. Once daily administration of the SGLT2 inhibitor, empagliflozin, attenuates markers of renal fibrosis without improving albuminuria in diabetic db/db mice. Sci Rep 2016;6:26428.

[33] Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28.

[34] Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262–74.

[35] Monami M, Nardini C, Mannucci E. Efficacy and safety of sodium glucose co-transport-2 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2014;16:457–66.