Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus

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OBJECTIVE

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have lately become the recommended treatment in patients with type 2 diabetes and high cardiovascular risk. Patients with posttransplant diabetes mellitus (PTDM) also have high cardiovascular risk. The aim of this study was to investigate the safety and efficacy of empagliflozin in renal transplant recipients with PTDM.

RESEARCH DESIGN AND METHODS

Forty-nine renal transplant recipients were included in an investigator-initiated, single-center, prospective, double-blind study and randomized to receive either 10 mg empagliflozin or placebo once daily for 24 weeks. Patients transplanted >1 year ago, diagnosed with PTDM, with stable renal function (estimated glomerular filtration rate [eGFR] >30 mL/min/1.73 m^2), and with stable immunosuppressive therapy were studied.

RESULTS

Forty-four renal transplant recipients (22 empagliflozin/22 placebo, 34 males) completed the study. Median (interquartile range) change in glycated hemoglobin (HbA_{1c}) was significantly reduced with empagliflozin compared with placebo: −0.2% (−0.6, −0.1) (−2.0 mmol/mol [−6.5, −1.0]) vs. 0.1% (−0.1, 0.4) (1.0 mmol/mol [−0.75, 3.8]) (P = 0.025). The magnitude of glucose reduction was dependent on GFR and baseline HbA_{1c}. The treatment also resulted in a significant reduction in body weight of −2.5 kg (−4.0, −0.05) compared with an increase of 1.0 kg (0.0, 2.0) in the placebo group (P = 0.014). There were no significant differences between the groups in adverse events, immunosuppressive drug levels, or eGFR.

CONCLUSIONS

Empagliflozin appeared safe and improved glycemic control in renal transplant recipients with PTDM compared with placebo. A concomitant reduction in body weight was seen.

Posttransplant diabetes mellitus (PTDM) is a serious condition that may follow renal transplantation. In the early posttransplant period, hyperglycemia is common in renal transplant recipients mainly due to high doses of immunosuppressive therapy (1,2). However, 10–20% of renal transplant recipients without a prior history of diabetes develop persisting hyperglycemia after renal transplantation, defined as PTDM (3–6). This is associated with an increased risk of cardiovascular disease and impaired patient

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survival (5,7,8). PTDM has many traits in common with type 2 diabetes, but it is considered to be a separate type of diabetes where immunosuppressive therapy and/or viral infections (e.g., cytomegalovirus and hepatitis C) affect both insulin secretion and insulin sensitivity (9–12). In addition to β-cell dysfunction and insulin resistance, increased release of glucagon also seems to be an important mechanism (13).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a preferred treatment in patients with type 2 diabetes and high cardiovascular risk (14). SGLT2 inhibition increases renal glucose excretion with a daily loss of 60–80 g glucose in patients with two kidneys and normal renal function, corresponding to an energy loss of 240–320 kcal (15). Glycated hemoglobin (HbA_{1c}) is reduced, together with relevant reductions in blood pressure and body weight (16). These would all be favorable effects in patients with PTDM. However, the glucose-lowering efficiency of SGLT2 inhibitors is generally impaired or even absent when glomerular filtration rate (GFR) is <45–60 mL/min/1.73 m^2 (17,18).

Even with modern low-target tacrolimus immunosuppression, renal transplant recipients typically have impaired renal function, generally with a GFR <70 mL/min/1.73 m^2 due to a single functioning kidney (19). SGLT2 inhibition will decrease GFR further due to vasoconstriction of the afferent arteriole, which initially lowers intraglomerular pressure and then stabilizes kidney function over time (15,20,21). A major issue in solid organ transplant recipients is also to what extent glucose-lowering drugs interact with pharmacokinetics of the immunosuppressive drugs.

Empagliflozin is a selective inhibitor of SGLT2 (22) and has recently been shown not only to improve glycemia in patients with type 2 diabetes but also to protect against cardiovascular events in patients at high cardiovascular risk (23). If proven safe and efficient, SGLT2 inhibition could potentially have a long-term beneficial effect also in patients with PTDM, both for patient and graft survival.

The objective of the current study was to investigate whether empagliflozin can be used safely to improve glucose metabolism in renal transplant recipients with PTDM.

RESEARCH DESIGN AND METHODS

Patients

Patients with PTDM, defined as renal transplant recipients without diabetes prior to transplantation with persistent hyperglycemia for at least 1 year after transplantation according to American Diabetes Association's (ADA's) criteria for diabetes (24), were considered to be potential participants in the study. Patients were identified based on oral glucose tolerance tests (OGTTs) and/or HbA_{1c} values obtained prior to transplantation and during the in-depth investigation performed in all patients at our center 1 year after renal transplantation. Patients who qualified for inclusion were invited to the transplant center for affirmative investigations of the glucose metabolism status. Renal transplant recipients with diabetes according to ADA's criteria (24) (fasting plasma glucose [FPG] ≥7.0 mmol/L or 2-h plasma glucose of ≥11.1 mmol/L after a 75-g OGTT or HbA_{1c} ≥6.5% [48 mmol/mol]) were eligible to participate in the study based on the following inclusion criteria: ≥18 years of age, transplanted ≥1 year ago, stable renal function (<20% deviation in serum creatinine within the last 2 months), and stable immunosuppressive therapy for at least 3 months before inclusion. Patients with estimated GFR (eGFR) <30 mL/min/1.73 m^2 and pregnant or nursing mothers were not eligible to participate in the study. All patients received oral and written information according to good clinical practice, and written informed consent was collected before patient inclusion. Based on the above-mentioned criteria, 104 patients were screened for inclusion from November 2016 to January 2018. In total, 49 patients were randomized and included in the study.

Study Design and Randomization

This is a single-center, prospective, double-blind study where patients were randomized to receive either 10 mg empagliflozin or placebo once daily for 24 weeks. The randomization was performed by the R package "blockrand" using simple randomization (25), one block, and equal probabilities of each sequence. A person not directly involved in the practical implementation of the study performed the allocation. For each new patient entering the study, a study number was assigned with a prelisted drug package. Both patient and investigator/study personnel were blinded with regards to study drug (active/placebo) until statistical analyses were performed.

Both active drug and placebo (lactose monohydrate) were encapsulated in red nontransparent capsules (Capsugel AAEL) to maintain blinding and allocated according to the preprepared randomization list at Kragerø Tablet Production AS. The study was approved by the Regional Committees for Medical and Health Research Ethics (REK number 2016/911) and the Norwegian Medicines Agency (EudraCT number 2016-001705-17) and performed according to the Declaration of Helsinki.

Study Visits, End Points, and Procedures

The study design included four visits (baseline and weeks 8, 16, and 24) (Supplementary Fig. 1). At baseline and week 24, the investigations were performed on two consecutive days, including OGTT, office blood pressure recording (including investigation of orthostatic hypotension), 24-h blood pressure, waist-to-hip ratio (WHR), measurement of arterial stiffness (SphygmoCor), DXA, and 24-h urine collection. Demographic data as age, height, weight, smoking habits, physical activity, and concomitant medication were all registered in case report forms at each study visit.

The participants were informed to maintain their usual diet and exercise habits during the study period, and concomitant medication was to be kept unchanged, unless reduction in glucose-lowering treatment was indicated. Adherence was controlled by capsule counting at weeks 8 and 24. Safety was assessed at weeks 8, 16, and 24. Safety analyses included a physical examination, standard safety blood samples, and trough levels of immunosuppressive drugs. Patients were specifically interviewed for adverse episodes, and all adverse events were recorded.

Fasting blood samples for standard safety analyses were analyzed at the hospital central laboratory (Department of Medical Biochemistry, Rikshospitalet). Plasma glucose, C-peptide, and serum insulin were measured before and 30 and 120 min after oral administration of 75 g glucose dissolved in 3 dL water. Blood pressure was measured in a seated

position by Mediana M30 (Mediana Co., Ltd., Wonju-si, Gangwon-do, South Korea) after 10 min rest, and the mean of the last two out of three measurements obtained during 5 min was used. Orthostatic blood pressure was also assessed as blood pressure 1 and 3 min after standing. Blood pressure (24 h) (Oscar 2 24-Hr ABP; SunTech Medical, Inc., Morrisville, NC) was measured every 45 min between 10:00 P.M. and 07:00 A.M., and every 20 min the rest of the day. Height and weight were measured to calculate BMI. The smallest area around the waist and the widest area around the hip were measured to calculate WHR. SphygmoCor (AtCor Medical Pty Ltd., West Ryde, Australia) was used to measure pulse wave velocity. Body composition, including visceral fat, was measured using DXA scan in the CoreScan software (encore version 14.10; GE Healthcare). Urine was collected for 24 h in a container supplied with 5 mL of acetic acid. Glucose excretion, magnesium, creatinine, protein, and albumin were analyzed in the collected urine (Cobas 8000 autoanalyzer with reagents from Roche Diagnostics, Mannheim, Germany). The analytical coefficient of variation for all the analytes was <4%.

Calculations and Statistical Analyses

The primary end point was prespecified as change in weighted mean glucose estimated with continuous glucose monitoring from iPro2 (iPro Continuous Glucose Monitoring System; Medtronic, Inc., Dublin, Ireland) from baseline to week 24 compared with placebo. However, the primary end point was not possible to analyze due to study technical error. Hence, only secondary end points are reported, and they include change in HbA_{1c}, FPG, 2-h plasma glucose after OGTT, body weight, WHR, body composition including visceral fat, blood pressure, and eGFR from baseline to week 24 compared with placebo.

Insulin Secretion and Sensitivity

First- and second-phase insulin secretion were calculated according to the equations by Stumvoll et al. (26): $Secr1.Phase = 1{,}283 + 1.829 \times Ins_{30} - 138.7 \times Gluc_{30} + 3.772 \times Ins_0$ and $Secr2.Phase = 287 + 0.4164 \times Ins_{30} - 26.07 \times Gluc_{30} + 0.9226 \times Ins_0$, where Ins_0 and Ins_{30} (pmol/L) are serum insulin 0 and 30 min after OGTT and $Gluc_{30}$ (mmol/L) is plasma glucose 30 min after OGTT.

Insulin sensitivity index modified for renal transplant recipients (ISI_{TX}) was calculated by using the following formula (27): $ISI_{TX} = 0.208 - 0.0032 \times BMI - 0.0000645 \times Ins_{120} - 0.00375 \times Gluc_{120}$, where Ins_{120} (pmol/L) and $Gluc_{120}$ (mmol/L) are serum insulin and plasma glucose 120 min after OGTT.

C-peptide was corrected for glucose and renal function to estimate insulin secretion (C-peptide/plasma glucose creatinine ratio [CPGCR]) according to the following formula (28): CPGCR = (C-peptide [nmol/L] × 100)/(glucose [mmol/L] × creatinine [μmol/L]).

eGFR

eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on creatinine and cystatin C (29,30): $256 \times age^{-0.285} \times creatinine\ (mg/dL)^{-0.388} \times cystatin\ C\ (mg/L)^{-0.404} \times 0.833$ (if female).

WHR

WHR was calculated from waist and hip measurements: WHR = waist (cm)/hip (cm).

Adherence

Study drug adherence was calculated after manual capsule counting at weeks 8 and 24. Adherence rate = number of capsules estimated to be left/number of counted capsules × 100 (%), and patients with a rate between 80% and 120% were considered adherent.

Statistical Considerations

In total, 42 patients were needed to assure a power of 90% to show a difference at a 5% significance level. The aim was to include 50 patients, to allow for a 20% dropout rate.

All variables were analyzed as difference in change from baseline to week 24 between empagliflozin and placebo. Efficacy variables were analyzed per protocol and safety variables (adverse events, hematology, magnesium, uric acid, lipid variables, cystatin C, and trough levels of immunosuppressive drugs) by intention to treat. Missing values were replaced by the last observation carried forward method in case of intention-to-treat analysis and left missing in case of per protocol analysis. To adjust for multiple outcome assessment, Bonferroni correction was used for secondary efficacy outcomes defined per protocol (HbA_{1c}, FPG, 2-h plasma glucose, body weight, BMI, WHR, percentage visceral adipose tissue [VAT %], 24-h systolic and diastolic blood pressure, and eGFR) in addition to renal glucose excretion, hemoglobin, and hematocrit. Shapiro Wilk test was used to control for normal distribution. The data were not normally distributed, and therefore nonparametric tests were used for statistical evaluation. Wilcoxon rank sum test was used for comparing quantitative data and Chi-Quadrat test for categorical data between groups. P values ≤0.05 were considered statistically significant. The data are presented as median (interquartile range [IQR]) if not otherwise stated. All statistical analyses were performed using R for windows (version 1.1.456) (31).

RESULTS

Patients

In total, 49 patients were included and randomized in the study. Five patients were excluded during the study period, two in the empagliflozin group (repeated urinary tract infections and urosepsis, respectively) and three in the placebo group (withdrawal of consent, colon cancer, and no longer fulfilling PTDM criteria, respectively). Forty-four patients completed the study, 22 patients in each group.

Patient characteristics at baseline are shown in Table 1. In general, the groups were well matched according to age, sex, body weight, and comorbidities. Median HbA_{1c} was similar in both groups, whereas median FPG was numerically higher in the empagliflozin group. Seventy-five percent of the participants received treatment with one or more glucose-lowering drugs. Kidney function varied from slightly to moderately impaired, i.e., chronic kidney disease stage 2–3 (32). All included patients had been transplanted with a first transplant, and the immunosuppressive therapy consisted of tacrolimus (n = 35), cyclosporine (n = 6) or everolimus (n = 2), mycophenolate (n = 40), and prednisolone (n = 43).

Glycemic Control

Figure 1 presents the effect of empagliflozin on glycemic control, disregarding the fact that two patients in the empagliflozin group had to reduce their concomitant insulin dose (from 80 units to 50 units/day and from 18 units to 10 units/day, respectively) during the

Table 1—Baseline characteristics presented as median (absolute range) or number of patients (%)

	Empagliflozin, *n* = 22	Placebo, *n* = 22
Sex (male/female), *n*	17/5	17/5
Age (years)	63 (31, 72)	59 (21, 75)
Time since transplantation (years)	3 (1, 16)	3 (1, 15)
BMI (kg/m^2)	28.8 (24.7, 39.3)	27.5 (22.4, 45.8)
WHR (cm)	1.01 (0.82, 1.25)	0.98 (0.80, 111)
Systolic blood pressure (mmHg)	143 (111, 176)	140 (100, 163)
Diastolic blood pressure (mmHg)	79 (63, 94)	82 (55, 94)
HbA_{1c} (%)	6.9 (6.5, 8.2)	6.8 (6.1, 7.2)
HbA_{1c} (mmol/mol)	52 (38, 83)	51 (40, 73)
FPG (mmol/L)	8.0 (5.0, 13.1)	7.3 (4.5, 12.5)
eGFR (mL/min/1.73 m^2)	66 (41, 83)	59 (44, 82)
LDL (mmol/L)	2.8 (1.2, 4.2)	2.8 (2.0, 3.8)
Triglycerides (mmol/L)	1.8 (1.1, 3.2)	2.2 (1.1, 5.6)
Smoking, *n*		
Smoker	4 (18.2)	0 (0.00)
Ex-smoker	13 (59.1)	11 (50.0)
Never smoked	5 (22.7)	11 (50.0)
Donor (living/dead), *n*	9/13	7/15
Indication for kidney transplant, *n*		
Nephrosclerosis	3 (13.6)	3 (13.6)
Glomerulonephritis	9 (40.9)	11 (50.0)
Polycystic kidney disease	3 (13.6)	4 (18.2)
None of the above	7 (31.8)	4 (18.2)
Immunosuppressive therapy, *n*		
Tacrolimus	18 (81.8)	17 (77.3)
Cyclosporine	3 (13.6)	3 (13.6)
Everolimus	1 (4.55)	1 (4.55)
Prednisolone	21 (95.5)	22 (100.0)
Mycophenolate	19 (86.4)	21 (95.5)
Glucose-lowering therapy, *n*		
DPP-4 inhibitors	8 (36.4)	11 (50.0)
Metformin	1 (4.55)	1 (4.55)
Sulfonylurea	3 (13.6)	4 (18.2)
Insulin	5 (22.7)	3 (13.6)
No treatment	7 (31.8)	7 (31.8)
Other therapy, *n*		
Antihypertensive	19 (86.4)	19 (86.4)
Statin	20 (90.9)	18 (81.8)
Platelet inhibitor/anticoagulant	17 (77.3)	17 (77.3)

study. The median change in HbA_{1c} was significantly reduced after 24 weeks of empagliflozin treatment compared with placebo (Table 2). There was no difference in FPG (P = 0.27) or 2-h plasma glucose (P = 1), nor fasting concentrations of plasma insulin (P = 0.11), C-peptide (P = 0.92), or 2-h insulin concentrations (P = 0.38). However, 2-h C-peptide increased in the empagliflozin group (309 pmol/L [−60, 1,214]) compared with a reduction in C-peptide concentrations in the placebo group (−318 pmol/L [−828, 428]) ($P < 0.01$).

A sensitivity analysis revealed that empagliflozin-treated patients with HbA_{1c} baseline values >8% (64 mmol/mol) had a greater median (IQR) reduction in HbA_{1c}: −1.0% (−1.8, −0.7) (−11 mmol/mol [−19.5, −7.8]) compared with −0.1% (−0.2, −0.1) (−1.5 mmol/mol [−2.3, −0.8]) in patients with HbA_{1c} ≤8% (64 mmol/mol). Furthermore, empagliflozin-treated patients with eGFR ≥60 mL/min/1.73 m^2 tended to have a greater reduction in HbA_{1c} compared with patients with eGFR <60 mL/min/1.73 m^2 (Fig. 2*A*).

First- and second-phase insulin secretion were not significantly changed with empagliflozin treatment (P = 0.249 and P = 0.262, respectively), neither was CPGCR (P = 0.25). Furthermore, there was no significant difference in insulin sensitivity index during treatment (P = 0.59). Details are presented in Supplementary Table 1.

Glucose Excretion

Renal 24-h glucose excretion increased in the group treated with empagliflozin (Table 2). Median (IQR) change from baseline was (46 g/24 h [36, 64]) in the empagliflozin group, whereas the placebo group did not change glucose excretion (0.2 g/24 h [0.0, 1.6]) ($P <$ 0.01). A sensitivity analysis revealed that renal glucose excretion decreased with decreasing renal function. Figure 2*B* shows the correlation between glucose excretion and eGFR in the empagliflozin group (r = 0.58, $P < 0.01$).

The 24-h urine collection did not show any significant difference between the groups in urine volume or in magnesium, creatinine, albumin, and protein excretion (Supplementary Table 1).

Body Weight, WHR, and VAT

Empagliflozin treatment induced a significant weight reduction during the study period compared with placebo. The treatment did however not change WHR or VAT %. VAT % results were based on data from 40 patients (21 in the empagliflozin group and 19 in the placebo group) because it was not possible to perform measurements in 4 patients due to technical reasons. Details are presented in Table 2.

A sensitivity analysis of the body weight data did not reveal any significant differences in weight reduction between patients with baseline eGFR >60 mL/min/1.73 m^2 (−2.5 kg) and eGFR <60 mL/min/1.73 m^2 (−2.5 kg) in the empagliflozin group (P = 0.97).

Blood Pressure

Twenty four–hour blood pressure measurements (n = 43) revealed no significant differences between the empagliflozin group and the placebo group with respect to change in systolic blood pressure, diastolic blood pressure, or pulse (Table 2), but two people in the empagliflozin group had to reduce their dose of antihypertensive medication.

Furthermore, there were no significant differences between the groups in standard blood pressure measurements. Median change from baseline in systolic blood pressure was −5 mmHg (−12, 1) in the empagliflozin group and 2 mmHg

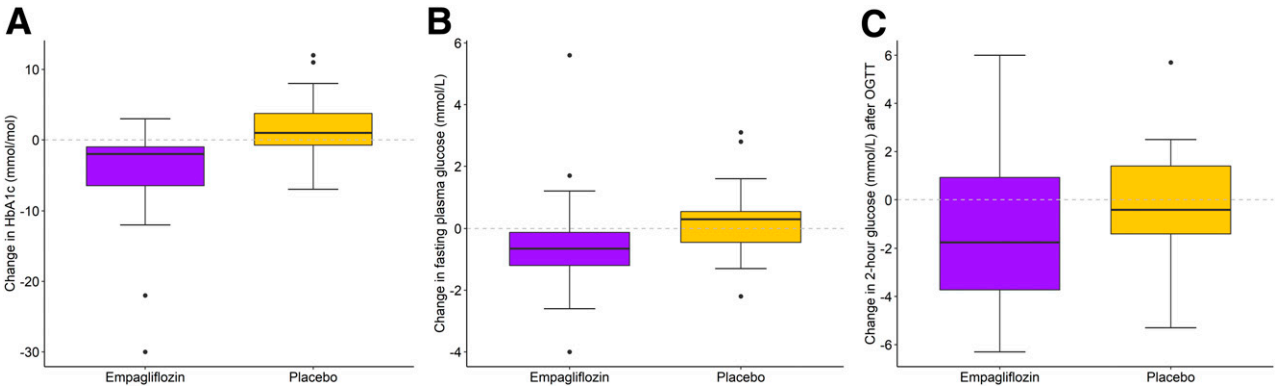

Figure 1—Median (IQR) change from baseline to week 24 in HbA_{1c} ($P = 0.018$) (*A*), FPG ($P = 0.27$) (*B*), and 2-h glucose after an OGTT ($P = 1$) (*C*) in the two intervention groups.

(−6, 8) in the placebo group ($P = 0.06$). The median change in diastolic blood pressure was −4 mmHg (−9, 1) vs. 1 mmHg (−5, 6), respectively ($P = 0.105$). A sensitivity analysis of systolic and diastolic blood pressure data from the 8-week safety control did not reveal any significant differences in change from baseline to week 8 ($P = 0.19$ and $P = 0.21$, respectively) or from week 8 to week 24 between the groups ($P = 0.97$ and $P = 1.00$, respectively).

Table 2—Outcomes presented as median (IQR)

	Empagliflozin			Placebo			
	Baseline	Week 24	Δ	Baseline	Week 24	Δ	*P* value*
HbA_{1c} (%)	6.9 (6.5, 8.2)	6.7 (6.3, 7.5)	−0.2 (−0.6, −0.1)	6.6 (6.1, 7.2)	6.9 (6.4, 7.4)	0.1 (−0.1, 0.4)	0.025
HbA_{1c} (mmol/mol)	52 (48, 66)	50 (45, 58)	−2.0 (−6.5, −1.0)	51 (43, 55)	52 (46, 57)	1.0 (−0.75, 3.8)	0.018
FPG (mmol/L)	8.0 (7.3, 8.6)	7.2 (6.6, 8.1)	−0.65 (−1.2, −0.13)	7.3 (6.5, 8.6)	7.5 (6.8, 8.4)	0.30 (−0.45, 0.55)	0.272
2-h glucose after OGTT (mmol/L)	15.6 (13.3, 17.7)	14.2 (12.4, 15.6)	−1.75 (−3.7, 0.93)	13.3 (10.3, 17.4)	14.1 (10.5, 16.9)	−0.40 (−1.4, 1.4)	1
Body weight (kg)	92.0 (81.8, 104.5)	88.8 (79.0, 100.0)	−2.5 (−4, −0.05)	84.0 (79.3, 94.0)	85.0 (79.5, 97.5)	1.0 (0.0, 2.0)	0.014
BMI (kg/m^2)	28.8 (26.7, 34.2)	28.1 (25.8, 33.8)	−0.80 (−1.4, 0.0)	27.5 (25.2, 32.1)	28.1 (25.4, 32.1)	0.35 (0.0, 0.60)	0.011
WHR (cm)	1.0 (0.94, 1.1)	1.0 (0.96, 1.0)	−0.01 (−0.03, 0.02)	0.98 (0.94, 1.01)	0.98 (0.96, 1.02)	0.00 (−0.02, 0.05)	1
VAT (%)	7.5 (6.0, 8.6)	7.8 (5.5, 9.0)	0.10 (−0.85, 0.50)	6.8 (5.8, 8.5)	7.0 (4.7, 8.5)	−0.25 (−1.63, 0.38)	1
Mean 24-h SBP (mmHg)	136 (131, 147)	142 (126, 148)	2 (−5, 6)	135 (127, 146)	137 (132, 143)	2 (−7, 6)	1
Mean 24-h DBP (mmHg)	76 (71, 82)	76 (70, 82)	0 (−5, 2)	78 (74, 85)	80 (74, 86)	1 (−3, 4)	1
Mean 24-h pulse	74 (66, 79)	74 (63, 78)	0 (−2, 2)	74 (70, 77)	75 (72, 79)	−1 (−2, 2)	0.85
eGFR ($mL/min/1.73\ m^2$)	66 (57, 68)	61 (56, 67)	−3 (−7, 0)	59 (52, 72)	59 (52, 67)	−1.0 (−2.8, 0.75)	1
Renal glucose excretion (g/24 h)	0.45 (0.20, 1.48)	46.0 (36.8, 68.6)	45.9 (36.1, 64.3)	0.5 (0.1, 2.3)	1.5 (0.2, 4.5)	0.20 (0.0, 1.6)	<0.001
Hemoglobin (g/dL)	13.9 (13.1, 14.4)	14.5 (13.5, 15.2)	0.45 (−0.03, 0.83)	13.2 (12.1, 14.6)	13.5 (12.4, 14.3)	0.0 (−0.40, 0.20)	0.047
Hematocrit	0.43 (0.39, 0.45)	0.45 (0.40, 0.46)	0.01 (0.00, 0.02)	0.43 (0.39, 0.44)	0.42 (0.38, 0.44)	−0.01 (−0.01, 0.00)	0.027
Uric acid (μmol/L)	400 (343, 445)	327 (295, 390)	−53 (−90, −38)	380 (347, 460)	383 (358, 489)	0 (−15, 36)	<0.001
Tacrolimus (C_0)	5.4 (4.6, 6.9)	5.2 (4.5, 6.2)	−0.05 (−1.1, 0.43)	6.2 (5.0, 6.8)	5.7 (4.9, 6.5)	0.00 (−0.75, 0.45)	0.77
Cyclosporine (C_0)	94 (80, 105)	88 (79, 97)	−6 (−8, −1)	100 (94, 100)	76 (65, 102)	−24 (−30, 2)	0.70
Everolimus (C_0)	6.2 (6.2, 6.2)	5.8 (5.8, 5.8)	−0.4 (−0.4, −0.4)	10 (10, 10)	7 (7, 7)	−3 (−3, −3)	1

Efficacy variables were analyzed per protocol ($n = 44$) and safety variables by intention to treat ($n = 49$). DBP, diastolic blood pressure; SBP, systolic blood pressure. **P* values are calculated from difference in change at week 24 from baseline compared with placebo.

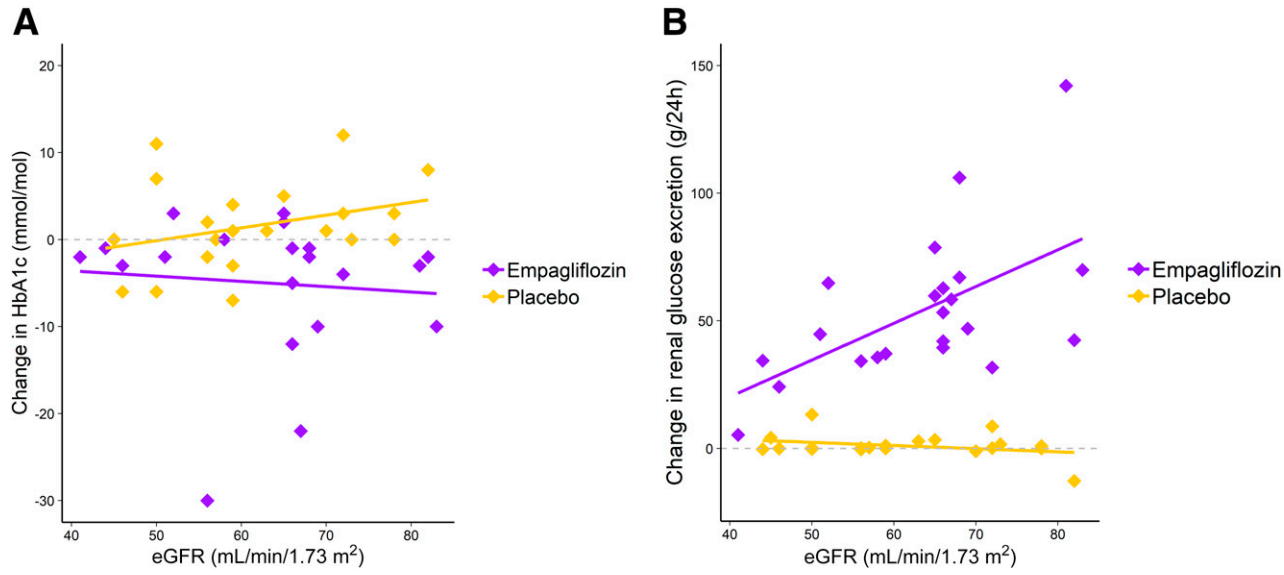

Figure 2—The relationship between baseline eGFR and change in HbA_{1c} (*A*) and renal glucose excretion (*B*) from baseline to week 24. Panel *A* shows a trend toward a decreased reduction in HbA_{1c} with decreased eGFR in the empagliflozin group. However, no significant correlation was observed in any of the groups: $r = -0.09$ and $P = 0.70$ in the empagliflozin group vs. $r = 0.33$ and $P = 0.13$ in the placebo group. Panel *B* shows that the glucose excretion decreased with decreasing eGFR in the empagliflozin group ($r = 0.58$, $P < 0.01$), which was not seen in the placebo group ($r = -0.31$, $P = 0.16$). A linear trend line was added for visualization purposes.

Arterial Stiffness

Pulse wave velocity decreased (−0.50 m/s [−1.3, 0.60]) in the empagliflozin group and increased (0.45 m/s [0.13, 0.98]) in the placebo group, but the difference between groups did not reach statistical significance ($P = 0.09$). However, investigations of pulse wave velocity were not possible in all patients for technical reasons. Valid pulse wave velocity analyses were obtained in 20 patients in the empagliflozin group and 18 patients in the placebo group.

Kidney Function

There was no significant difference in kidney function between the groups after 24 weeks of treatment (Table 2). A sensitivity analysis of the kidney function data from the study visit at week 8 revealed that eGFR was significantly reduced in the empagliflozin group after 8 weeks of treatment (−4 mL/min/1.73 m^2 [−7, −1]) compared with the placebo group (−1 mL/min/1.73 m^2 [−2, 2]) ($P < 0.05$). There was, however, no difference in change in eGFR between the two groups from week 8 to week 24: 0 mL/min/1.73 m^2 (−2, 4) in the empagliflozin group vs. 0 mL/min/1.73 m^2 (−2, 2) in the placebo group ($P = 0.61$).

Safety

Adverse Events

In general, empagliflozin was well tolerated with no serious adverse events reported, except for one patient in the empagliflozin group who was withdrawn from the study due to urosepsis. Twenty-seven percent of the participants reported adverse events, seven patients in the empagliflozin group and six patients in the placebo group ($P = 0.68$) (Supplementary Table 2). No patients were suspected of having a rejection episode during the study period.

Hematology

Empagliflozin-treated patients showed a significant median increase in hemoglobin and hematocrit compared with placebo. Details are presented in Table 2.

Other Data

Treatment with empagliflozin also resulted in a significant median reduction in uric acid ($P < 0.01$) (Table 2). In addition, magnesium levels increased in patients treated with empagliflozin compared with placebo ($P < 0.01$) (Supplementary Table 1).

Immunosuppressive Drugs

Seven patients underwent dose adjustments or changes in their immunosuppressive therapy during the study period. In the empagliflozin group, one patient changed from twice daily (Prograf) to once daily (Advagraf) tacrolimus formulation, and in the placebo group, one patient changed once daily tacrolimus brand (from Advagraf to Envarsus) and one patient switched from tacrolimus (Envarsus) to cyclosporine (Sandimmun Neoral). Four patients had their calcineurin inhibitor dose adjusted, one in the empagliflozin group and three in the placebo group. During the course of the study, no difference in trough levels of immunosuppressive drugs was observed (Table 2).

Adherence

Median (IQR) adherence was acceptable (100.0% [74.5, 100.0]). Adherence was <80% for five patients in the empagliflozin group and nine patients in the placebo group. One patient in the empagliflozin group forgot to bring the study medication at week 24, and capsule count was not done for this patient.

CONCLUSIONS

To the best of our knowledge, this is the first randomized placebo-controlled study on SGLT2 inhibitor therapy in renal transplant recipients with PTDM. Empagliflozin appeared to be safe and effective in this population. Glycemic control was significantly improved compared with placebo, especially in those with HbA_{1c} >8.0% (64 mmol/mol) at inclusion. Additionally, empagliflozin treatment was associated with a concomitant reduction of body weight after 24 weeks of treatment. One case of urosepsis was observed, but the relationship to drug treatment is uncertain since this person

also had experienced previous episodes of urinary tract infections prior to the study participation. We would in any case suggest caution when SGLT2 inhibition is considered for treatment in renal transplant recipients with a history of recurrent urinary tract infections.

Reduced glucose-lowering effect of empagliflozin was related to lower GFR at baseline. Patients were included with a single kidney GFR of at least 30 mL/min/1.73 m^2. Previous studies in patients with type 2 diabetes and two kidneys have shown a similar dependence on GFR (17,18).

Urinary glucose excretion with empagliflozin was, as expected, inversely associated with GFR (33). On the other hand, renal function did not seem to impact the reductions in body weight in the current study. We could not find that empagliflozin had any effect on VAT, even though this has been shown with dapagliflozin in patients with native kidneys (34). It could be that our study did not have the power to detect such a difference, or that at least part of the weight loss was caused by loss of body water.

Empagliflozin reduces blood pressure in patients with type 2 diabetes (35,36). We could not demonstrate such an effect in the current study. Hypertension is more common in renal transplant recipients and may not be compared with hypertension in patients with type 2 diabetes due to additional pathogenetic mechanisms, e.g., mechanisms related to immunosuppressive therapy and single kidney impaired renal function. This may at least in part explain a lack of effect on blood pressure in our study. Another possible explanation is of course that our study was not powered to show a difference in blood pressure–lowering effect between the two groups.

Empagliflozin was well tolerated, but the small number of participants makes it difficult to evaluate adverse events in depth. Urinary tract infections and especially genital infections are frequently reported as adverse events in studies with SGLT2 inhibitors (37–39). One could suspect an even higher frequency of these events in renal transplant recipients since their immune system is suppressed by medication. The current study did not show any serious adverse events, other than one case of urosepsis, nor any difference in adverse events. One case of genital yeast infection was reported by a female in the empagliflozin group. Empagliflozin did not reveal any signal on relevant pharmacokinetic interactions with the immunosuppressive drugs. When interpreting these findings, it should however be kept in mind that this is based on trough concentration measurements only, and hence no in-depth investigations of full pharmacokinetic profiles have been performed.

We found that eGFR decreased during the first 8 weeks of empagliflozin treatment but subsequently stabilized. An initial decrease in GFR with empagliflozin is in accordance with findings in other studies (15,21). Empagliflozin is considered to be associated with renoprotection in the long-term, but our study was not powered to demonstrate such an effect.

Increased hemoglobin and hematocrit appear to be important mediators for the cardiovascular benefits seen with em pagliflozin treatment (40). An increase in these mediators was also seen in this study and can be of particular relevance for patients with PTDM. It has been speculated that increased hematocrit may mediate a more favorable aerobic metabolism (40). In addition, empagliflozin treatment resulted in reduced uric acid plasma concentrations, which also can have a positive impact on cardiovascular risk (40). Hypoglycemic events were not seen in the study period, and hypoglycemia is not expected with SGLT2 inhibition unless combined with insulin or sulfonylurea therapy.

The limitations of the current study include a relatively small sample size with regards to capturing side effects and a prespecified primary end point that was not possible to analyze due to technical error. The major strength of the current study is its study design: prospective, randomized, placebo controlled, and double blinded. In addition, the study participants represented the overall population of renal transplant recipients with PTDM in our clinic.

In conclusion, empagliflozin improves glycemic control compared with placebo, with a concomitant reduction of body weight in stable renal transplant recipients. The treatment was well tolerated with apparently no relevant pharmacokinetic interactions with the immunosuppressive therapy. Thus, empagliflozin seems to represent a novel treatment option for renal transplant recipients with PTDM, but more studies are warranted.

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