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Safety and Efficacy of Sodium-glucose Cotransporter 2 Inhibitors in Kidney Transplant Recipients With Pretransplant Type 2 Diabetes Mellitus: A Retrospective, Single-center, Inverse Probability of Treatment Weighting Analysis of 85 Transplant Patients

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Background. Whether sodium-glucose cotransporter 2 (SGLT2) inhibitors can be used effectively and safely in kidney transplant (KT) recipients with pretransplant type 2 diabetes as the primary cause of end-stage renal disease (ESRD) remains unclear. In this study, we retrospectively analyzed the efficacy and safety of SGLT2 inhibitors compared with other oral hypoglycemic agents (OHAs) in KT recipients with pretransplant type 2 diabetes as the primary cause of ESRD. **Methods.** In this retrospective, observational, single-center, inverse probability of treatment weighting (IPTW) analysis study, we compared the outcomes of SGLT2 inhibitors (SGLT2 group) and other OHAs (control group) following KT. A total of 85 recipients with type 2 diabetic nephropathy as the major cause of ESRD before KT who were treated at our institute between October 2003 and October 2019 were screened and included. The variables considered for IPTW were recipient age, sex, body mass index, history of cardiovascular disease, ABO incompatibility, insulin therapy, estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c) at the initiation of additional OHAs. Primary endpoints were changes in HbA1c, body weight, and eGFR 1 y after the initiation of additional OHAs. **Results.** After IPTW analysis, there were 26 patients in the SGLT2 group and 59 patients in the control group (n = 85 overall). The body weights were significantly reduced in the SGLT2 group. There was no statistical difference in changes in HbA1c and eGFR. Similarly, there was no significant difference in the incidence of urinary infection, acute rejection, or other side effects between the groups. **Conclusions.** Our findings suggested that SGLT2 inhibitors reduced the body weight of KT recipients and were used safely without increasing side effects.

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Diabetes is the leading cause of end-stage renal disease (ESRD) worldwide, and the number of kidney transplant (KT) patients with diabetic nephropathy is increasing. According to the United States Renal Data System 2020 Annual Report, diabetes is the most common primary cause of ESRD among new KT recipients, accounting for 25.6% of these cases.[1] According to the Annual Progress Report from the Japanese Renal Transplant Registry: Number of Renal Transplantations in 2019 and Follow-up Survey, 19.4% of living KT recipients in Japan had diabetic nephropathy, which was the second most common cause for requiring KT after glomerulonephritis.[2] Because poor glycemic control can lead

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to vascular complications and damage the transplanted kidney, the appropriate management of KT recipients with pretransplant diabetes is essential for improving graft and patient survival.[3–5]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of oral hypoglycemic agents (OHAs) that reduce blood glucose levels by promoting the excretion of glucose in urine. These drugs are known to exert hypoglycemic, weight loss, and blood pressure-lowering effects.[6] Furthermore, several large clinical trials have shown that these drugs reduce the risk of cardiovascular disease (CVD) and exhibit beneficial effects on renal outcomes.[7–10] Therefore, the administration of SGLT2 inhibitors in type 2 diabetes (T2DM) patients is associated with various long-term benefits. Previous studies on the prognostic and renoprotective effects of SGLT2 inhibitors have focused primarily on nontransplant chronic kidney disease (CKD) patients with T2DM.

The efficacy and safety of SGLT2 inhibitors in KT recipients remain incompletely evaluated. Several studies have investigated the use of SGLT2 inhibitors in KT recipients, including one randomized controlled trial,[11] but most analyzed posttransplant diabetes (PTDM) patients. The background and characteristics of patients, such as etiologic factors, duration of diabetes, and degree of vascular complications, may differ greatly between those with PTDM or pretransplant T2DM. A population cohort study of 5248 KT recipients reported that KT patients with pretransplant diabetes were considerably different from KT patients with new-onset diabetes after transplantation.[12] They described that the incidence rates of major adverse cardiovascular events in patients with pretransplant diabetes were substantially higher than recipients with new-onset diabetes after transplantation.

The efficacy and safety of SGLT2 inhibitors in KT recipients with pretransplant T2DM as the primary cause of ESRD remain unclear. There are concerns that the use of SGLT2 inhibitors in KT recipients carries potential risks of side effects that are detrimental to the kidney graft, such as dehydration, acute kidney injury, or urinary tract infection (UTI).[13,14] The lack of evident efficacy is another disadvantage in selecting SGLT2 inhibitors for KT recipients. Therefore, clarifying the efficacy and safety of SGLT2 inhibitors in KT patients with pretransplant T2DM may expand the drug options for the management of diabetes.

In our study, we surveyed patients with pretransplant diabetes that had progressed to diabetic nephropathy for several years. These patients were at a substantially higher risk for many aspects, including CVD, than those who were diabetic pretransplantation but had not deteriorated to diabetic nephropathy.

MATERIALS AND METHODS

Patients

We retrospectively analyzed ESRD patients with type 2 diabetic nephropathy who underwent KT at Kyushu University Hospital from October 2003 to October 2019 and were newly administered OHAs during posttransplant follow-up. ESRD patients with type 2 diabetic nephropathy were defined as those who underwent diagnosis by nephrologists and had preexisting diabetic retinopathy. The addition of OHAs was defined as the initiation of any class of OHA during an outpatient visit following KT, regardless of the reason for initiation. Patients followed-up by diabetologists at institutions other than Kyushu University Hospital were excluded because details regarding diabetes treatment and glycemic control could not be assessed accurately. To examine 1-y outcomes following the addition of OHAs, patients with an observation period of <1 y were excluded. Furthermore, patients with missing data on variates requiring analysis were also excluded. Eligible patients were divided into 2 groups according to the class of newly added OHA: the SGLT2 group and the control group (administered other classes of OHAs). The following patient features were extracted from the electronic medical database: recipient age/sex/body mass index (BMI), donor age/sex/BMI, history of CVD, insulin therapy, ABO incompatibility, and immunosuppressive therapy. BMI was calculated by dividing patient weight in kilograms by their square height in meters.

To assess the short-term outcomes of SGLT2 inhibitors in terms of efficacy and safety, recipients were observed for 1 y following the initiation of newly added OHAs, and the following clinical data were collected from the electronic medical database: glycemic control, body weight, blood pressure, lipid control, urinary protein, kidney function, adverse events, and biopsy-proven acute rejection. Glycemic control was assessed by hemoglobin A1c (HbA1c). Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were used to assess lipid control. Urinary protein was assessed as the spot urinary protein/creatinine ratio. To evaluate kidney function, the estimated glomerular filtration rate (eGFR) was calculated using the appropriate equation for Japanese CKD patients.[15] Allograft diagnosis was performed with episode biopsies or 3- and 12-mo protocol biopsies in accordance with the Banff 2013 classification.[16]

Primary endpoints were 1-y changes in HbA1c, body weight, and eGFR after the introduction of additional OHAs. Secondary endpoints were 1-y changes in blood pressure, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides after the initiation of additional OHAs.

The study protocol was approved by the Ethics Committee of Kyushu University (IRB-No. 24-54). This study is registered in the University Hospital Medical Information Network Clinical Trials Registry System (UMIN000008475).

Immunosuppression

All recipients received triple-drug maintenance immunosuppression with tacrolimus or cyclosporine, mycophenolate mofetil or everolimus, and methylprednisolone. When a patient was diagnosed with acute rejection, treatment was administered in accordance with appropriate guidelines.[17] T cell-mediated rejection was treated with steroid pulse therapy (250–500 mg methylprednisolone for 3 d) for borderline changes and Banff grade I rejection and antithymocyte globulin (1.5 mg/kg/d for 3–7 d) for steroid-resistant rejection and Banff grades II and III rejection. Patients diagnosed with antibody-mediated rejection were treated with plasma exchange, intravenous immunoglobulin, and rituximab.

Statistical Analyses

Data are presented as the mean ± SD for normally distributed variables and the median (interquartile range) for non-normally distributed variables. Categorical variables are presented as counts and percentages. The normality of variables was tested using the Kolmogorov-Smirnov test. Comparisons between

parametric continuous data were performed using the Student *t* test. For comparisons between nonparametric continuous data, the Mann-Whitney *U* test was used. Categorical variables were compared with χ^2 test or Fisher exact test where appropriate. Time-dependent changes in eGFR were evaluated by repeated measures analysis of variance (ANOVA) between the SGLT2 inhibitor and control groups. The Bonferroni correction was used to reduce type I errors because of multiple comparisons between various time points. To overcome bias caused by the different distribution of covariates between the 2 study groups, inverse probability of treatment weighting (IPTW) was performed using logistic regression analysis to generate propensity scores for both groups of patients. The following variables that affected the primary outcomes were included in the IPTW analysis: recipient age/sex/BMI, history of CVD, insulin therapy, ABO incompatibility, eGFR, and HbA1c at the induction of additional OHAs. All tests were 2-sided, and P <0.05 was considered significant. All statistical analyses were performed using JMP Pro 15 (SAS Institute, Cary, NC).

RESULTS

Patient Features

From October 2003 to October 2019, a total of 183 patients with type 2 diabetic nephropathy underwent KT at Kyushu University Hospital (Figure 1). Among them, 105 patients were newly administered OHAs during a posttransplant outpatient visit. Sixteen patients were excluded from this study, including 5 that were not followed-up by diabetologists from our hospital, 8 who were observed for <1 y, and 3 patients with missing data. Therefore, a total of 89 patients were included in the analysis and matched using IPTW. SGLT2 inhibitors were initiated in 29 patients: canagliflozin in 9 patients, ipragliflozin in 7 patients, luseogliflozin in 5 patients, empagliflozin in 4 patients, dapagliflozin in 3 patients, and tofogliflozin in 1 patient. In contrast, 60 patients were newly administered other classes of OHAs: dipeptidyl peptidase-4 inhibitors in 42 patients, glinides in 9 patients, metformin in 4 patients, sulfonylureas in 4 patients, and α-glucosidase inhibitors in 1 patient. Table 1 shows the baseline characteristics of each group before and after IPTW analysis. Before IPTW, BMI was significantly higher in the SGLT2 group than in the control group (P < 0.001). After IPTW, there were 26 patients in the SGLT2 group and 59 patients in the control group (n = 85 overall; Figure 1).

Comparison of Efficacy Between the SGLT2 Inhibitor and Control Groups

Table 2 shows the changes in HbA1c and body weight over 48 wk following drug administration. The mean change in HbA1c was −0.1% in the SGLT2 group and −0.2% in the control group, with no statistical significance between the 2 groups (P = 0.527). The mean change in body weight was −0.7 kg in the SGLT2 group compared with +1.6 kg in the control group. Patients in the SGLT2 group showed significantly reduced body weights (P = 0.040).

Table 2 shows all parameters before and 48 wk after the administration of OHAs in the matched cohort. We compared changes in these parameters over 48 wk between the 2 groups.

Renal Function Over 48 Wk Following the Administration of OHAs

To assess safety, renal function was compared between the 2 groups following the addition of OHAs. The mean eGFR was stable over 48 wk following SGLT2 inhibitor administration, and repeated measures ANOVA showed no significant time-dependent interaction of eGFR between the 2 groups (Figure 2, P = 0.051).

Side Effects

All side effects that occurred within 1 y following the addition of OHAs are shown in Table 2. In the SGLT2 inhibitor group, 2 patients (6.4%) developed UTIs at 56 and 123 d after the addition of SGLT2 inhibitors. There were no statistical differences in the 1-y incidence of these side effects between the 2 groups.

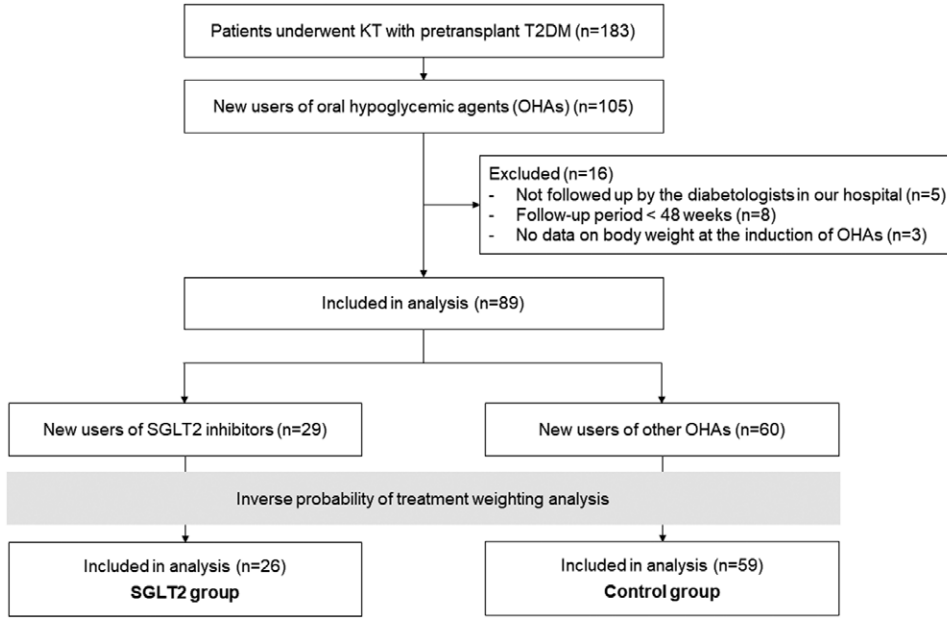

FIGURE 1. Patient selection in the 2 groups. KT, kidney transplant; OHA, oral hypoglycemic agent; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes.

TABLE 1.

Baseline features of donors and recipients

Variables	Overall (n = 92)			After IPTW (n = 85)		
	SGLT2 (n = 29)	Control (n = 60)	*P*	SGLT2 (n = 28)	Control (n = 57)	*P*
Donor factors						
Age, mean ± SD, y	52.9 ± 12.5	56.6 ± 12.1	0.182	50.8 ± 13.7	56.7 ± 11.3	0.038
Sex, male:female	12:17	16:44	0.161	9:19	17:40	0.832
BMI, mean ± SD, kg/m^2	23.9 ± 4.1	23.3 ± 3.2	0.462	23.6 ± 4.2	23.4 ± 3.0	0.900
Recipient factors						
Age, mean ± SD, y	56.4 ± 8.7	55.9 ± 10.2	0.713	54.8 ± 7.0	55.7 ± 9.5	0.688
Sex, male:female	21:8	48:13	0.422	22:6	43:14	0.832
BMI, mean ± SD, kg/m^2	29.1 ± 4.0	24.3 ± 3.1	<0.001	26.1 ± 4.0	25.5 ± 3.4	0.477
History of CVD, n (%)	10 (34.5)	25 (41.7)	0.516	16 (57.3)	27 (46.3)	0.339
Insulin therapy, n (%)	21 (72.4)	46 (76.7)	0.663	17 (60.7)	44 (76.1)	0.139
ABO incompatible, n (%)	13 (44.8)	19 (31.7)	0.225	14 (50.1)	20 (35.4)	0.194
eGFR, mean ± SD, mL/min per 1.73 m^2	53.3 ± 17.1	46.2 ± 14.0	0.038	50.4 ± 13.9	47.5 ± 13.1	0.346
HbA1c, mean ± SD, g/dL	7.8 ± 1.0	7.5 ± 1.4	0.267	7.7 ± 0.9	7.6 ± 1.3	0.712
Immunosuppression						
Tac:CyA	29:0	58:2	1.000	28:0	55:3	1.000
MMF:EVR	22:7	39:21	0.301	23:5	38:20	0.151

BMI, body mass index; CVD, cardiovascular disease; CyA, cyclosporin; eGFR, estimated glomerular filtration rate; EVR, everolimus; HbA1c, hemoglobin A1c; IPTW, inverse probability of treatment weighting; MMF, mycophenolate mofetil; SGLT2, sodium-glucose cotransporter 2; Tac, tacrolimus.

Biopsy-proven Acute Rejection

During the observation period, 1 patient in each group was pathologically diagnosed with acute rejection. There were no significant changes between the 2 groups ($P = 0.329$) (Table 2).

DISCUSSION

In our study, SGLT2 inhibitors reduced body weight without increasing other side effects. In addition, the efficacy of SGLT2 inhibitors was comparable to that of other OHAs.

Several previous studies have analyzed the use of SGLT2 inhibitors in KT recipients. Halden et al[11] reported the results of a randomized controlled trial that evaluated the efficacy and safety of empagliflozin for 24 wk in KT recipients diagnosed with PTDM. Empagliflozin treatment resulted in weight loss and a significant decrease in HbA1c. Moreover, there were no significant differences in adverse events, immunosuppressive drug levels, or renal function between the placebo and empagliflozin groups. Apart from the present study, a few case series have shown similar results in terms of the safety and efficacy of SGLT2 inhibitor use for 6 to 12 mo

TABLE 2.

Outcomes to evaluate the efficacy and safety of SGLT2 inhibitors after an inverse probability of treatment weighting analysis

Variables	SGLT2 (n = 28)			Control (n = 57)			*P*
	Baseline	48 wk	Δ	Baseline	48 wk	Δ	
Primary outcomes, mean ± SD							
HbA1c, %	7.7 ± 0.9	7.6 ± 1.1	−0.1 ± 1.0	7.6 ± 1.1	7.5 ± 1.1	−0.2 ± 0.9	0.527
Body weight, kg	73.2 ± 11.4	72.2 ± 9.5	−0.7 ± 5.1	69.9 ± 9.9	71.6 ± 10.9	1.6 ± 4.5	0.040
eGFR, mL/min per 1.73 m^2	50.4 ± 13.9	51.4 ± 14.8	0.9 ± 6.7	47.5 ± 13.1	46.3 ± 14.2	−1.2 ± 8.0	0.233
Secondary outcomes, mean ± SD							
sBP, mm Hg	123 ± 16	129 ± 10	7 ± 20	130 ± 15	125 ± 16	−3 ± 24	0.084
dBP, mm Hg	74 ± 10	72 ± 10	−2 ± 10	73 ± 10	71 ± 10	−1 ± 11	0.549
TC, mg/dL	173 ± 51	168 ± 30	−5 ± 38	200 ± 50	186 ± 39	−14 ± 47	0.409
LDL-C, mg/dL	92 ± 36	86 ± 24	−6 ± 28	103 ± 38	95 ± 28	−6 ± 37	1.000
HDL-C, mg/dL	48 ± 13	49 ± 16	1 ± 9	61 ± 21	61 ± 21	−2 ± 22	0.352
TG, mg/dL	177 ± 71	177 ± 78	0 ± 49	158 ± 101	160 ± 84	2 ± 76	0.943
UP/UCr, g/gCr	0.41 ± 0.51	0.40 ± 0.43	0 ± 0.5	0.34 ± 0.63	0.36 ± 0.83	0 ± 0.5	0.779
Adverse events and rejection over 48 wk, n (%)							
Urinary tract infection		2 (6.4)			0 (0)		0.106
Cardiovascular disease		0 (1.6)			2 (3.3)		1.000
Biopsy-proven acute rejection		1 (2.5)			1 (1.2)		0.329
Other adverse events		1 (2.4)			7 (11.9)		0.262

P values were calculated from the comparison of differences in changes from baseline to 12 mo between the 2 groups.
dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; sBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; TC, total cholesterol; TG, triglyceride; UP/UCr, urinary protein/creatinine ratio.

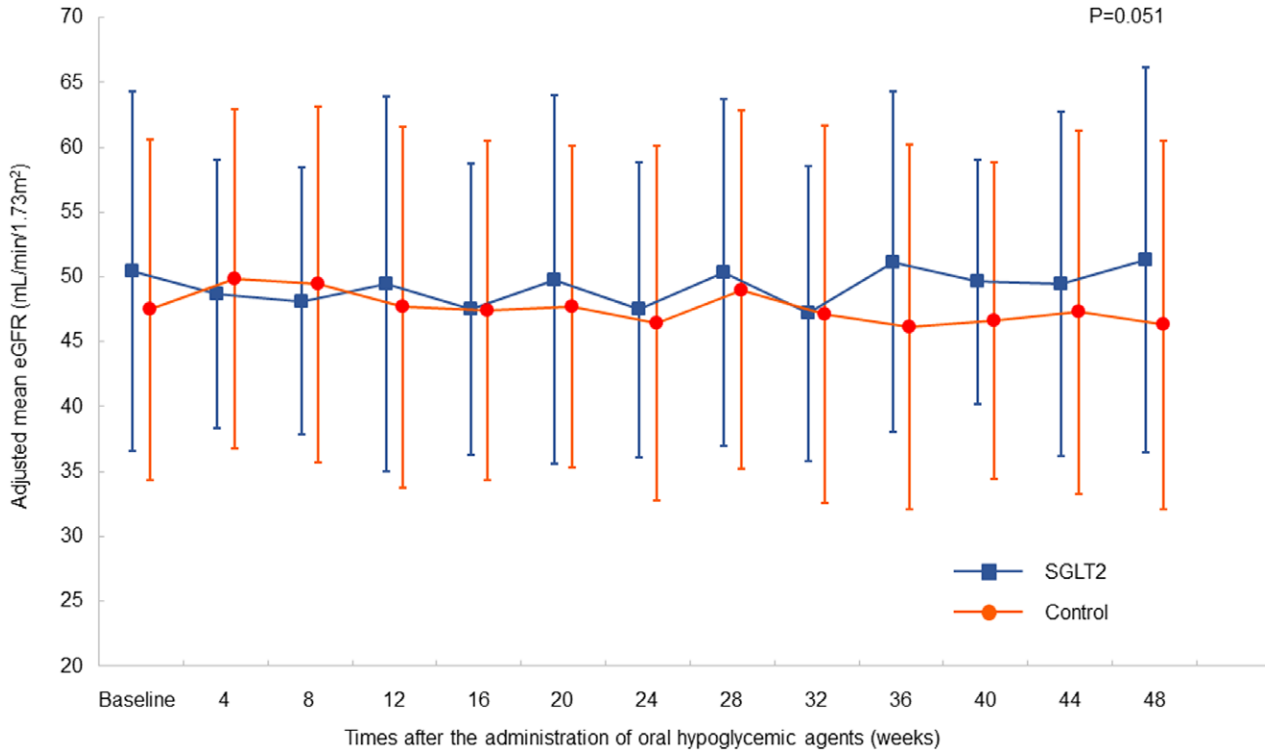

FIGURE 2. Adjusted estimated glomerular filtration rate (eGFR; mean ± SD) from the baseline to 48 wk after the administration of oral hypoglycemic agents. Repeated measures ANOVA showed no significant time-dependent interaction of eGFR between the 2 groups ($P = 0.051$). ANOVA, analysis of variance; SGLT2, sodium-glucose cotransporter 2.

in KT recipients.[18–22] Most of these studies analyzed patients with PTDM, and none have focused on the administration of SGLT2 inhibitors in KT recipients with pretransplant T2DM. To determine whether SGLT2 inhibitors can be used safely and effectively in patients with pretransplant T2DM, we conducted the present study. Here, we found that SGLT2 inhibitor administration in KT recipients with pretransplant T2DM reduced body weight without causing major side effects or worsening renal graft function, and the effects were comparable to those of other OHAs. These observations were consistent with those from previous studies on the use of SGLT2 inhibitors for KT recipients with PTDM.

HbA1c is suggested to be an appropriate marker for the treatment of diabetes. The American Diabetes Association recently reported that HbA1c is the primary indicator of glycemic control and that it has a strong predictive value for diabetes complications.[23] Furthermore, Kim et al[5] reported that HbA1c predicted graft outcomes in KT patients. In our study, changes in HbA1c were similar between both groups. The HbA1c-lowering effect in the SGLT2 group appeared to be relatively weak, although this may have been because of the low baseline eGFR in the study population. The increases in urinary glucose excretion and decreases in HbA1c associated with SGLT2 inhibitor use have been reported to be significantly related to the baseline eGFR.[11,24] The patients in this study had a median baseline eGFR of 51.1 mL/min per 1.73 m^2, which was lower than in previous studies.[11,18–21] To accurately evaluate the short-term efficacy of SGLT2 inhibitors stratified by eGFR in KT recipients with pretransplant T2DM, larger numbers of patients should be studied prospectively.

During the 48-wk period following SGLT2 inhibitor introduction, the eGFR was stable and comparable to that in the control group. Following the administration of SGLT2 inhibitors, an initial acute reduction in eGFR, known as the initial dip, was reported in several randomized controlled trials in both nontransplant and transplant CKD patients.[9,11,25] SGLT2 inhibitors decrease proximal tubular sodium reabsorption and fluid volume, thereby activating tubuloglomerular feedback, which leads to afferent vascular regulation and decreases hyperfiltration.[9] This effect causes an initial dip during the first 3 to 8 wk, after which the eGFR recovers and remains stable.[10,25] In our study, there appeared to be an initial dip in the eGFR within 4 wk following SGLT2 inhibitor administration, but this was not significant ($P = 0.279$). In addition, repeated measures ANOVA showed a trend toward a time-dependent interaction of eGFR between the 2 groups during the first 4 to 48 wk of treatment ($P = 0.078$). Although this effect is not significant, the eGFR in the SGLT2 group appeared to be better preserved than that of the control group. A temporary dip in eGFR is sometimes a concern with SGLT2 inhibitor use in KT recipients, but SGLT2 inhibitors can be used safely in KT recipients with pretransplant T2DM without an irreversible decline in the eGFR.

UTI is one of the most alarming complications associated with SGLT2 inhibitors. It is believed that SGLT2 inhibitors increase the incidence of UTIs because glucose excretion in urine is increased. However, a meta-analysis of 77 randomized control trials comprising 50 820 nontransplant T2DM participants found no significant increase in the risk of UTI with SGLT2 inhibitors.[14] Furthermore, a report of 50 KT recipients treated with SGLT2 inhibitors showed no significant increase in UTIs.[26] In our study, no significant increase in UTIs was observed in the SGLT2 group. In addition, 1 of 2 patients who developed UTIs after SGLT2 inhibitor use had vesicoureteral

reflux and had been treated several times for this condition before SGLT2 inhibitor use. In this case, the effects of SGLT2 inhibitors on UTIs appeared to be minimal. Therefore, we could not conclude that SGLT2 inhibitors were associated with UTIs in our study. Adequate fluid intake in KT recipients may prevent UTI.[27] Because UTI is the most common complication following KT and can lead to impaired graft function, graft loss, and death,[28] careful monitoring is required after SGLT2 inhibitor administration. Other side effects and acute rejection were also similar between the SGLT2 inhibitor and control groups. No serious adverse events occurred in either group in the present study. Our results indicate that SGLT2 inhibitors are relatively well tolerated in KT recipients with pretransplant T2DM.

Several large trials recently showed the long-term benefits of SGLT2 inhibitor use. In particular, they reduced CVD risk and exerted renoprotective effects in nontransplant T2DM patients.[7–9,29] Moreover, these outcomes appeared to be independent of the blood glucose-lowering effect.[30,31] For example, a recent study showed that SGLT2 inhibitors protected the kidney and reduced the eGFR slope in CKD patients, regardless of the presence or absence of diabetes.[10] Cardioprotection and renoprotection are particularly important for KT recipients with T2DM because they are at extremely high risk of CVD,[32] and renal graft function should be carefully maintained. We found that the use of SGLT2 inhibitors in KT recipients with pretransplant T2DM was safe. Therefore, the administration of SGLT2 inhibitors may be an acceptable option for achieving long-term benefits, which can improve long-term patient survival.

As shown in Table 2, there were no significant changes in blood pressure in either group. We compared antihypertensive medication use in the 2 groups at the initiation of additional OHAs and 1 y after (Table S3, SDC, http://links.lww.com/TXD/A368). The use of α-blockers appeared to be reduced from 16.0% to 5.9% in the SGLT2 group. However, no changes in other antihypertensive medications, such as diuretic therapy and angiotensin blocking agents, were observed in the 2 groups. Based on our study, the effects of SGLT2 inhibitors on blood pressure remain uncertain.

We next evaluated the effects of SGLT2 inhibitors or other OHAs on the calcineurin inhibitor trough concentration. The effects on tacrolimus concentration and dose are usually evaluated by the following formula: tacrolimus trough blood concentration (C0)/tacrolimus dose (d). We surveyed tacrolimus C0/d at the initiation of additional OHAs and 1 y after and compared changes in the tacrolimus C0/d between the 2 groups. Our results revealed that there were no significant differences between the 2 groups ($P = 0.755$; Table S4, SDC, http://links.lww.com/TXD/A368).

Because we included patients who received KT between 2003 and 2019, but SGLT2 inhibitors became available in 2013, a time bias existed in our study. To address this, we extracted and reanalyzed only patients who received KT from 2013 to 2019. The reanalyzed results are shown in Tables S1 and S2, SDC, http://links.lww.com/TXD/A368. Body weight was significantly reduced in the SGLT2 group. In addition, there were no significant differences in changes in HbA1c and eGFR between the SGLT2 and control groups. These results were similar to those obtained with patients who received KT from 2003 to 2019 in our study (Tables S1 and S2, SDC, http://links.lww.com/TXD/A368).

The present study had several limitations. First, this was a single-center, retrospective, observational study. There may have been unmeasured confounders, although IPTW was performed to match background factors. Additionally, we were only able to include patients who were followed-up by diabetologists at our institution, which may have caused selection bias in terms of patient compliance and difficulty in glycemic control. Furthermore, we focused on patients who required additional OHAs for various factors, which may have led to selection bias. Moreover, because newly administered OHAs were determined at the discretion of each diabetologist, the patients received different types of SGLT2 inhibitors. The sample size was also small, and the observational period was short. Therefore, the study may have been underpowered. Finally, a time bias existed in our study. However, as discussed above, the effect of this bias appeared to be minimal.

In conclusion, our findings suggested that SGLT2 inhibitors reduced body weight in patients with pretransplant T2DM without increasing side effects. The efficacy and safety of SGLT2 inhibitors in KT recipients with pretransplant T2DM were comparable to those of other OHAs. We believe that SGLT2 inhibitors may represent a useful option for the management of diabetes in KT recipients with pretransplant T2DM.

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