Association of diuretic use with increased risk for long-term post-transplantation diabetes mellitus in kidney transplant recipients

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Running title: Diuretic use and risk of PTDM
ABSTRACT

Background. Post-transplantation diabetes mellitus (PTDM) is a major clinical problem in kidney transplant recipients (KTRs). Diuretic-induced hyperglycemia and diabetes have been described in the general population. We aimed to investigate whether diuretics also increase PTDM risk in KTRs.

Methods. We included 486 stable outpatient KTRs (with a functioning graft ≥1 year) without diabetes from a prospective cohort study. Participants were classified as diuretic users and non-users based on their medication use verified by medical records.

Results. At current baseline study, 168 (35%) KTRs used a diuretic (thiazide, n=74; loop diuretic, n=76; others, n=18) and 318 KTRs did not use a diuretic. After 5.2 (IQR, 4.0–5.9) years of follow up, 54 (11%) KTRs developed PTDM. In Cox regression analyses, diuretic use was associated with incident PTDM, independent of age, sex, fasting plasma glucose (FPG), and HbA1c (hazard ratio[HR] 3.28, 95% CI 1.84-5.83; p<0.001). Further adjustment for potential confounders, including lifestyle, family history of cardiovascular disease, use of other medication, kidney function, transplantation specific parameters, BMI, lipids, and blood pressure did not materially change the association. Moreover, in Cox regression analyses, both thiazide and loop diuretics associated with the development of PTDM, independent of age, sex, FPG, and HbA1c ([HR 2.70, 95% CI 1.24-5.29; p=0.012], and [HR 5.08, 95% CI 2.49-10.34; p<0.001], respectively).

Conclusions. This study demonstrates that diuretics overall are associated with increased risk of developing PTDM in KTRs, independent of established risk factors for PTDM development. The association was present both for thiazide and loop diuretics.

Keywords: diuretics, kidney transplant recipients, loop diuretics, post-transplantation diabetes mellitus, thiazide
KEY LEARNING POINTS

What is already known about this subject?

- Use of anti-hypertensive drugs such as diuretics has been known to be associated with increased risk of new onset of diabetes in the general population.
- This has not been investigated in kidney transplant recipients (KTRs).

What this study adds?

- We explored the associations between diuretic use with incident Post-transplantation diabetes mellitus (PTDM) in KTRs.
- We found that use of diuretics is a strong and independent risk factor for incident PTDM.
- Our finding highlight the association of thiazide diuretics and particularly loop diuretics with increased risk for PTDM

What impact this may have on practice or policy?

- Our findings, call for careful evaluation of the necessity of diuretics use in KTRs.
- We identified diuretic use as a potentially modifiable risk factor for PTDM development.
INTRODUCTION

Post-transplantation diabetes mellitus (PTDM) is a well-recognized risk factor for graft failure and cardiovascular mortality in kidney transplant recipients (KTRs) (1). Hypertension is another common disease among KTRs which need to be controlled adequately by antihypertensive medications (2). In the general population, antihypertensive drugs such as diuretics are well known to trigger hyperglycemia and subsequently new onset of diabetes mellitus (3). Several long-term, randomized clinical trials on antihypertensive drug therapy have shown considerable differences with regards to the incidence of diabetes between treatment groups (4–6). In a large randomized clinical trial, hypertensive patients treated with low-dose diuretic therapy had higher incidence of diabetes compared to those treated with long-acting nifedipine (7). Similarly, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the incidence of diabetes was significantly higher in the thiazide group than those receiving other anti-hypertensive medications (8). A recent network meta-analysis further suggests that diuretic use, followed by beta blockers, are strongly associated with incident diabetes (3). Diuretic-induced hyperglycemia and glucose intolerance has been mainly attributed to impairment of insulin secretion, secondary to potassium loss following diuretic treatment (8–10).

Diuretics are frequently prescribed in KTRs as the initial choice of antihypertensive medications and volume optimization (11). However, it is currently unknown whether diuretic use is associated with incident PTDM in KTRs. Therefore, we aimed to prospectively investigate the association between diuretic use and PTDM in KTRs.

MATERIALS AND METHODS

Design and study population

We conducted longitudinal analyses in a large, single-center KTRs cohort study from the Transplantlines Food and Nutrition Biobank and Cohort Study (NCT02811835). All adult
KTRs (aged≥18 years) with one year or longer after transplantation were approached for participation during outpatient clinic visits at the University Medical Center Groningen (UMCG), Groningen, the Netherlands between 2008 and 2011, as described previously (12) (see Supplementary data). Of 817 initially invited KTRs, 707 signed written informed consent to participate in the present study. For the present study, we excluded patient with diabetes or a history of diabetes at baseline, leaving 486 KTRs who were eligible for analysis. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Institutional Review Board (METc 2008/186).

Data Collection

The baseline measurements were performed once at baseline during a morning visit to the outpatient clinic as described previously (12) (see Supplementary data). Participants were classified as diuretics users and non-users. The KTRs used diuretics categorized into three groups based on the type of diuretics used: thiazide, loop, and other diuretics (mainly potassium-sparing diuretics). Because data on patient reported medication use and medical record reported medication use, even if the one is verified by the other, always remains subjective and non-use cannot be excluded, we have added objective data on evidence of diuretic use by measuring metabolites on diuretics in 24h urine samples. Molecular evidence of laboratory-confirmed hydrochlorothiazide and loop diuretic was obtained through liquid chromatography-mass spectrometry (LC-MS)-based metabolomics analysis of urine (13). Blood pressure (BP) and heart rate were measured according to a standardized protocol with a semiautomatic device (Dinamap1846; Critikon, Tampa, FL) , which has been used in clinical studies and cohort studies from our department (14–16) (see Supplementary data).
Fasting plasma glucose (FPG) was measured by an enzymatic assay and \( \text{HbA}_1c \) was measured using a turbidimetric inhibition immunoassay. Other markers were measured according to standard laboratory procedures (see Supplementary data).

**Outcome Definition**

The diagnosis of PTDM was defined according to the American Diabetes Association criteria with at least one of the following requirements: fasting plasma glucose (FPG) \( \geq 7.0 \) mmol/L (126 mg/dL); \( \text{HbA}_1c \) \( \geq 6.5\% \) (48 mmol/mol); nonfasting plasma glucose concentration \( \geq 11.1 \) mmol/L (200 mg/dL) and classic symptoms of diabetes (e.g., polyuria, polydipsia, unexplained weight loss), or start of use of glucose-lowering medication (17,18) (see Supplementary data).

**Statistical analyses**

Statistical analyses were performed using statistical packages IBM SPSS (version 24.0.1; SPSS, Chicago, IL, USA) and STATA/SE (version 14; StataCorp., College Station, Texas, USA). A two-sided \( p \)-value less than 0.05 was considered statistically significant. Difference between diuretic users versus diuretic non-users was tested utilizing independent sample T tests for normally distributed continuous data, Mann-Whitney U-test for skewed data, and Chi-square tests for categorical data. Data are expressed as mean ± SD for normally distributed data, median (interquartile range [IQR]) for skewed data, and percentages for categorical data.

In prospective analyses, Kaplan-Meier curves were constructed and a Log-rank test was used to compare the estimated differences between diuretic users and non-users, as well as thiazide, loop diuretics, and non-diuretic users. To investigate the prospective association between diuretic use and incident PTDM, we performed Cox proportional hazards regression analyses to calculate hazard ratio (HR) for incident PTDM for diuretic use, as well as thiazide use and loop diuretic use, separately. First, we calculated HRs with 95% confidence intervals (95%
CI) for the crude model. Model 1 was adjusted for age, sex, FPG, and HbA1c. Subsequently, we performed additive adjustments in Cox regression analyses to avoid too many covariates included, based on the number of events. In additive multivariable models, we adjusted for smoking status, alcohol use, Quesionnaire to ASsess Health-enhancing physical activity (SQUASH) score, and history of cardiovascular disease (model 2); estimated glomerular filtration rate (eGFR), urinary albumin excretion, cytomegalovirus (CMV) infection, and time since transplantation (model 3); lipid-lowering medication use, prednisolone dose, calcineurin inhibitor use, and proliferation inhibitor use (model 4); plasma sodium, potassium, uric acid, calcium, phosphate, and plasma albumin (model 5); Body Mass Index (BMI), systolic blood pressure (SBP), high-density lipoprotein (HDL-C) cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides (model 6). Lastly, in model 7, we performed additional adjustment for presence of metabolic syndrome.

To explore a potential dose-response relationship, we performed additional Cox regression analyses in which KTRs were divided into 5 subgroups based on daily diuretic dose defined according to thiazide and loop diuretic equivalents: no diuretics, low-dose thiazide (hydrochlorothiazide ≤25 mg/day), high-dose thiazide (hydrochlorothiazide >25 mg/day), low-dose loop diuretic (furosemide ≤40 mg/day or bumetanide ≤1 mg/day) and high-dose loop diuretic (furosemide >40 mg/day or bumetanide >1 mg/day).

To confirm that our results are consistent if we only include patients which are using diuretics for a long time (≥6 months), we performed additional Cox regression analyses in which KTRs were excluded if they used diuretics less than 6 months (n=6), or if duration of exposure to diuretics was unknown (n=13).

Further investigations of the association between diuretic use and PTDM development including potential effect modification, laboratory confirmed diuretic use analyses, and
sensitivity analyses were performed using Cox proportional hazards regression analyses (see Supplementary data).

RESULTS

Characteristics of KTRs at baseline

Clinical baseline characteristics of 168 diuretic-using KTRs (n= 76 loop diuretic, n=74 thiazide, n=18 others) compared with KTRs not using a diuretic (n=318) are presented in Table 1. The median time between transplantation and study baseline was 5.4 years (IQR 1.8–12.0 years). Diuretic users were significantly older with a higher BMI, larger waist circumference, higher SBP, triglycerides, LDL-C, FPG, and HbA1c at baseline in comparison with KTRs not using diuretics. Proportion of KTRs with metabolic syndrome was also higher among diuretic users, while proportion of KTRs with pre-diabetes did not differ between the groups. The dialysis duration was longer in KTRs using diuretics, whereas the percentage of living donors and eGFR was lower in diuretic users. No differences in immunosuppressive use, use of a corticosteroid free immunosuppressive regimen, or other medication use was observed between the groups.

In addition, KTRs on diuretics had higher plasma uric acid, phosphate and serum creatinine but a lower plasma albumin. Twenty-four-hour urinary excretion of uric acid, magnesium, calcium, and phosphate was lower in KTRs who used a diuretic (Table 2).

Association between the use of any diuretic, a thiazide and a loop diuretic with incident PTDM

In total, 54 KTRs (11%) developed PTDM during a median follow-up of 5.2 years (IQR 4.1-5.8 years). Among 168 KTRs who used diuretics, 31 individuals (18%) developed PTDM, compared to 23 of 318 (7%) among non-users (p<0.001). Among 74 KTRs who used a thiazide, 10 (13%) and among 76 KTRs used a loop diuretic, 17 (22%) developed PTDM.
Kaplan-Meier curves (Figure 1) showed a prospective association of diuretic use with higher PTDM incidence (log-rank test, \( p<0.001 \)). Subsequently, we used Kaplan-Meier analyses to compare PTDM risk among KTRs who used a thiazide, used loop diuretics, other diuretics, and who did not use diuretics (Figure S1). Risk of PTDM development was significantly higher for loop diuretic users than thiazide users and for non-diuretic users (log-rank test, \( p<0.001 \)).

Furthermore, we performed Cox proportional hazard regression analyses for any diuretic use and incident PTDM. The association between any diuretic use and incident PTDM are shown in Table 3. Using a diuretic was found to be associated with a higher risk of PTDM development in crude analyses (HR, 3.15; 95 %CI, 1.84-5.42; \( p<0.001 \)). After adjustment for age, sex, FPG, and HbA1c (model 1), the association remained statistically significant (HR, 3.28; 95 %CI, 1.84-5.83; \( p<0.001 \)). Adjustment for additional variables including alcohol consumption, smoking status, physical activity, and history of cardiovascular disease (model 2), eGFR, albuminuria, CMV infection, and time after transplantation (model 3), use of lipid-lowering medication, prednisolone dose, calcineurin inhibitor, and proliferation inhibitor (model 4), plasma sodium, potassium, uric acid, calcium, phosphate, and plasma albumin (model 5), BMI, SBP, LDL cholesterol, HDL cholesterol, and triglycerides (model 6), and metabolic syndrome (model 7), did not materially change the association.

Next, we performed Cox proportional hazard regression analyses among different types of diuretic (thiazide, loop diuretic, and other diuretics) and incident PTDM (Table 3). In crude analyses, there was a statistically borderline association of use of thiazides and incident PTDM (HR, 2.10; 95 %CI, 1.00-4.41; \( p=0.050 \)). However, after adjustment for other covariates including age, sex, FPG, and HbA1c in model 1, the association reached significance (HR, 2.63; 95 %CI, 1.22-5.65; \( p=0.013 \)). In the final model adjusted for metabolic variables, and metabolic syndrome, the association remained significant (HR,
Furthermore, use of a loop diuretic was associated with PTDM development in crude analyses (HR, 4.30; 95 %CI, 2.29-8.01; p<0.001), as well as after adjusting for age, sex, FPG, HbA1c, and other covariates in models 1 to 7 (Table 3). Although use of other diuretics was associated with incident PTDM (HR, 3.90; 95 %CI, 1.35-11.31; p=0.012), the association lost statistical significance after adjustment for relevant covariates.

**Association between dosage and duration of diuretic use with incident PTDM**

Among 73 KTRs using low-dose thiazide (hydrochlorothiazide ≤25 mg/day), 10 developed PTDM. Use of low-dose thiazide diuretics was associated with a higher risk of PTDM development compared to no use of diuretics in crude and multivariable Cox proportional hazard regression analyses (Table 4). Because of low numbers (n=1), no meaningful analyses could be performed for high-dose thiazide diuretics (hydrochlorothiazide >25 mg/day).

Among 40 KTRs using low-dose loop diuretics (furosemide ≤40 mg/day or bumetanide ≤1mg/day), 8 developed PTDM and among 36 KTRs using high-dose loop diuretics (furosemide >40 mg/day or bumetanide >1mg/day), 9 developed PTDM. Both low and high dose use of loop diuretic were associated with incident PTDM in crude analyses and adjusted models (Table 4), with a lower point estimate of the HR for KTRs using low-dose loop diuretics compared to KTRs using high-dose loop diuretics.

Among 155 subjects with available data on duration of diuretic use, 149 KTRs (88%) used diuretics for ≥6 months, with a median use of 3.9 (1.8-6.8) years. The association between use of any diuretic ≥6 months with incident PTDM remained materially unchanged compared to the main results (Table 5).
Association between diuretic use with incident PTDM among men and women

To find potential effect modifications, we tested for interactions by sex, age, BMI, SBP, glucose, HbA1c, time after transplantation, eGFR, metabolic syndrome and diuretic use. We found a significant modification by sex ($p=0.032$). Next, we performed further Cox regression analyses to discern the associations between using diuretic separately in men and women with incident PTDM (Table S1). Among 278 men, 33 and among 208 women 21 individuals developed PTDM. In crude analyses, there was no significant association between diuretic use and development of PTDM in men. However, after adjustment for covariates in model 1 the association became statistically significant. Use of a diuretic was associated with incident PTDM in women both in crude analyses and adjusted models.

Association between laboratory-confirmed hydrochlorothiazide and loop diuretic use and incident PTDM

Urine metabolomics analyses yielded molecular evidence of hydrochlorothiazide use in 76 subjects and loop diuretic use in 96 subjects (90 furosemide and 6 bumetanide). In two subjects, both furosemide and hydrochlorothiazide metabolites were detected and they were excluded from the analyses. We performed Cox proportional hazard regression analyses for laboratory-confirmed diuretic use and incident PTDM (Tables S2). First, we found that laboratory-confirmed diuretic use was associated with incident PTDM after adjustment for age, sex, glucose, HbA1c and other potential confounders, including lifestyle, family history of cardiovascular disease, use of other medications, kidney function, transplantation-specific parameters, BMI, lipids, blood pressure, and metabolic syndrome. The association between laboratory-confirmed hydrochlorothiazide use and incident PTDM remained the same as our main results in crude and multivariable-adjusted analyses. Moreover, laboratory-confirmed loop diuretics use remained significantly associated with the risk of PTDM (HR, 2.99; 95
%CI, 1.63-5.49; \( p<0.001 \)). This finding remained materially unchanged in further multivariable analyses (Table S2).

**Sensitivity analyses on diuretic use and PTDM**

In sensitivity analyses with 168 diuretic users and 168 non-diuretic users matched by age and sex, the association between use of any diuretic, a thiazide and a loop diuretic with incident PTDM remained the same as our main results (Table S3).

**Other anti-hypertensive medications and PTDM**

We performed Cox proportional hazard regression analyses for other types of anti-hypertensive medications use (beta-blockers, RAAS inhibitors, ACE inhibitors, ARBs, and CCBs) and incident PTDM (Figure S2). We did not find any associations between these classes of anti-hypertensive medications and the risk for PTDM development after adjustment for age, sex, and metabolic variables (FPG, HbA1c, BMI, SBP, HDL cholesterol, LDL cholesterol, and triglycerides).

**DISCUSSION**

In this study, we demonstrated that the use of diuretics by KTRs is associated with an increased risk of long-term PTDM development. The association between diuretic use and incident PTDM remained independent of potential confounders including FPG, HbA1c, lifestyle, use of other medication such as immunosuppressive medication, kidney function, transplantation-specific parameters, BMI, lipids, and blood pressure. Both KTRs using a thiazide and a loop diuretic were at higher risk of PTDM development as compared to KTRs who not using diuretics.

Diuretic use was previously reported to be associated with an increased risk of type 2 diabetes in the general population (7,8,19,20). The effect of diuretics on incident new onset of diabetes was examined in large outcome trials. The INSIGHT (Intervention as a Goal in Hypertension Treatment) study found that the incidence of new onset of diabetes was higher in patients who
used diuretics than patients who used the calcium antagonist, nifedipine, after about 4 years of follow-up (7). In the ANBP2 (Second Australian National Blood Pressure Study) study, elderly individuals on diuretics (mainly hydrochlorothiazide) had a higher risk of developing diabetes compared with individuals on ACE inhibitors treatment (21). Thus, diuretics have a potential adverse effect on glucose metabolism and will increase the risk of new onset of diabetes especially in individuals with metabolic syndrome (22).

Metabolic alterations in KTRs are characterized by the clustering of insulin resistance, dyslipidemia and hypertension, all being risk factors of PTDM development (23–25). Because of the adverse effect of PTDM, there is a great clinical need to find modifiable factors that may pose patients at risk for developing diabetes. While current guidelines do not recommend the use of any specific class of antihypertensive agent after kidney transplantation (26), diuretics are commonly used to treat hypertension or fluid overload after transplantation in KTRs (11). In a retrospective study of 303 KTRs, diuretic use was a modifiable risk factor associated with a 2.5 times increased risk of PTDM development during the first year after transplantation in a multivariable analysis along with other variables including age, family history of diabetes, and smoking habits (27). We investigated the association between diuretic use and PTDM development in a larger KTRs population with longer follow-up and beyond the first year after transplantation. In addition, we specifically assessed two main types of diuretic (thiazide and loop diuretics) separately. In line with our findings, a high incidence of glucose intolerance in KTRs has been reported in association with furosemide treatment (28).

Apart from observational studies which demonstrated the association between diuretic use and incident new onset of diabetes, many clinical studies have investigated pathophysiological changes that occur due to reduction in insulin sensitivity (IS), secondary to diuretic-induced hypokalemia (8–10). While elevated free fatty acid levels and enhanced hepatic glucose production could be other possible mechanisms resulting in thiazide-induced hyperglycemia
(29,30), reduction of glucose phosphorylation and glycolysis rates in muscle tissue, as well as inhibition of glucose transport in adipose tissue may explain the furosemide-induced hyperglycemia (31). Although it was found that the risk of developing potassium disturbances is increased by use of thiazides in KTRs in the short term, the association between thiazide and development of hyperglycemia has not been studied previously (32). In addition, diuretics can cause hyperuricemia and hypomagnesaemia which were found to be associated with increased risk of new onset of diabetes both in the general population and in KTRs (33–36). Although serum uric acid was higher in KTRs using diuretics, we could not find any indirect effect of serum uric acid, serum magnesium or serum potassium on the development of PTDM elicited by using diuretics. Thus, we were not able to conclude causality on these potential pathways in the current study. Interventional studies are required to compare the effect of antihypertensive agents on glucose hemostasis.

Diuretic dose and duration of treatment may affect the incidence of drug-induced hyperglycemia (7,8,20). We observed a higher risk of PTDM development in KTRs using high-dose loop diuretic compared to KTRs using low-dose diuretics, which is consistent with a dose-effect relationship. Our findings were consistent for KTRs with ≥6 months diuretic exposure. Because of low numbers of KTRs using diuretics for <6 months, we were unable to perform meaningful analyses for exposure of shorter duration.

The association between diuretic use and incident PTDM was stronger in women than in men. This could be the consequence of sex-related differences in pharmacokinetics and pharmacodynamics of diuretics. Since female sex is a risk factor for adverse effects including hypokalemia and hyperglycemia because of lower distribution volume, higher activity of hepatic CYP3A4, and presence of sex hormones (37).
The agreement between subjective self-reported drug use and objective laboratory-obtained information (metabolomics) was good (82% and 92% for thiazide and loop diuretic respectively). The slight disagreement can likely be explained by recall bias for self-reported data (38) and analytical bias for metabolomics data (13). Still, although the concept of providing molecular evidence of drug use is not commonly used, we were able to use metabolomics to confirm our finding of an association with development of PTDM, thereby strengthening our main results which relied on self-reported information.

While the effect of other antihypertensive medications on glycemic control and incident type 2 diabetes have been investigated in previous epidemiological studies in the general population, we also took into account the association between other types of antihypertensive drugs and incident PTDM in further analyses. The broad conclusion of previous studies is that beta-blockers may increase risk of incident of type 2 diabetes, while ACE inhibitors, ARBs, and CCBs have neutral or beneficial effects on glycemic control and incident type 2 diabetes (3,4,6). Similarly, we did not find any significant association between ACE inhibitors, ARBs, and CCBs, but we also found no association for use of beta-blockers with PTDM in the KTRs studied.

Our study was carried out in a relative large population of stable KTRs in which the endpoint evaluation was completed after 5.2 years of follow-up. KTRs with transient posttransplantation hyperglycemia were excluded from our study by including only KTRs with a functioning graft more than 1 year after transplantation. This study was an observational study in which contribution of casualty could not be explained in the current study.

In conclusion, diuretic use is associated with an increased risk of developing PTDM during long-term in KTRs, independently of several established risk factors for PTDM development.
including metabolic factors, lifestyle, immunosuppressive therapy, kidney function, and transplantation-specific, electrolytes parameters. Moreover, the association was consistent for both thiazide (low-dose) and loop diuretics (both low and high dose). Although future interventional studies are needed to confirm causality, these results call for careful evaluation of the necessity of diuretics use in KTRs.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS

S.S. and S.J.L.B drafted the manuscript. S.S. and S.J.L.B researched the literature. S.S, S.C.T, and S.J.L.B contributed to the statistical analysis. S.S, F.K, D.M, R.M.D, G.H, and S.J.L.B collected the epidemiological and clinical data. H.J.L.H and S.J.L.B contribute to funding acquisition. R.P.F.D, H.J.L.H, and S.J.L.B supervised the study. S.S, F.K, S.C.T, D.M, R.M.D, G.H, R.P.F.D, H.J.L.H, and S.J.L.B writing, reviewing, and editing. All authors read and approved the final version of the manuscript.

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Table 1. Baseline clinical and laboratory characteristics of 318 KTRs did not use a diuretic and 168 KTRs who used a diuretic

| Variables                                      | Use diuretics | P value  |
|-----------------------------------------------|---------------|----------|
| **Participants, n**                           | 168           | 318      |
| **General characteristics**                   |               |          |
| Men, %                                        | 56.5          | 57.5     | 0.848    |
| **Age, year**                                 | 55.0±11.5     | 49.8±13.6| <0.001   |
| **Current smoker, %**                         | 16.7          | 11.8     | 0.156    |
| **Alcohol use, never, %**                     | 10.4          | 10.4     | 1.000    |
| **Physical activity score, time×intensity**   | 5730 (2205-91912) | 5565 (3235-8347) | 0.985   |
| **Weight, kg**                                | 81.4±16.0     | 77.6±15.5| 0.012    |
| **Height, cm**                                | 173.9±9.1     | 174.1±9.9| 0.871    |
| **BMI, kg/m²**                                | 226.8±4.6     | 25.5±4.3 | 0.002    |
| **Waist circumference, cm**                   | 99.5±13.8     | 94.9±14.1| 0.001    |
| **Transplant demographics**                   |               |          |
| **Time since renal transplantation, y**       | 5.8 (2.4-13.7) | 5.1 (1.7-11.1) | 0.220   |
| **Donor age, y**                              | 42.9±15.2     | 42.8±15.6| 0.976    |
| **Living donor, %**                           | 28.6          | 39.3     | 0.022    |
| **Dialysis duration, months**                 | 32 (13-62)    | 24 (6-48) | 0.003    |
| **Delayed graft function, %**                 | 7.7           | 5.7      | 0.435    |
| **Rejection, %**                              | 28.0          | 22.6     | 0.222    |
| **Blood pressure**                            |               |          |
| **Systolic blood pressure, mmHg**             | 138.2±18.5    | 134.2±16.2| 0.020   |
| **Distolic blood pressure, mmHg**             | 84.2±10.5     | 82.4±11.2| 0.079    |
| **Lipids**                                    |               |          |
| **Total cholesterol, mmol/L**                 | 5.3 (4.4-6.0) | 4.9 (4.3-5.6) | 0.007   |
| **LDL cholesterol, mmol/L**                   | 3.0 (2.5-3.6) | 2.8 (2.3-3.4) | 0.014   |
| **HDL cholesterol, mmol/L**                   | 1.3 (1.1-1.7) | 1.3 (1.1-1.7) | 0.004   |
| **Triglycerides, mmol/L**                     | 1.8 (1.3-2.4) | 1.5 (1.1-2.0) | 0.001   |
| **Hypertension, %**                           |               |          |
| **Glucose Homeostasis**                       |               |          |
| **Glucose, mmol/L**                           | 5.2±0.6       | 5.1±0.6  | 0.029    |
| **HbA1c, %**                                  | 5.7±0.3       | 5.6±0.4  | 0.003    |
| **Pre-diabetes, %**                           | 26.3          | 21.2     | 0.201    |
| **Metabolic syndrome, %**                     | 63.1          | 35.7     | 0.010    |
| **Hs-CRP, mg/L**                              | 1.4 (0.7-4.8) | 1.4 (0.6-3.4) | 0.240   |
| **Renal function**                            |               |          |
| **eGFR, mL/min per 1.73 m²**                  | 37.1 (24.6-52.6) | 48.4 (36.4-61.6) | <0.001  |
| **CMV infection, %**                          | 28.2          | 25.9     | 0.645    |
| **Medication use**                            |               |          |
| **Statin use, %**                             | 53.0          | 48.1     | 0.340    |
| **Anti-hypertensive medication, %**           | 100           | 79.6     | <0.001   |
| **Prednisolone, mg/day**                      | 8.7±2.1       | 8.8±1.8  | 0.491    |
| **Corticosteroids free regimen, %**           | 1.2           | 0.3      | 0.275    |
| **Calcineurin inhibitor, %**                  | 60.1          | 52.8     | 0.126    |
| **Cyclosporine, %**                           | 41.1          | 36.5     |          |
| **Tacrolimus, %**                             | 19.6          | 16.4     |          |
| **Proliferation inhibitor, %**                | 81.5          | 86.2     | 0.189    |
| **Azathioprine, %**                           | 25.0          | 15.4     |          |
| **Myco phenolic acid, %**                     | 56.5          | 70.8     |          |

Data are the mean±SD, median (interquartile range) unless otherwise indicated. Significance was tested by t-tests and Wilcoxon tests where appropriate.

KTR: Renal transplant recipients; BMI: Body mass index; hsCRP: high sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; CMV: Cytomegalo virus.
Table 2. Plasma and urinary biochemical measurements Baseline characteristics of 318 KTRs who did not use a diuretic and 168 KTRs who used a diuretic

| Variables          | Use diuretics | P value |
|--------------------|---------------|---------|
| Participants, n    | Yes           | No      |
| Sodium, mmol/L     | 140.6±3.1     | 141.1±2.6 | 0.080 |
| Potassium, mmol/L  | 3.9±0.5       | 3.9±0.4  | 0.290 |
| Uric acid, mmol/L  | 0.5 (0.4-0.6) | 0.4 (0.3-0.5) | <0.001 |
| Magnesium, mmol/L  | 0.8±0.1       | 0.8±0.1  | 0.171 |
| Calcium, mmol/L    | 2.4±0.1       | 2.4±0.1  | 0.072 |
| Phosphate, mmol/L  | 1.0±0.2       | 0.9±0.2  | 0.032 |
| Albumin, g/L       | 42.4±3.2      | 43.7±2.7 | <0.001 |
| Creatinine, µmol/L | 137.0 (107.0-181.0) | 117.5 (98.0-148.7) | <0.001 |

Urinary excretion of

| Variables          | Use diuretics | P value |
|--------------------|---------------|---------|
| Sodium, mmol/24h   | 147 (116-192) | 144 (113-187) | 0.645 |
| Potassium, mmol/24h| 69.9 (54.4-90.9) | 71.4 (55.6-87.2) | 0.945 |
| Uric acid, mmol/24h| 2.3 (1.8-2.9) | 2.6 (2.1-3.3) | <0.001 |
| Magnesium, mmol/24h| 3.0 (2.2-4.3) | 3.4 (2.4-4.5) | 0.042 |
| Calcium , mmol/24h | 1.9 (0.8-3.5) | 2.5 (1.2-4.1) | 0.011 |
| Phosphate, mmol/24h| 22.7 (17.4-30.4) | 25.2 (19.6-31.2) | 0.028 |
| Albumin, mg/24 h   | 43.7 (10.7-242.3) | 30.2 (8.4-119.2) | 0.055 |
| Creatinin, mmol/24h| 11.7±3.6      | 11.9±3.1  | 0.514 |
| Urinary volume     | 2463 (1991-2849) | 2403 (1836-2863) | 0.373 |

Data are the mean±SD, median (interquartile range) unless otherwise indicated. Significance was tested by t-tests and Wilcoxon tests where appropriate.

KTRs: Renal transplant recipients.
Table 3. Association of Diuretic use, Thiazide use and Loop diuretic use with PTDM development

|                      | No diuretic | Diuretic |
|----------------------|-------------|----------|
| Number of events/participants | 23/318      | 31/168   |
| HR (95%CI)           |             |          |
| Crude analysis       | 1.00 (Ref)  | 3.15 (1.84-5.42) | <0.001 |
| Model 1              | 1.00 (Ref)  | 3.28 (1.84-5.83)  | <0.001 |
| Model 2              | 1.00 (Ref)  | 2.77 (1.50-5.12)  | 0.001  |
| Model 3              | 1.00 (Ref)  | 2.62 (1.42-4.82)  | 0.002  |
| Model 4              | 1.00 (Ref)  | 3.26 (1.81-5.84)  | <0.001 |
| Model 5              | 1.00 (Ref)  | 2.98 (1.50-5.90)  | 0.002  |
| Model 6              | 1.00 (Ref)  | 2.86 (1.57-5.21)  | 0.001  |
| Model 7              | 1.00 (Ref)  | 3.09 (1.73-5.50)  | <0.001 |

|                      | Thiazide | Loop diuretic | Other diuretics |
|----------------------|----------|---------------|-----------------|
| Number of events/participants | 23/318 | 10/74 | 17/76 |
| HR (95%CI) P value     | 2.10 (1.00-4.42) 0.050 | 4.30 (2.29-8.01) <0.001 | 3.90 (1.35-11.31) 0.012 |
| Model 1               | 2.63 (1.22-5.65) 0.013 | 4.49 (2.24-8.99) <0.001 | 2.35 (0.78-7.08) 0.128 |
| Model 2               | 2.07 (0.90-4.79) 0.086 | 4.34 (2.05-9.18) <0.001 | 1.70 (0.47-6.18) 0.419 |
| Model 3               | 2.53 (1.05-6.10) 0.038 | 3.89 (1.87-8.08) <0.001 | 1.49 (0.41-5.44) 0.547 |
| Model 4               | 2.84 (1.30-6.22) 0.009 | 4.10 (2.02-8.31) <0.001 | 2.36 (0.78-7.18) 0.129 |
| Model 5               | 2.34 (0.99-5.55) 0.054 | 4.09 (1.84-9.07) 0.001 | 1.92 (0.47-7.83) 0.365 |
| Model 6               | 2.61 (1.20-5.67) 0.015 | 3.98 (1.94-8.19) <0.001 | 1.36 (0.36-5.13) 0.650 |
| Model 7               | 2.56 (1.17-5.61) 0.018 | 5.21 (2/54-10.70) <0.001 | 1.98 (0.64-6.10) 0.236 |

HRs (95% CIs) were derived from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, fasting plasma glucose, and HbA1c. Model 2 was adjusted for model 1 variables, and alcohol consumption, smoking, and physical activity, history of cardiovascular disease; Model 3 was adjusted for model 1 variables and eGFR, urinary albumin excretion, CMV infection, time after transplantation; Model 4 was adjusted for model 1 variables and treatment (lipid-lowering medication, prednisolone dose, calcineurin inhibitors, and proliferation inhibitors); Model 5 was adjusted for model 1 variables, and plasma sodium, potassium, uric acid, calcium, phosphate, and albumin; Model 6 was adjusted for model 1 variables and BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, and triglycerides; Model 7 was adjusted for model 1 and metabolic syndrome.

PTDM: Post transplantation diabetes; eGFR: estimated glomerular filtration rate; CMV: Cytomegalo virus; BMI: Body mass index.
Table 4. Association of diuretic dosage and PTDM development

|                     | No diuretic |                                           | Thiazide                        |                                           | Loop diuretic                       |
|---------------------|-------------|--------------------------------------------|----------------------------------|------------------------------------------|-------------------------------------|
|                     |             | Low-dose | High-dose | P value | Low-dose | High-dose | P value |
| Number of           |             | 23/318  | 10/73    | 0/1     | 8/40     | 9/36      |         |
| participants/events |             |          |          |         |          |          |         |
| Crude analysis      | 1.00 (Ref)  | 2.13 (1.01-4.48) | 0.046 | -       | 3.44 (1.53-7.73) | 0.003 | 5.74 (2.64-12.49) | <0.001 |
| Model 1             | 1.00 (Ref)  | 2.71 (1.24-5.93) | 0.012 | -       | 3.61 (1.44-9.06) | 0.006 | 9.28 (3.88-22.20) | <0.001 |
| Model 2             | 1.00 (Ref)  | 2.46 (1.04-5.83) | 0.041 | -       | 2.46 (0.82-7.33) | 0.110 | 9.74 (3.99-23.74) | <0.001 |
| Model 3             | 1.00 (Ref)  | 2.53 (1.06-6.02) | 0.037 | -       | 2.64 (1.02-6.96) | 0.041 | 7.59 (3.07-18.74) | <0.001 |
| Model 4             | 1.00 (Ref)  | 3.16 (1.39-7.18) | 0.006 | -       | 3.12 (1.19-8.23) | 0.021 | 8.57 (3.58-20.52) | <0.001 |
| Model 5             | 1.00 (Ref)  | 2.49 (0.93-6.55) | 0.070 | -       | 2.92 (0.99-8.81) | 0.059 | 9.02 (3.17-25.68) | <0.001 |
| Model 6             | 1.00 (Ref)  | 2.81 (1.26-6.28) | 0.012 | -       | 3.42 (1.31-8.94) | 0.012 | 10.24 (3.80-27.60) | <0.001 |
| Model 7             | 1.00 (Ref)  | 2.56 (1.17-5.61) | 0.018 | -       | 4.07 (1.56-10.59) | 0.004 | 8.27 (3.42-20.01) | <0.001 |

HRs (95% CIs) were derived from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, fasting plasma glucose, and HbA1c. Model 2 was adjusted for model 1 variables, and alcohol consumption, smoking, and physical activity, history of cardiovascular disease; Model 3 was adjusted for model 1 variables and eGFR, urinary albumin excretion, CMV infection, time after transplantation; Model 4 was adjusted for model 1 variables and treatment (lipid-lowering medication, prednisolone dose, calcineurin inhibitors, and proliferation inhibitors); Model 5 was adjusted for model 1 variables and plasma sodium, potassium, uric acid, calcium, phosphate, and albumin; Model 6 was adjusted for model 1 variables and BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, and triglycerides; Model 7 was adjusted for model 1 and metabolic syndrome.

low-dose thiazide: hydrochlorothiazide ≤25 mg/day; high-dose thiazide: hydrochlorothiazide >25 mg/day; low-dose loop diuretic: furosemide ≤40 mg/day or bumetanide ≤1mg/day; high-dose loop diuretic: furosemide >40 mg/day or bumetanide >1mg/day.

eGFR: estimated glomerular filtration rate; CMV: Cytomegalovirus; BMI: Body mass index.
| Number of participants/events | No diuretic | Diuretic use before the baseline | P value |
|-------------------------------|------------|---------------------------------|---------|
|                               | 23/318     | 26/149                          |         |

**Crude analysis**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.93 (1.67-5.15)  
- P value: <0.001  

**Model 1**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.94 (1.61-6.37)  
- P value: <0.001  

**Model 2**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.53 (1.34-4.78)  
- P value: 0.004  

**Model 3**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.30 (1.21-4.36)  
- P value: 0.011  

**Model 4**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.96 (1.60-5.46)  
- P value: 0.001  

**Model 5**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.27 (1.09-4.70)  
- P value: 0.028  

**Model 6**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.59 (1.38-4.85)  
- P value: 0.003  

**Model 7**  
- HR: 1.00 (Ref)  
- Diuretic use: 2.76 (1.51-5.05)  
- P value: 0.001

HRs (95% CIs) were derived from Cox proportional hazard models. Multivariable model 1 was adjusted for age, sex, fasting plasma glucose, and HbA1c. Model 2 was adjusted for model 1 variables, and alcohol consumption, smoking, and physical activity, history of cardiovascular disease; Model 3 was adjusted for model 1 variables and eGFR, urinary albumin excretion, CMV infection, time after transplantation; Model 4 was adjusted for model 1 variables and treatment (lipid-lowering medication, prednisolone dose, calcineurin inhibitors, and proliferation inhibitors); Model 5 was adjusted for model 1 variables, and plasma sodium, potassium, uric acid, calcium, phosphate, and albumin; Model 6 was adjusted for model 1 variables and BMI, systolic blood pressure, LDL cholesterol, HDL cholesterol, and triglycerides; Model 7 was adjusted for model 1 and metabolic syndrome.

eGFR: estimated glomerular filtration rate; CMV: Cytomegalovirus; BMI: Body mass index.
Figure 1. Kaplan-Meier curves depicting PTDM incident according to diuretic users (n=186) to non-diuretic users (n=318). PTDM: Post transplantation diabetes.