

Kidney Function and Glycemic Control in Pretransplant versus Post-Transplant Diabetes: A Long-Term Study of Predominantly Non-Kidney Solid-Organ Transplant Recipients

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Abstract

Background

Diabetes contributes substantially to long-term morbidity after solid-organ transplantation, but comparisons of kidney function and glycemic control between pretransplant diabetes mellitus (PDM) and post-transplant diabetes mellitus (PTDM) remain limited.

Methods

This single-center retrospective cross-sectional study included 113 solid-organ transplant recipients with diabetes evaluated between May 2017 and May 2026. Kidney function, glycemic control, albuminuria, and treatment patterns were assessed. The primary analysis compared PDM with PTDM; comparisons of early- versus late-onset PTDM and sodium-glucose cotransporter 2 (SGLT2) inhibitor users versus non-users were exploratory. Multivariable linear regression models evaluated estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), and glycated hemoglobin (HbA1c), with adjustment for clinical and treatment variables.

Results

The cohort included liver (51.3%), kidney (36.3%), and heart (12.4%) transplant recipients; 61.6% had PTDM. Mean time since transplantation was 10.73 ± 7.60 years, mean eGFR was 60.77 ± 28.39 mL/min/1.73 m², and mean HbA1c was $7.40 \pm 1.84\%$; 53.2% had HbA1c > 7%. Compared with PTDM, patients with PDM were older (62.37 ± 10.71 vs. 57.80 ± 11.76 years; $P = 0.041$), had shorter time since transplantation (6.98 ± 5.78 vs. 13.07 ± 7.69 years; $P < 0.001$), and lower eGFR (53.06 ± 21.82 vs. 65.78 ± 31.02 mL/min/1.73 m²; $P = 0.024$), while glycemic control was similar. After multivariable adjustment, the eGFR difference was no longer significant (adjusted difference 8.6 mL/min/1.73 m² higher in PTDM; 95% CI - 3.8 to 21.0; $P = 0.170$). Albuminuria (UACR ≥ 30 mg/g) was present in 45.9% of 98 patients with available measurements. Median UACR was higher in PTDM than PDM (28.1 vs. 19.5 mg/g; $P = 0.037$), and LDL cholesterol was independently associated with UACR ($\beta = 0.072$ log₁₀ mg/g per 10 mg/dL; 95% CI 0.031–0.113; $P < 0.001$). Early- and late-onset PTDM had similar kidney function and glycemic control; SGLT2 inhibitor comparisons were nonsignificant after multiplicity adjustment. Only 40% of patients with albuminuria were receiving an SGLT2 inhibitor.

Conclusions

Long-term solid-organ transplant recipients with diabetes showed substantial kidney dysfunction and suboptimal glycemic control. Kidney dysfunction was frequently non-albuminuric, whereas albuminuria

identified a distinct high-risk subgroup with limited use of cardiorenal-protective therapy. Prospective studies are needed to define longitudinal outcomes and the role of newer glucose-lowering therapies.

BACKGROUND

Diabetes mellitus is a common and clinically consequential condition in solid-organ transplant recipients. Hyperglycemia may be present before transplantation as pretransplant diabetes mellitus (PDM) or may develop after transplantation as post-transplant diabetes mellitus (PTDM). Both conditions are associated with increased risks of cardiovascular disease, infection, hospitalization, graft dysfunction, and mortality, making long-term metabolic care an integral component of transplant follow-up [1–4].

The pathophysiology of post-transplant hyperglycemia is multifactorial. Calcineurin inhibitors, particularly tacrolimus, impair pancreatic beta-cell function and insulin secretion, whereas glucocorticoids increase hepatic glucose production, reduce peripheral glucose uptake, and promote weight gain and insulin resistance [1, 3, 5, 6]. Surgical stress, systemic inflammation, infections, changes in body composition, and pre-existing susceptibility to type 2 diabetes further contribute to dysglycemia. Consequently, PTDM may arise from a variable combination of beta-cell toxicity and insulin resistance, while recipients with PDM may experience worsening glycemic control after transplantation because of the same exposures [1–6].

Kidney dysfunction is also frequent after solid-organ transplantation and may reflect the combined effects of diabetes, aging, perioperative kidney injury, infection, hypertension, and chronic exposure to nephrotoxic immunosuppressive agents. Diabetic kidney disease is characterized by albuminuria and progressive loss of glomerular filtration, whereas calcineurin-inhibitor nephrotoxicity involves vascular, tubulointerstitial, and glomerular injury [7–9]. Importantly, chronic kidney disease is not confined to kidney transplant recipients; clinically relevant reductions in kidney function are also common after transplantation of nonrenal organs [10].

Despite the prognostic importance of hyperglycemia and kidney dysfunction, several uncertainties remain. Most studies have focused on the incidence and early course of PTDM, kidney transplant populations, or outcomes associated with PDM and PTDM separately. Direct comparisons of long-term glycemic control and kidney function between PDM and PTDM are scarce, particularly in cohorts predominantly composed of liver and heart transplant recipients. It also remains unclear whether the timing of PTDM onset retains clinical relevance after many years of follow-up and how newer cardiorenal-protective glucose-lowering therapies are used in routine transplant care. This study therefore compared kidney function and glycemic control between patients with PDM and PTDM in a long-term, single-center cohort of solid-organ transplant recipients, most of whom had received non-kidney transplants. Secondary analyses compared early- and late-onset PTDM and characterized recipients treated with SGLT2 inhibitors.

METHODS

Study design and setting

This single-center, retrospective, cross-sectional study was conducted at the transplant outpatient clinic of the Endocrinology Service, Federal University of Minas Gerais, Belo Horizonte, Brazil. The medical records of all potentially eligible adult solid-organ transplant recipients with diabetes who attended the clinic were reviewed; for each patient, the most recent outpatient visit with available laboratory data (index visit; May 2017 to May 2026) was used for analysis

Study population

Patients were eligible if they were 18 years or older, had undergone solid-organ transplantation, and had been diagnosed with diabetes mellitus either before or after transplantation. Recipients of simultaneous pancreas-kidney transplantation and recipients of hematopoietic stem-cell (bone-marrow) transplantation were excluded. Patients whose medical records lacked information on specific variables were excluded from the corresponding analyses.

Data collection and study variables

Data were obtained through a standardized retrospective review of medical records. The variables assessed were sex, age, transplanted organ, date of transplantation, time since transplantation, timing of diabetes diagnosis in relation to transplantation, duration of diabetes, interval between transplantation and PTDM diagnosis, current glucose-lowering therapy, most recent HbA1c measurement, body mass index (BMI), serum creatinine, eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, urinary albumin-to-creatinine ratio (UACR), lipid profile (total, LDL and HDL cholesterol and triglycerides), statin use, and current immunosuppressive therapy, including glucocorticoids, tacrolimus, everolimus, sirolimus, cyclosporine, and mycophenolate. Age, time since transplantation, and duration of diabetes were computed at the index visit.

Exposure to immunosuppressive therapy

Exposure to each immunosuppressive agent was defined as documented use throughout at least two consecutive outpatient follow-up intervals. Because visits were generally scheduled at 3-month intervals, this definition corresponded to an estimated minimum exposure of approximately 6 months.

Definitions and study groups

Patients were classified as having PDM or PTDM. PDM was defined as diabetes diagnosed before transplantation. PTDM was defined as newly diagnosed diabetes after transplantation in individuals

without documented diabetes before transplantation.

PTDM was diagnosed at least 3 months after transplantation when either of the following criteria was met: fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L) on two separate occasions or a 2-h plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test. After the first post-transplant year, an HbA1c level $\geq 6.5\%$ (48 mmol/mol) was also accepted as a diagnostic criterion for PTDM.

The PTDM group was further stratified according to the timing of diagnosis. Early-onset PTDM was defined as PTDM diagnosed within the first year after transplantation, whereas late-onset PTDM was defined as PTDM diagnosed more than 1 year after transplantation.

Kidney function was categorized by eGFR according to KDIGO (G1 ≥ 90 , G2 60–89, G3a 45–59, G3b 30–44, G4 15–29, and G5 < 15 mL/min/1.73 m²). Albuminuria was assessed by the UACR in a spot urine sample obtained closest to the index visit and categorized as A1 (< 30 mg/g), A2 (30–299 mg/g), or A3 (≥ 300 mg/g); albuminuria was defined as UACR ≥ 30 mg/g. When only 24-h urinary albumin excretion ($n = 2$) or a protein-to-creatinine ratio ($n = 2$) was available, the KDIGO-equivalent category was assigned. Patients were also classified into KDIGO risk categories (low, moderate, high, or very high) by combining eGFR and albuminuria categories.

Statistical analysis

Records were deduplicated by patient before analysis. Age, time since transplantation, and duration of diabetes were computed at the index visit. Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables as absolute frequencies and percentages, according to data availability. The comparison between patients with PDM and PTDM was the primary analysis; comparisons between early- and late-onset PTDM and between SGLT2 inhibitor users and non-users were exploratory and hypothesis-generating. Continuous variables were compared using the independent-samples Student *t* test (with the Welch correction when variances were unequal). Because UACR was markedly right-skewed, it is reported as median [interquartile range] and was compared using the Mann–Whitney *U* or Kruskal–Wallis test; correlations between UACR and continuous variables were assessed with Spearman's coefficient. Categorical variables were compared using the Pearson chi-square test or Fisher exact test, as appropriate. Because of the number of comparisons, *P* values adjusted within each table by the Holm procedure (family-wise error rate) and by the Benjamini–Hochberg procedure (false discovery rate) are reported alongside unadjusted values, and only differences that remained significant after Holm adjustment were interpreted as findings. Multivariable linear regression models were fitted for eGFR (primary model), log₁₀(UACR + 1), and HbA1c, with age, sex, diabetes group, time since transplantation, transplanted organ, BMI, and glucose-lowering and immunosuppressive therapy as covariates; full model specifications, coefficients, and diagnostics are given in Supplementary Table S1. The univariable comparisons between patients with and without albuminuria are presented in the Supplementary Material. Missing observations were excluded from the

corresponding analysis. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using Python 3.12 (pandas, SciPy 1.18, and statsmodels 0.14).

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the study population are summarized in Table 1. A total of 113 patients were included. Mean age at the index visit was 59.26 ± 11.91 years, mean BMI was 27.75 ± 5.23 kg/m², and 66.1% of participants were male. Liver transplantation was the most common procedure, accounting for 51.3% of the cohort, followed by kidney transplantation (36.3%) and heart transplantation (12.4%).

Mean time since transplantation was 10.73 ± 7.60 years. Mean eGFR was 60.77 ± 28.39 mL/min/1.73 m², and 49.5% of participants were in eGFR categories G3-G5. Mean HbA1c was $7.40 \pm 1.84\%$, and 53.2% of participants had an HbA1c level $> 7\%$. Insulin was used by 76.1% of participants, metformin by 54.0%, SGLT2 inhibitors by 31.0%, sulfonylureas by 8.0%, and DPP-4 inhibitors by 4.4%. Tacrolimus was used by 70.8%, corticosteroids by 47.8%, cyclosporine by 14.2%, sirolimus by 6.2%, and statins by 67.3%. UACR was available for 98 patients (86.7%): median UACR was 24.4 mg/g [interquartile range 8.1–143.7], and 54.1%, 32.7%, and 13.3% of these patients were in albuminuria categories A1, A2, and A3, respectively. Mean LDL cholesterol was 82.34 ± 54.45 mg/dL.

Table 1. Baseline characteristics of the study population	
Characteristic	Value
Age, years	59.26 ± 11.91
Sex, %	
Male	66.1
Female	33.9
BMI, kg/m ²	27.75 ± 5.23
Transplanted organ, %	
Heart	12.4
Kidney	36.3
Liver	51.3
Time since transplantation, years	10.73 ± 7.60
eGFR, mL/min/1.73 m ²	60.77 ± 28.39
CKD category, %	
G1	15.6
G2	34.9
G3a	18.3
G3b	20.2
G4	4.6
G5	6.4
UACR, mg/g, median [IQR]	24.4 [8.1–143.7]
Albuminuria category, %	
A1	54.1
A2	32.7
A3	13.3
CKD by KDIGO criteria, % (n = 95 with both measurements)	
No CKD (G1–G2 and A1)	27.4
CKD (G3–G5 and/or A2–A3)	72.6
of which: reduced eGFR only (G3–G5 and A1)	27.4

Table 1. Baseline characteristics of the study population	
Characteristic	Value
albuminuria only (G1–G2 and A2–A3)	22.1
both (G3–G5 and A2–A3)	23.2
HbA1c, %	7.40 ± 1.84
HbA1c, ≤ 7%	46.8%
HbA1c, > 7%	53.2%
Glucose-lowering therapy, %	
Insulin	76.1
Metformin	54.0
Sulfonylureas	8.0
DPP-4 inhibitors	4.4
SGLT2 inhibitors	31.0
Other pharmacological therapies, %	
Glucocorticoids	47.8
Tacrolimus	70.8
Sirolimus	6.2
Cyclosporine	14.2
Statins	67.3
LDL cholesterol, mg/dL	82.34 ± 54.45
Triglycerides, mg/dL	174.79 ± 145.58

BMI, body mass index; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PDM, pre-existing diabetes mellitus; PTDM, post-transplant diabetes mellitus; SGLT2, sodium–glucose cotransporter 2.

Comparison between patients with PDM and PTDM

The clinical and transplant-related characteristics of patients with PDM and PTDM are presented in Table 2. Regarding diabetes-group classification, data were available for 112 participants due to one missing value: 43 (38.4%) had PDM and 69 (61.6%) had PTDM.

Patients with PDM were older than those with PTDM (62.37 ± 10.71 vs. 57.80 ± 11.76 years; $P = 0.041$), had a shorter time since transplantation (6.98 ± 5.78 vs. 13.07 ± 7.69 years; $P < 0.001$), and had lower mean eGFR (53.06 ± 21.82 vs. 65.78 ± 31.02 mL/min/1.73 m²; $P = 0.024$) and a higher proportion in eGFR categories G3-G5 (68.3% vs. 37.3%; $P = 0.002$). After Holm adjustment for the comparisons in Table 2, the differences in time since transplantation (adjusted $P < 0.001$) and in the proportion in eGFR categories G3-G5 (adjusted $P = 0.038$) remained significant, whereas the differences in age and mean eGFR did not (adjusted $P = 0.656$ and 0.432).

No significant between-group differences were observed in sex distribution, BMI, transplanted organ, HbA1c, or the use of insulin, metformin, sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, statins, tacrolimus, cyclosporine, sirolimus, or corticosteroids.

Table 2
Comparison of clinical characteristics between the PDM and PTDM groups

Characteristic	PDM	PTDM	P value	Holm-adjusted P	BH-adjusted P
<i>n</i>	43	69			
Age, years	62.37 ± 10.71	57.80 ± 11.76	0.041	0.656	0.164
Sex, % Male	69.0	63.8	0.570	1.000	0.746
Female	31.0	36.2			
BMI, kg/m ²	27.01 ± 4.55	27.88 ± 4.96	0.389	1.000	0.707
Transplanted organ, %	32.6	37.7	0.839	1.000	0.839
Kidney					
Heart	14.0	11.6			
Liver	53.5	50.7			
Time since transplantation, years	6.98 ± 5.78	13.07 ± 7.69	< 0.001	< 0.001	< 0.001
eGFR, mL/min/1.73 m ²	53.06 ± 21.82	65.78 ± 31.02	0.024	0.432	0.160
UACR, mg/g, median [IQR]	19.5 [4.8–52.4]	28.1 [11.0–223.3]	0.037	0.628	0.164
Albuminuria (A2–A3), %	42.1	48.3	0.547	1.000	0.746
HbA1c, %	7.35 ± 1.56	7.44 ± 2.01	0.796	1.000	0.838
Insulin use, %	83.7	72.5	0.170	1.000	0.429
SGLT2 inhibitor use, %	34.9	29.0	0.512	1.000	0.746
Tacrolimus use, %	74.4	68.1	0.477	1.000	0.746
Cyclosporine use, %	16.3	13.0	0.634	1.000	0.746
Sirolimus use, %	4.7	7.2	0.706	1.000	0.784
Corticosteroid use, %	39.5	52.2	0.193	1.000	0.429
Metformin use, %	46.5	59.4	0.182	1.000	0.429
Sulfonylurea use, %	2.3	10.1	0.150	1.000	0.429
DPP-4 inhibitor use, %	7.0	2.9	0.370	1.000	0.707

Characteristic	PDM	PTDM	P value	Holm-adjusted P	BH-adjusted P
Statin use, %	69.8	65.2	0.619	1.000	0.746

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PDM, pre-existing diabetes mellitus; PTDM, post-transplant diabetes mellitus; SGLT2, sodium–glucose cotransporter 2. The last two columns present P values adjusted within the table by the Holm and Benjamini–Hochberg (BH) procedures (20 comparisons, including the comparison of eGFR categories G3-G5 reported in the text). UACR was compared with the Mann–Whitney U test; 20 comparisons were included in the Holm and BH adjustments.

Comparison between early- and late-onset PTDM

The characteristics of patients with early- and late-onset PTDM are presented in Table 3. Among the 65 patients with precise information on the timing of PTDM diagnosis, 30 developed PTDM within the first year after transplantation and 35 developed PTDM more than 1 year after transplantation. Four patients were excluded from this analysis because the timing of PTDM diagnosis was not precisely documented.

The distribution of transplanted organs differed at the threshold of statistical significance ($P = 0.050$): heart transplantation was more frequent in early-onset PTDM than in late-onset PTDM (23.3% vs. 2.9%), whereas kidney and liver transplantation were proportionally more frequent in the late-onset group. Time since diabetes diagnosis tended to be longer in the early-onset group (10.34 ± 6.87 vs. 7.86 ± 4.91 years; $P = 0.097$), whereas time since transplantation was shorter (10.20 ± 6.80 vs. 16.20 ± 7.54 years; $P = 0.001$). After Holm adjustment, only the difference in time since transplantation remained significant (adjusted $P = 0.021$).

In this exploratory comparison, no significant differences were observed in age, sex distribution, BMI, eGFR, the proportion of patients in eGFR categories G3-G5, HbA1c, or the evaluated glucose-lowering, immunosuppressive, and statin therapies, although male sex (76.7% vs. 57.1%; $P = 0.097$) and metformin use (50.0% vs. 71.4%; $P = 0.077$) showed non-significant trends.

Table 3

Comparison of characteristics between early- and late-onset PTDM groups* Characteristic Early PTDM
(n = 30) Late PTDM (n = 35) P value

Age, years	57.07 ± 11.29	58.26 ± 12.74	0.694	1.000	0.921
Sex, n (%)			0.097	1.000	0.340
Male	23 (76.7)	20 (57.1)			
Female	7 (23.3)	15 (42.9)			
BMI, kg/m ²	26.63 ± 3.79	28.80 ± 5.55	0.097	1.000	0.340
Transplanted organ, n (%)			0.050	1.000	0.340
Heart	7 (23.3)	1 (2.9)			
Kidney	10 (33.3)	15 (42.9)			
Liver	13 (43.3)	19 (54.3)			
Time since diabetes diagnosis, years	10.34 ± 6.87	7.86 ± 4.91	0.097	1.000	0.340
eGFR, mL/min/1.73 m ²	67.90 ± 31.90	62.03 ± 31.53	0.467	1.000	0.754
eGFR categories G3–G5, n (%)	9 (31.0)	16 (47.1)	0.195	1.000	0.512
UACR, mg/g, median [IQR]	28.1 [14.1–151.3]	27.0 [11.0–221.1]	0.987	1.000	1.000
Albuminuria (A2–A3), n (%)	11 (45.8)	16 (48.5)	0.843	1.000	1.000
HbA1c, %	7.80 ± 2.44	7.34 ± 1.55	0.367	1.000	0.701
Insulin use, n (%)	20 (66.7)	28 (80.0)	0.223	1.000	0.520
Metformin use, n (%)	15 (50.0)	25 (71.4)	0.077	1.000	0.340
Sulfonylurea use, n (%)	2 (6.7)	5 (14.3)	0.437	1.000	0.754
DPP-4 inhibitor use, n (%)	0 (0.0)	1 (2.9)	1.000	1.000	1.000
SGLT2 inhibitor use, n (%)	8 (26.7)	12 (34.3)	0.507	1.000	0.760
Glucocorticoid use, n (%)	16 (53.3)	17 (48.6)	0.702	1.000	0.921

Tacrolimus use, n (%)	18 (60.0)	25 (71.4)	0.332	1.000	0.697
Sirolimus use, n (%)	4 (13.3)	1 (2.9)	0.173	1.000	0.512
Cyclosporine use, n (%)	4 (13.3)	5 (14.3)	1.000	1.000	1.000
Statin use, n (%)	20 (66.7)	24 (68.6)	0.870	1.000	1.000

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PDM, pre-existing diabetes mellitus; PTDM, post-transplant diabetes mellitus; SGLT2, sodium–glucose cotransporter 2. The last two columns present P values adjusted within the table by the Holm and Benjamini–Hochberg (BH) procedures (21 comparisons, including time since transplantation reported in the text). UACR was compared with the Mann–Whitney U test; 21 comparisons were included in the Holm and BH adjustments.

Comparison between SGLT2 inhibitor users and non-users

The characteristics of SGLT2 inhibitor users and non-users are presented in Table 4. In this exploratory comparison, SGLT2 inhibitor users were older than non-users (63.29 ± 7.76 vs. 57.45 ± 13.00 years; $P = 0.015$). The distribution of transplanted organs differed between groups ($P = 0.021$): heart and kidney transplantation were more frequent among users, whereas liver transplantation was more frequent among non-users.

The proportion of patients in eGFR categories G3-G5 was higher among SGLT2 inhibitor users than among non-users (65.7% vs. 41.9%; $P = 0.020$), although mean eGFR did not differ significantly (54.27 ± 21.24 vs. 63.84 ± 30.87 mL/min/1.73 m²; $P = 0.101$).

Metformin use (71.4% vs. 46.2%; $P = 0.013$) and statin use (91.4% vs. 56.4%; $P < 0.001$) were more frequent among SGLT2 inhibitor users. No significant differences were observed in sex distribution, BMI, time since diabetes diagnosis, diabetes group, HbA1c, or the use of insulin, sulfonylureas, DPP-4 inhibitors, corticosteroids, tacrolimus, sirolimus, or cyclosporine, nor in UACR or the prevalence of albuminuria (51.4% vs. 42.9%; $P = 0.415$). After Holm adjustment, only the difference in statin use remained significant (adjusted $P = 0.005$); the differences in age, eGFR category, and metformin use did not (adjusted $P = 0.270$, 0.340, and 0.247).

Table 4
Comparison of characteristics between SGLT2 inhibitor users and non-users

Characteristic	SGLT2 inhibitor users (n = 35)	Non-users (n = 78)	P value	Holm-adjusted P	BH-adjusted P
Age, years	63.29 ± 7.76	57.45 ± 13.00	0.015	0.270	0.084
Sex, n (%)			0.957	1.000	1.000
Male	23 (65.7)	51 (66.2)			
Female	12 (34.3)	26 (33.8)			
BMI, kg/m ²	26.84 ± 4.49	28.24 ± 5.55	0.211	1.000	0.422
Transplanted organ, n (%)			0.021	0.340	0.084
Heart	8 (22.9)	6 (7.7)			
Kidney	15 (42.9)	26 (33.3)			
Liver	12 (34.3)	46 (59.0)			
Time since diabetes diagnosis, years	14.00 ± 9.24	11.84 ± 8.65	0.241	1.000	0.433
Diabetes group, n (%)			0.512	1.000	0.731
PDM	15 (42.9)	28 (36.4)			
PTDM	20 (57.1)	49 (63.6)			
eGFR categories G3-G5, n (%)	23 (65.7)	31 (41.9)	0.020	0.340	0.084
eGFR, mL/min/1.73 m ²	54.27 ± 21.24	63.84 ± 30.87	0.101	1.000	0.224
UACR, mg/g, median [IQR]	40.6 [7.9–203.5]	20.1 [8.8–124.7]	0.558	1.000	0.743
Albuminuria (A2–A3), n (%)	18 (51.4)	27 (42.9)	0.415	1.000	0.638
HbA1c, %	7.31 ± 1.24	7.45 ± 2.07	0.706	1.000	0.845
Insulin use, n (%)	29 (82.9)	57 (73.1)	0.260	1.000	0.433
Metformin use, n (%)	25 (71.4)	36 (46.2)	0.013	0.247	0.084
Sulfonylurea use, n (%)	2 (5.7)	7 (9.0)	0.718	1.000	0.845
DPP-4 inhibitor use, n (%)	1 (2.9)	4 (5.1)	1.000	1.000	1.000

Characteristic	SGLT2 inhibitor users (n = 35)	Non-users (n = 78)	P value	Holm-adjusted P	BH-adjusted P
Glucocorticoid use, n (%)	21 (60.0)	33 (42.3)	0.082	1.000	0.224
Tacrolimus use, n (%)	21 (60.0)	59 (75.6)	0.091	1.000	0.224
Sirolimus use, n (%)	2 (5.7)	5 (6.4)	1.000	1.000	1.000
Cyclosporine use, n (%)	8 (22.9)	8 (10.3)	0.087	1.000	0.224
Statin use, n (%)	32 (91.4)	44 (56.4)	< 0.001	0.005	0.005

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; PDM, pretransplant diabetes mellitus; PTDM, post-transplant diabetes mellitus; SGLT2, sodium-glucose cotransporter 2. The last two columns present P values adjusted within the table by the Holm and Benjamini–Hochberg (BH) procedures (20 comparisons). UACR was compared with the Mann–Whitney U test; 20 comparisons were included in the Holm and BH adjustments.

Multivariable analysis of eGFR

The unadjusted 12.7 mL/min/1.73 m² eGFR difference between PDM and PTDM was attenuated and no longer significant after adjustment (8.6 mL/min/1.73 m² higher in PTDM; 95% CI – 3.8 to 21.0; P = 0.170; n = 96, adjusted R² = 0.12). HbA1c remained associated with eGFR (+ 3.0 mL/min/1.73 m² per 1%; 95% CI 0.1–6.0; P = 0.043), with a non-significant trend for kidney transplantation (– 15.3 mL/min/1.73 m²; P = 0.063). The lower eGFR in PDM appears to be explained largely by age, time since transplantation, and transplanted organ rather than by diabetes classification itself. Models for UACR and HbA1c are presented in Supplementary Table S1: LDL cholesterol was the only variable independently associated with UACR (1.18-fold per 10 mg/dL; P < 0.001), and insulin use and eGFR were associated with HbA1c.

Relationship between albuminuria and eGFR

Among the 95 patients with both eGFR and UACR, 27.4% were at low, 26.3% at moderate, 24.2% at high, and 22.1% at very high KDIGO risk (Fig. 1). UACR was not correlated with eGFR (Spearman ρ = –0.05; P = 0.61) (Fig. 2): 26 of 48 patients (54.2%) with eGFR < 60 mL/min/1.73 m² had no albuminuria, whereas 21 of 43 patients (48.8%) with albuminuria had eGFR ≥ 60 mL/min/1.73 m².

Univariable comparisons between patients with and without albuminuria are presented in Supplementary Table S2; the multivariable linear model for UACR is presented in Supplementary Table S1.

Median UACR was higher in PTDM than in PDM (28.1 [11.0–223.3] vs. 19.5 [4.8–52.4] mg/g; P = 0.037) (Table 2), and severely increased albuminuria was numerically more frequent in PTDM (16.7% vs. 7.9%; P = 0.212), whereas the prevalence of albuminuria ≥ 30 mg/g was similar (48.3% vs. 42.1%; P = 0.547). The distribution of KDIGO risk categories differed between groups (P = 0.033), with fewer patients with

PDM at low risk (10.8% vs. 37.9%). UACR and albuminuria did not differ between early- and late-onset PTDM (median 28.1 vs. 27.0 mg/g; $P = 0.987$; albuminuria 45.8% vs. 48.5%; $P = 0.843$).

Only 18 of 45 patients with albuminuria (40.0%) and 28 of 65 patients (43.1%) with a guideline-based indication for SGLT2 inhibition (albuminuria ≥ 30 mg/g or eGFR 20–59 mL/min/1.73 m²) were receiving an SGLT2 inhibitor.

DISCUSSION

This single-center, real-world study evaluated solid-organ transplant recipients with diabetes after a prolonged post-transplant period, averaging approximately 11 years. Liver transplantation accounted for more than half of the procedures, reflecting the center's extensive experience with these recipients. PTDM was more frequent than PDM among participants with available classification. The cohort had a substantial metabolic and kidney disease burden: mean eGFR was approximately 60 mL/min/1.73 m², 49.5% of participants were in eGFR categories G3-G5, mean HbA1c was 7.40%, 53.2% had an HbA1c level $> 7\%$, and approximately three-quarters were receiving insulin. These findings characterize a clinically complex population in which diabetes, immunosuppressive exposure, aging, and transplant-related factors likely contributed to kidney dysfunction and suboptimal glycemic control [1, 2, 7, 10].

Patients with PDM were older, had a shorter time since transplantation, and had lower mean eGFR than those with PTDM in unadjusted analysis. In multivariable linear regression, the difference in eGFR between groups was attenuated and no longer significant after adjustment for age, time since transplantation, transplanted organ, and other covariates. Thus, the observed difference in kidney function appears to be explained at least partly by differences in age and post-transplant follow-up rather than by diabetes classification itself. The direction of the follow-up difference is clinically noteworthy: despite having spent fewer years after transplantation, patients with PDM had lower unadjusted eGFR, potentially reflecting older age, longer lifetime exposure to diabetes, greater pretransplant cardiorenal burden, or kidney injury already present at transplantation. Because pretransplant kidney function and diabetes duration were not uniformly available, these mechanisms could not be tested directly. Previous studies have linked pretransplant diabetes with adverse kidney, graft, and survival outcomes after liver and kidney transplantation, although differences in study populations and outcomes limit direct comparison [7, 10–12].

HbA1c was similar between PDM and PTDM, with mean values above 7% in both groups; overall, 53.2% of participants had an HbA1c level $> 7\%$, and insulin use was frequent. Although individualized and less stringent glycemic targets may be appropriate for older recipients, patients with chronic kidney disease, or those at high risk of hypoglycemia, the combination of long-standing diabetes, frequent insulin treatment, and more than half of the cohort having HbA1c $> 7\%$ suggests room for improvement at the population level. Progressive beta-cell dysfunction, cumulative hyperglycemic exposure, aging, calcineurin-inhibitor use, hypertension, and previous kidney injury may all contribute to the difficulty of achieving glycemic targets and preserving kidney function [1, 2, 7–10].

Early- and late-onset PTDM showed broadly similar long-term kidney, glycemic, and treatment profiles. Mean eGFR and HbA1c were comparable, while the only differences approaching statistical significance were the distribution of transplanted organs, with more heart transplant recipients in the early-onset group, and a longer duration of diabetes in the early-onset group; none of these exploratory differences withstood adjustment for multiple comparisons, whereas the longer time since transplantation in late-onset PTDM did. Early post-transplant hyperglycemia may initially result from surgical stress, infection, high-dose corticosteroids, and calcineurin-inhibitor toxicity, whereas late-onset PTDM may more closely resemble type 2 diabetes associated with aging, weight gain, insulin resistance, progressive beta-cell dysfunction, and prolonged immunosuppressive exposure [1, 2]. Over time, however, these mechanisms may converge into a common chronic phenotype characterized by beta-cell failure, greater treatment intensity, and cardiorenal complications. Previous studies have similarly emphasized the prognostic importance of persistent rather than transient PTDM [13, 14].

In exploratory analyses, SGLT2 inhibitor users were older and more frequently had moderate-to-advanced chronic kidney disease than non-users, despite similar mean HbA1c and eGFR; these differences did not withstand adjustment for multiple comparisons and should be regarded as hypothesis-generating. This pattern probably reflects preferential selection of patients at higher cardiorenal risk rather than an adverse effect of SGLT2 inhibitor therapy. More frequent metformin and statin use among SGLT2 inhibitor users also suggests a more intensive cardiometabolic treatment strategy. Medication-access criteria within the Brazilian public health system may additionally influence prescribing patterns [15]. Although transplant-specific evidence remains limited, a randomized trial in stable kidney transplant recipients with PTDM found that empagliflozin improved glycemic control and body weight without relevant changes in eGFR, immunosuppressive drug concentrations, or adverse events [16]. Systematic reviews and observational studies have reported favorable glycemic and metabolic effects without major kidney safety signals, but most evidence is short-term and focused on kidney transplantation [17, 18]. Confounding by indication prevents the present cross-sectional analysis from establishing effectiveness or safety.

Albuminuria was present in almost half of the patients with an available UACR, but it was largely dissociated from eGFR: more than half of the patients with reduced eGFR had no albuminuria, and about half of those with albuminuria had preserved eGFR. This pattern differs from classical diabetic kidney disease, in which albuminuria usually precedes the decline in glomerular filtration, and is consistent with the predominance of non-albuminuric mechanisms of kidney injury after transplantation, particularly calcineurin-inhibitor nephrotoxicity, hypertension, and vascular aging [7–9]. It also implies that eGFR alone underestimates kidney risk in this population: more than one in five patients with both measurements was at very high KDIGO risk. In multivariable linear regression, LDL cholesterol was the only variable independently associated with UACR, whereas eGFR, diabetes group, transplanted organ, HbA1c, BMI, and immunosuppressive regimens were not, which suggests that albuminuria in this population tracks with an atherogenic lipid profile rather than with the degree of kidney function impairment or the immunosuppressive regimen. Finally, fewer than half of the patients with a guideline-

based indication for SGLT2 inhibitors were receiving one, highlighting a treatment gap in a group in which these agents may offer cardiorenal protection [16–18].

This study has several strengths. It describes a real-world cohort evaluated late after transplantation, with a mean post-transplant follow-up of approximately 11 years. Care in a specialized endocrine transplant clinic provided relative consistency in assessment and management. Most participants were non-kidney transplant recipients, particularly liver transplant recipients, an underrepresented group in studies of PTDM and newer glucose-lowering therapies. In these patients, eGFR predominantly reflects native kidney function and may capture the cumulative effects of diabetes, aging, calcineurin inhibitors, perioperative injury, and other post-transplant exposures. The comparisons between PDM and PTDM, early- and late-onset PTDM, and SGLT2 inhibitor users and non-users provided complementary perspectives on this heterogeneous population.

The study also has important limitations. Its retrospective, cross-sectional design, with a single index visit per patient, precludes causal inference and any assessment of eGFR or HbA1c trajectories; the cross-sectional gradient between time since transplantation and eGFR must not be read as a rate of decline. Index visits spanned nine years and included the last documented visit of patients who subsequently died, so the cohort is heterogeneous in calendar time. The single-center setting and relatively small sample limited statistical power and generalizability. The subgroup comparisons were exploratory, and only a minority of the unadjusted differences survived correction for multiple testing. Including liver, kidney, and heart transplant recipients introduced clinical heterogeneity. Although the multivariable model adjusted for age and time since transplantation, residual confounding remains possible, and the model could not account for several clinically relevant variables. Serial HbA1c and eGFR measurements, pretransplant kidney function, acute kidney injury, rejection, graft function, tacrolimus concentrations, cumulative corticosteroid exposure, cardiovascular events, hypoglycemia, and continuous glucose-monitoring data were not consistently available. Some variables had missing observations. Albuminuria was available for 87% of the cohort and was based on a single UACR measurement, without confirmation in a second sample as recommended by KDIGO; in four patients, KDIGO-equivalent categories were derived from 24-h albumin excretion or protein-to-creatinine ratio. Analyses of glucose-lowering therapy were susceptible to confounding by indication and contraindication.

Prospective, multicenter, and organ-specific studies should assess longitudinal kidney, glycemic, cardiovascular, graft, and survival outcomes in transplant recipients with diabetes. SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists are promising, but transplant-specific evidence remains based mainly on small or observational kidney transplant studies [16, 17, 19]. Studies in liver and heart transplant recipients are particularly needed to determine whether earlier and more systematic use of cardiorenal-protective therapies can improve kidney trajectories, cardiovascular outcomes, graft survival, and mortality in patients with PDM or PTDM.

CONCLUSIONS

Long-term solid-organ transplant recipients with diabetes had a high burden of kidney dysfunction and suboptimal glycemic control. Patients with PDM were older, had a shorter time since transplantation, and had lower eGFR than those with PTDM in unadjusted analysis; however, this difference was attenuated after adjustment for age, time since transplantation, and transplanted organ. Early- and late-onset PTDM had similar long-term kidney and glycemic profiles. Albuminuria was present in almost half of the patients, was largely dissociated from eGFR, and was associated with a more atherogenic lipid profile, yet fewer than half of the patients with an indication were receiving SGLT2 inhibitors. In exploratory analyses, SGLT2 inhibitors were used more frequently in older patients and those with more advanced chronic kidney disease, likely reflecting selection for cardiorenal protection. Integrated metabolic, kidney, and cardiovascular care and prospective evaluation of newer therapies are warranted in this high-risk population.

DECLARATIONS

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Research Ethics Committee of the Federal University of Minas Gerais, Belo Horizonte, Brazil (approval number: 57752922.2.0000.5149)

Consent for publication

The final version of the manuscript has been reviewed and approved by all authors, who consented to the publication of the information described herein.

Competing interests

The authors declare no competing interests.

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Author Contribution

HBF, LBI, AGD, EMF and MWL wrote yhe main manuscriptHBF, AAW,IRC, YPHY and MWL prepared tables and figuresAll authors reviewed the manuscript

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Figures

KDIGO risk categories by eGFR and albuminuria (n = 95)

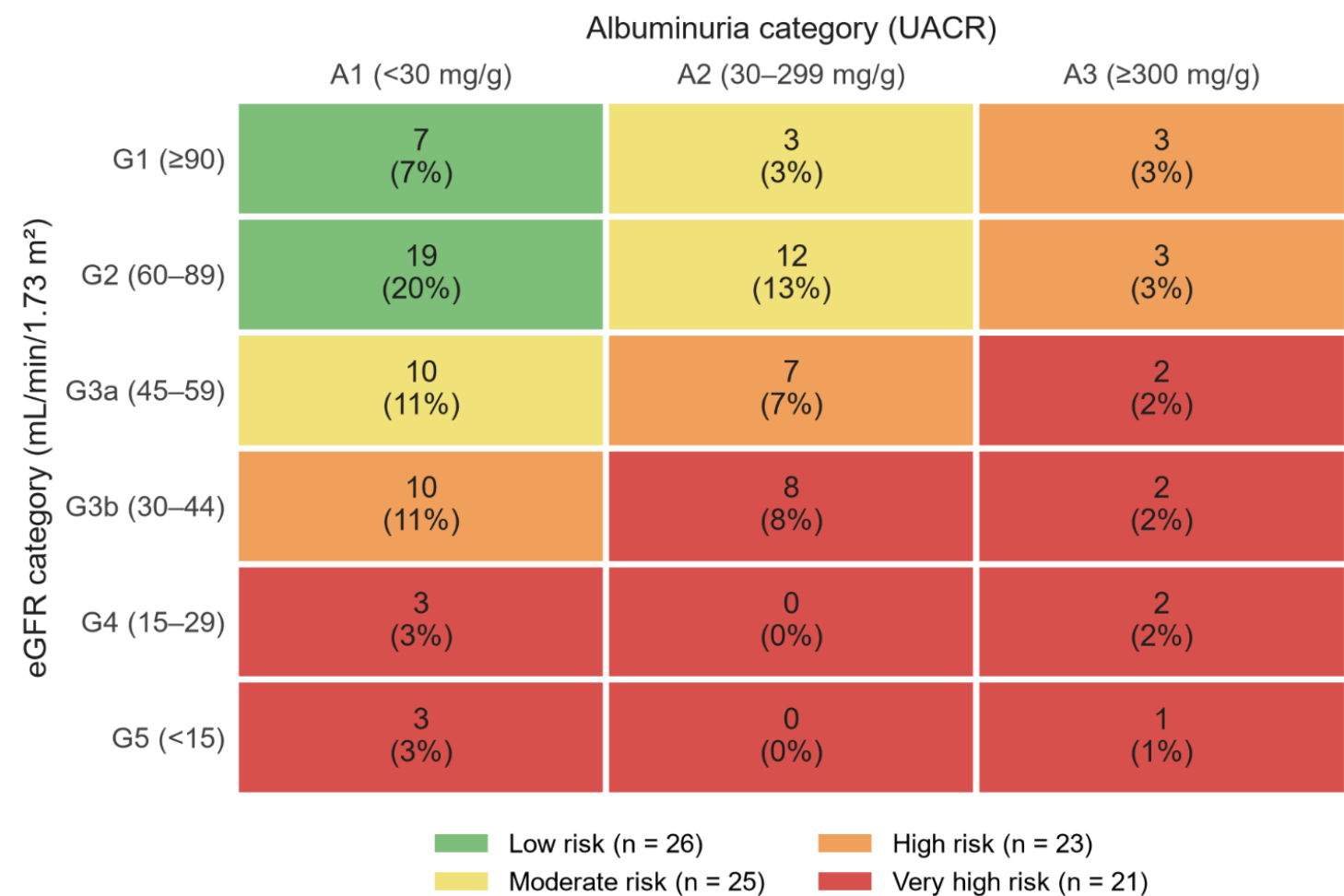


Figure 1

KDIGO risk categories according to eGFR and albuminuria categories (n = 95 patients with both measurements). Numbers are n (%).

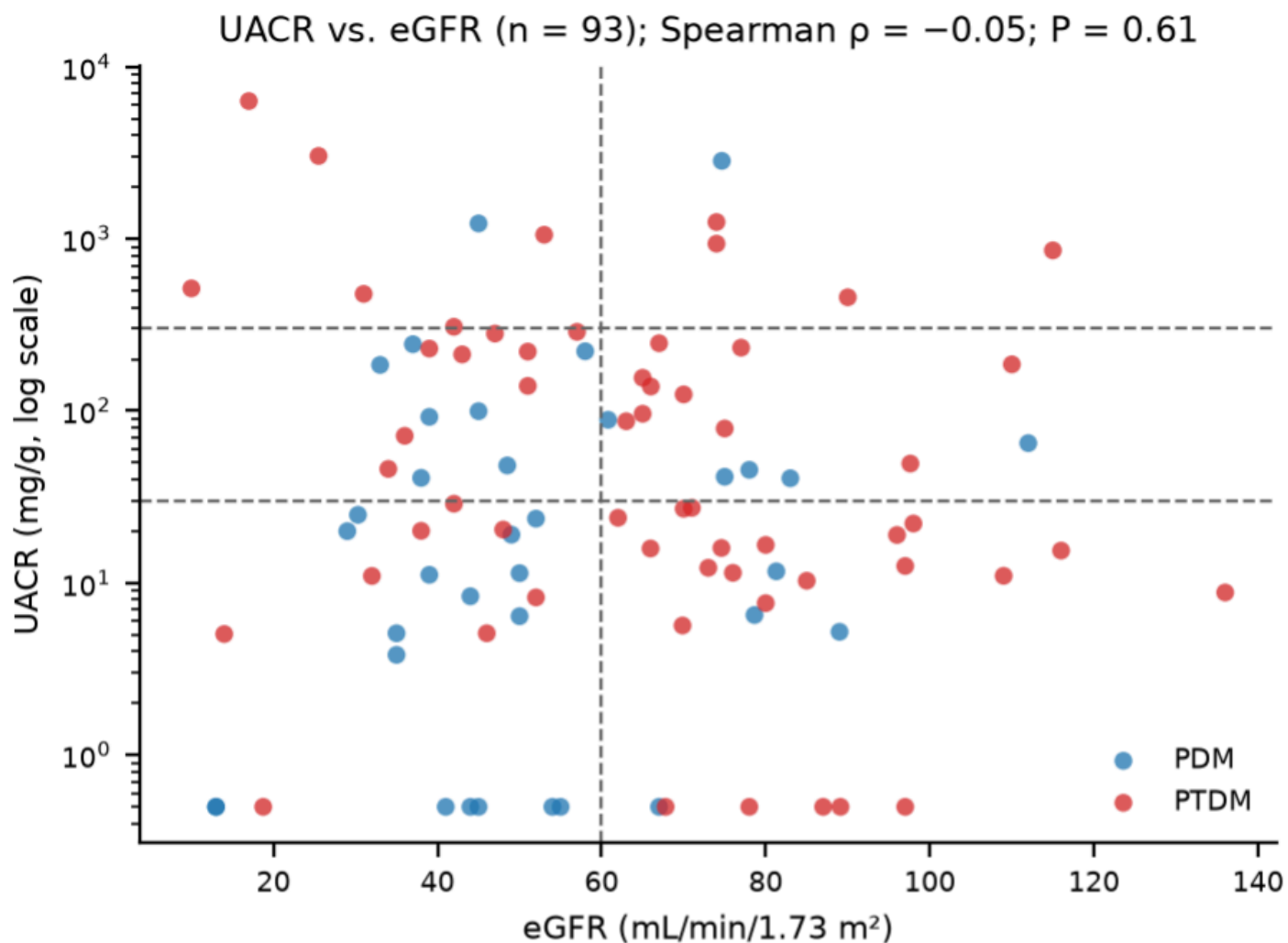


Figure 2

Urinary albumin-to-creatinine ratio (UACR, log scale) against eGFR in patients with PDM and PTDM. Dashed lines mark eGFR 60 mL/min/1.73 m² and UACR 30 and 300 mg/g. Spearman $\rho = -0.05$; P = 0.61.

Supplementary Files

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