Risk factors for developing post-transplant diabetes after pediatric kidney transplant in a Canadian tertiary care children's hospital between 1995-2016

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Key Messages:

- The cumulative incidence of post-transplant diabetes was 31% and 14.1% at 1- and 2-years transplant in a pediatric cohort of kidney transplant recipients seen at a tertiary care children's hospital serving the province of British Columbia
- Any dysglycemia (impaired glucose tolerance, impaired fasting glucose, or diabetes) in the peri-operative period (8-30 days post-transplant) increased the risk of PTDM at 1-year post-transplant by 3-fold
- No significant association was found between typical risk factors for type 2 diabetes (i.e. positive family history of type 2 diabetes, ethnicity, obesity) and post-transplant diabetes

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Abstract

Background: Post-transplant diabetes mellitus (PTDM) is a serious complication in kidney transplant recipients (KTR) due to its negative impact on graft and patient survival. Although reported in 3-20% of pediatric KTR, it is not characterized as well as in adults. This study describes the incidence and risk factors associated with the development of PTDM in pediatric KTR.

Methodology: Retrospective cohort study of non-diabetic pediatric patients, aged 6 months to 19 years, who underwent a first kidney transplant during 1995-2016. We estimated the cumulative incidence rate and used multivariable logistic regression to identify the diabetogenic risk factors for PTDM.

Results: A total of 142 KTR were included in this study. The cumulative incidence of PTDM was 31% and 14.1% in the first, and second year post-transplant, respectively. Significant risk factors for PTDM in the first-year post-transplant included: dysglycemia in the first 8-30 days post-transplant (adjusted odds ratio [aOR]: 3.02, 95% CI:1.21-7.53; p=0.018) and use of sirolimus in the first 30 days post-transplant (aOR: 5.33, 95% CI: 1.16-24.35; p=0.031). No significant association was found with typical diabetogenic factors.

Conclusion: The incidence of PTDM is high among pediatric KTR. Independent risk factors associated with PTDM, included meeting criteria for dysglycemia or diabetes and sirolimus use in the first month post-transplant. Typical diabetogenic risk factors for type 2 diabetes were not associated with an increased risk. This study provides important information for post-transplant medical care and future research.

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Introduction

Post-transplant diabetes mellitus (PTDM) is a well-known complication in solid organ transplant and has proven to have negative impacts on long-term graft and patient survival.[1,2] In a recently published population-based study[3], the overall risk of diabetes mellitus (DM) was nine times higher in children who received a solid organ transplant compared to children who had not received a transplant, and new-onset diabetes post-transplant was associated with a three-fold higher risk of mortality. While these patients remain at risk even 10 years after transplantation, the risk of diabetes was found to be highest in the first year after solid organ transplant. Specifically, in pediatric kidney transplant recipients (KTR), a Canadian study (N=274) reported a 2.7-fold higher risk of mortality in the presence of PTDM with cardiovascular events being the most common cause of death.[4]

Prior studies reported an increase in the incidence of PTDM, likely due to the use of diabetogenic immunosuppressive agents as well as the increasing burden of childhood obesity, poor dietary habits, and sedentary lifestyles.[1,4–9] In a recently published population-based study on pediatric solid organ transplant recipients, the incidence rate of diabetes in KTR was 18.8 (95% CI: 14.9-23.8) per 1000 person-years.[3] With recent advancements in our collective knowledge of the impact of PTDM on health outcomes in pediatric KTRs, there is a need for heightened awareness of PTDM, particularly among children and youth who are at higher risk.[5,10]

Studies in the adult population have demonstrated that many of the pathophysiological mechanisms of PTDM overlap with type 2 diabetes (T2DM) such as insulin resistance, impaired insulin secretion, reduced insulin-mediated glucose uptake in peripheral tissues, sub-optimal insulin suppression of hepatic glucose production and impairment of the incretin axis between the gut and pancreas further compromising pancreatic beta cell function.[11] Therefore, several risk factors implicated in the

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pathogenesis of T2DM, are also observed in PTDM, like ethnicity, obesity, and a positive family history of DM.[6,9] Characteristics unique to solid organ transplant recipients that further contribute to the risk of developing PTDM include: glucocorticoid use and in particular, high doses of intravenous methylprednisolone in the peri-operative period, calcineurin inhibitors (CNI) such as cyclosporine A (CyA) and tacrolimus (Tac) that are directly toxic to the beta cell, [2,12–14] viral infections such as hepatitis C and cytomegalovirus, [2,15–17] and hypomagnesemia.[18] Identifying risk factors for PTDM, initiating timely and consistent screening after transplantation, and intervening early may help to improve the health outcomes of pediatric KTRs.

In response to existing knowledge on the impact of PTDM on health outcomes of pediatric KTRs, as well as the opportunity to prevent PTDM by addressing modifiable risk factors such as glucocorticoid and CNI doses and unhealthy lifestyles, we aimed to determine the incidence of PTDM among pediatric KTR patients at our tertiary care children's hospital and identify pre- and peri-transplant risk factors that would inform a quality improvement initiative to achieve better screening and management of PTDM.

Methods

Study design and population

This retrospective cohort study included non-diabetic pediatric patients, aged 6 months to 19 years, who underwent a first kidney transplant at British Columbia Children's Hospital (BCCH) in Vancouver, British Columbia (BC), between 1995 and 2016, and who were followed for at least two consecutive years. BCCH is the only tertiary level hospital in the province and therefore, is the provincial site that manages all pediatric kidney transplant patients. Patients were excluded from the study if they had a previous diagnosis of cystic fibrosis, DM type 1 or 2, a record of a previous solid organ transplant or received a multiple organ transplant.

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Post-transplant diabetes mellitus and dysglycemia

The terms pre-diabetes and DM were defined based on the 2014 international and North American guidelines.[19–21] *PTDM* was defined as one or more of the following criteria present on more than one occasion, at any time after the first month post-transplant: i) a fasting plasma glucose (FPG) of ≥ 7.0 mmol/L (≥126 mg/dl), ii) a 2-hour plasma glucose after an oral glucose tolerance test (OGTT) of ≥11.1 mmol/L (≥200 mg/dl) or iii) a random plasma glucose (RPG) ≥11.1 mmol/L (≥200 mg/dl) with classic symptoms of hyperglycemia.

Post-transplant pre-diabetes (PTpreDM) was defined as: i) impaired fasting glucose (IFG) with a blood glucose between 5.6 mmol/L (100 mg/dl) and 6.9 mmol/L (125 mg/dl) *or*; ii) impaired glucose tolerance (IGT) with a blood glucose between 7.8 mmol/L (140 mg/dl) and 11 mmol/L (199 mg/dl) on more than one occasion, at any time after the first month post-transplant. *Dysglycemia* was defined as any blood glucose dysregulation (IFG, IGT or DM) at any time after transplantation.

Glycosylated hemoglobin (A1C) level was not taken into consideration when defining post-transplant dysglycemia or PTDM, due to potential for misinterpretation of A1C levels in KTR caused by reduced red blood cell survival, early post-transplant blood transfusions and lack of synthesized and glycated hemoglobin in the early post-transplant period. [22] Although the majority of patients received insulin for the treatment of hyperglycemia in the immediate post-operative period, due to the lack of clinical consensus on glycemic targets and timing of insulin initiation, we did not use insulin therapy as a criterion for defining PTDM. Diagnostic criteria are summarized in Table 1 and are based on venous samples and laboratory methods.

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Post-transplant hypomagnesemia

We defined post-transplant hypomagnesemia as magnesium levels below 0.7 mmol/L on more than one occasion in the first 30 days post-transplant.

Data source

Data was extracted from the ***P***atient ***R***ecords and ***O***utcome ***M***anagement ***I***nformation ***S***ystem (PROMIS), the provincial database that tracks the clinical data of all solid organ transplant recipients (adult and pediatric) from across the province of BC. Additional clinical data that was not available in PROMIS (i.e. family history of T2DM, blood pressure, antihypertensive agents, weight, height, BMI, hospital days post-transplant, type and dose of steroid used in early post-transplant period) was extracted from the clinical chart. The University of British Columbia and the Children's and Women's Health Centre of British Columbia Research Ethics Board (UBC C&W REB) approved this study protocol (H16-02351).

Data Collection

Recipient–related clinical data included sex, age at transplant, ethnicity, family history of T2DM, hypertension (defined as a systolic blood pressure ≥ 95 percentile for gender, age and height)[23], body mass index (BMI) z-score (calculated using gender, age, weight and height, applying the growth charts from the World Health Organization), underlying kidney disease and type of dialysis (hemodialysis, peritoneal dialysis). Transplant-related clinical data included: donor type (live or deceased), duration of post-transplant hospitalization (days), and magnesium levels.

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During period 1 (from 1995 to 2005), medications used for maintenance of immunosuppression post-transplant were a calcineurin inhibitor (CNI: tacrolimus (Tac) or cyclosporine (CyA)), either alone or combined with mycophenolate mofetil (MMF), azathioprine (Aza)) or a mammalian target of rapamycin (mTOR: sirolimus (Sir)). During Period 2 (from 2006 to 2016), Tac combined with MMF was used. Trough levels of CNI were documented in both periods. In both periods, antibody induction consisted mainly of anti-IL-2 receptor antibody treatment with basiliximab, although in select cases with either high risk or delayed allograft function, rabbit anti-thymocyte globulin (thymoglobulin) was used for induction. Since all individuals received glucocorticoids post-operatively, we only documented the cumulative dose of steroids in the first week post-transplant (mg/kg).

Statistical analysis

The analysis was carried out using SAS/STAT software version 9.4. All continuous data in the study were expressed as means and standard deviations (SD) and categorical data were expressed as number and percentages, unless otherwise indicated. Univariate and multivariable analysis for dysglycemia and PTDM were performed using the Cox proportional hazards model. The primary endpoint was time until development of PTDM during a 2-year follow-up. *A priori* defined risk factors for PTDM in unadjusted analysis were included in the multivariable multinomial logistic regression analysis. All the tests were two-sided with values of $p < 0.05$ as statistically significant.

Results

Population characteristics

A total of 142 pediatric KTR who did not have a diagnosis of diabetes pre-transplant were identified and included in this study. With a predominantly male representation (59%, n=83), mean age pre-transplant was 11.2 (5.5) years. Clinical and demographic characteristics of the cohort pre-transplant are shown in

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Table 2, as well as the clinical characteristics of the 44 and 20 patients who developed PTDM during year 1 (from days 31 to 365) and year 2 (from days 366 to 730) after transplant, respectively.

Cumulative incidence of prediabetes, diabetes and dysglycemia in time

Figure 1 shows the cumulative incidence of prediabetes, DM, and dysglycemia at different time points after transplant (with day 0 indicating the day of transplantation). A high proportion of patients experienced dysglycemia (80.3%; n=114) in the first 0-7 days post-transplant, with 65.5% (n=93) meeting the definition for DM. The proportion of patients with PTDM was highest 31-365 days post-transplant (31%, N=44) decreasing to 14.1% in the second year post-transplant. Rates of pre-diabetes remained consistent over the 2-year study period affecting about one-third of patients.

We stratified the cases into two time periods: Period 1 from 1995 to 2005 with a total of 77 patients and Period 2 from 2006 to 2016 with a total of 65 patients. (Figure 2) We found that dysglycemia decreased from 76.6% (n=59) to 52.3% (n=34) with the majority of this decrease attributed to a decrease in rates of PTDM from 40.2% (n= 31) to 20% (n=13) in the first-year post-transplant. During the second-year post-transplant, dysglycemia decreased from 59.7% (n=46) to 27.7% (n=18) and PTDM decreased from 22% (n= 17) to 4.6% (n=3).

Figure 3 shows the probability of PTDM free survival at different time points in the first two years post-transplant. In Period 1, PTDM free survival was 59% and 37% at 1-year and 2-years post-transplant, respectively. In Period 2, PTDM free survival was higher at these same time points (80% and 75%, respectively).

Immunosuppressive protocol during the first month post-transplant

In Figure 4, we stratified all KTR in our cohort based on the two time periods mentioned above and detailed the immunosuppressive therapy received during the first month after transplant. In the first period from 1995-2005 multiple protocols were used, with 42.8% of patients using a combination of CyA and

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MMF, 16.9% using CyA and Aza, and 16.9% using CyA and Sir. In the second period from 2006-2016, 100% (n=65) of cases received Tac and MMF.

Risk factors associated with PTDM at 1- and 2-years post-transplant

Unadjusted and adjusted analyses are shown in Tables 3 and 4. An additional independent variable, dysglycemia at 0-7 days and 8-30 days post-transplant was created and included in the analysis. On the multivariable analysis, a significant predictor of PTDM and any dysglycemia at 1-year post transplant was the presence of dysglycemia in the first 8-30 days post-transplant with an adjusted odds ratio (aOR) of 3.02 (95% CI:1.21-7.53; p=0.017) and 4.50 (95% CI: 1.74-11.61; p=0.001), respectively. The use of sirolimus in the first 30 days post-transplant was also a predictor of PTDM in the first year post-transplant with an aOR of 5.33 (95% CI: 1.16-24.35; p=0.031). At 2-years post-transplant, no significant predictors for PTDM were identified. Further, typical type 2 diabetogenic risk factors, including ethnicity, family history of T2DM and BMI z-score at the time of transplant were not predictors of pediatric PTDM at 1- and 2-years post-transplant.

Discussion

In this study, we report on a retrospective cohort of non-diabetic children and youth who received a kidney transplant between the years of 1995-2016 at BC Children's Hospital, the only tertiary care pediatric centre in the Canadian province of BC. Of 142 non-diabetic pediatric kidney transplant recipients, 44 (31%) and 20 (14.1%) developed PTDM in the first (31-365 days) and second (366-730 days) year post-transplant, respectively. Pre-diabetes (IFG or IGT) occurred in one-third of patients both in the first- and second year post-transplantation. When comparing the time period 1995-2005 to 2006-2016, rates of PTDM in year 1 and year 2 post-transplant decreased by at least half, coinciding with a change in immunosuppressant therapy from predominantly using CyA (in concert with other immunosuppressants) to exclusively using Tac. While typical T2DM risk factors did not increase risk for

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PTDM, the presence of any dysglycemia (IGT, IFG or DM) between days 8-30 post-transplant increased the risk of developing PTDM by 3-fold in the first-year post-transplant.

The North American Pediatric Renal Transplant Cooperative Study defined PTDM as the new requirement of insulin therapy for more than 2 weeks duration at any time post kidney transplantation and reported an incidence of PTDM of 2.6% from January 1992 to July 1997, with the majority of patients developing PTDM within the first 6 months after transplantation.[8] Greenspan *et al* reported a cumulative incidence of PTDM (defined as a serum glucose >11.1 mmol/L (200 mg/dl) on more than one occasion and requiring antihyperglycemic medication) of 20% from 1986-1999 with a mean time from transplantation to PTDM presentation of 1.2 years (range 1 day to 6.2 years).[6] Similar to our study, more recent studies have used the ADA definition of PTDM [20] yet reported lower cumulative incidence rates of PTDM in KTR, compared to our study. Prokai *et al* documented an incidence of 13% between the years 1990 to 2006, with onset of PTDM occurring less than one-year post-transplant in 70% of cases.[9] In a study reporting on diabetes in pediatric solid organ transplant recipients seen in a Canadian tertiary care pediatric hospital between January 2002 to December 2011, the cumulative incidence of PTDM in KTR was 8.3% after 5-years of follow-up.[24]

Our study showed a significantly higher cumulative incidence of PTDM compared to other published pediatric studies which may be due to varying definitions of PTDM, as well as variable follow-up in the post-transplant period. The use of insulin and other anti-hyperglycemic drugs were not included as criteria for defining PTDM in our study. Frequent blood glucose testing in the early post-transplant period may also explain the higher incidence of blood glucose dysregulation documented in the first year after transplantation. In our experience, insulin therapy is usually initiated in the context of persistent hyperglycemia and not for transient elevations in blood glucose levels that are often observed during acute infections or episodes of rejection where higher doses of steroids are required temporarily. We were

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not able to discriminate between transient and persistent hyperglycemia in our study which may have contributed to the higher incidence of diabetes and dysglycemia in our analysis.

Interestingly, when stratified by time period, our reported cumulative incidence of PTDM from 2006-2016 was lower (4.6%) and in keeping with rates observed in adult KTR.[1,5,25] Differences in the incidence of PTDM observed in the 1995-2005 and 2006-2016 periods, may be due to differences in the immunosuppressive protocols received, as well as modifications in dosing, with rapid reduction of CNI and steroid dosages as seen in other research studies.[26,27] Valderhaug *et al* documented a reduction in the incidence of PTDM and a 50% less odds of developing PTDM when a historical cohort of adult KTR (1995 -1996) was compared to a more recent cohort (2003-2005).[27]

Although cumulative incidence rates vary across studies, the onset of PTDM within one-year post-transplant in pediatric KTR appears to be a consistent finding. In a recent population-based cohort study of pediatric solid organ transplant recipients (i.e. kidney, liver, heart and multi-organ), the adjusted relative hazard of PTDM was highest in the first-year post-transplant (HR 20.7; 95% CI: 15.9-27.1)[3] In studies focused on KTR specifically, the majority of cases of PTDM occurred in the first year post-transplant[8,9] although between 30-50% of patients experienced reversal of their glucose metabolic disorder[6,8,9]. Nonetheless, PTDM is associated with adverse patient outcomes. Adult and pediatric studies examining the link between PTDM and graft loss in solid organ transplant recipients have been conflicting[7,8,27,28], however a 3-fold increased risk of mortality has been reported in pediatric solid organ transplant recipients[3]. In pediatric KTRs specifically, Koshy *et al* reported that PTDM was associated with an increased risk of mortality (hazard ratio [HR] 2.79, 95% CI:1.04-7.44) and cardiovascular events (HR 3.90, 95% CI: 1.31-11.59).[4] Therefore, identifying PTDM early and timely intervention may have a positive impact in the long-term health outcomes of pediatric KTR.

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Risk factors for T2DM such as ethnicity [8,28], a high BMI [6,7,28] and a family history of DM [6,9] have been reported to be associated with risk for PTDM in pediatric KTR. Further, factors unique to transplant recipients such as use of Tac, steroid dose, CMV positivity and hypomagnesemia may affect risk for PTDM [6,8,9,28]. In our study, after adjustment for early dysglycemia, none of these risk factors were associated with the development of PTDM including classic T2DM risk factors. We did find however that any blood glucose dysregulation (IGT, IFG or DM) in the first 30 days post-transplant increased the odds of PTDM by 3-fold and dysglycemia by 4.5-fold at 1-year post-transplant. Since magnesium (Mg) is necessary for insulin signaling and glucose metabolism, low blood levels have been linked with increased insulin resistance and are considered a potential risk factor for DM since CNIs increase magnesium renal excretion and wasting.[29] Nevertheless, in our data analysis, hypomagnesemia in the first 30 days post-transplant was not an individual predictor for the development of PTDM.

A high incidence of blood glucose dysregulation in the first 30 days post-transplant is not uncommon and is likely due to exposure to high doses of glucocorticoids and immunosuppressive agents, as well as surgery induced stress.[30,31] In adult KTR, hyperglycemia and requiring insulin in the first week post-transplantation has been found to be associated with an increased risk of PTDM.[32,33] Peri-transplant hyperglycemia was reported as an independent risk factor for PTDM by Greenspan *et al*, with 56% of the PTDM group having glucose levels >11.1 mmol/L (200 mg/dl) during the first 2-weeks post-transplant.[6]

Early hyperglycemia has been linked to an increase in infectious and cardiovascular complications in adult KTR, with early development of PTDM and IGT as predictors of mortality.[27] The development of hyperglycemia in the weeks following adult kidney transplant in non-diabetic patients increased the odds of PTDM by 29%, as well as cardiovascular complications.[32] Hecking *et al* studied the use of basal insulin in the early post-transplant period and reported fewer cases of PTDM 1-year post-transplant in the group who received intensive insulin therapy compared to the conventional treatment group.[34] It has been hypothesized that 'beta cell rest' in this peri-operative period may preserve beta cell longevity by

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preventing beta cell glucotoxicity and over stimulation of vulnerable cells.[11] The results of our study support further research in this area that includes pediatric KTR, as well as prompt treatment of hyperglycemia in the post-operative period.

Calcineurin inhibitors (CNIs) are usually part of a triple immunosuppressive regimen that often also includes prednisone and a proliferation inhibitor (i.e. mycophenolate). Cyclosporine A came into use in 1983 and tacrolimus a decade later, and although Tac is considered to be more diabetogenic [35], it has become the CNI of choice because it is superior in the prevention of graft rejection and cardiovascular events compared to CyA.[36] In our study, neither Tac nor CyA were significant independent risk factors for developing PTDM. However, the difference in rates of PTDM between our study's two time periods coincides with the change in practice from using CyA to Tac. On the other hand, Sir used in combination with steroids and CNI demonstrated a significant association with PTDM. This association was independent of the cumulative dose of steroids used in the first-week and trough levels of CNI measured in the first-month post-transplant. These findings are similar to those documented by Johnston *et al*, where Sir was an independent risk factor for PTDM, either if used alone or in combination with Tac or CyA[37]. Sir by its action through mammalian target of rapamycin has been linked to insulin resistance and direct beta cell toxicity.[14,38–40] Studies suggest Sir to be diabetogenic after conversion following CNI withdrawal [41], with a lower incidence of PTDM in Sir-free groups when compared to groups receiving the drug.[38] It is possible that the absence of Sir use in the second period of our study (2006-2016) may have contributed to the reduction in the incidence of dysglycemia and PTDM.

Lifestyle modification has been reported by Sharif *et al*, to reverse impaired glucose tolerance[42] and according to the recent CAVIAR trial, active lifestyle interventions reduced PTDM incidence by 15.6% in KTR.[43] It is possible that in the latter years of our study, improvements in the delivery of lifestyle counselling contributed to the reduction in the incidence of dysglycemia and diabetes however these

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lifestyle interventions are often not clearly documented in the medical chart making it challenging to evaluate this treatment approach on patient outcomes.

Our study is limited by its retrospective design and shorter duration of follow-up of 2 years post kidney transplantation. Our cohort was derived from a single tertiary level children's hospital however, our centre is the only site across the province that manages pediatric solid organ transplants and therefore, the likelihood of missing cases is relatively low. Our study may also be underpowered in detecting some predictors as evidenced in the wider confidence intervals. Our sample size of pediatric KTR is lower than some of the more recently published population-based studies on pediatric solid organ transplant recipients which may partially explain the non-association of multiple previously reported risk factors for pediatric PTDM. Strengths of our study include a provincial cohort that is relatively large and two years of comprehensive data from a clinical registry that was supplemented by comprehensive clinical chart reviews. Further, our study spanned 20 years of data (1995-2016) allowing us to capture the impact of changes in the medical management of pediatric KTR and its influence on rates of PTDM and dysglycemia.

Conclusion

Dysglycemia and PTDM are common in pediatric KTR, with dysglycemia in the first 30 days post-transplant being a significant risk factor for the development of PTDM. Prevention of PTDM necessitates clinicians to identify those at risk which is usually based on assessing for typical risk factors for T2DM (i.e. BMI, ethnicity, family history of diabetes). We demonstrate that pediatric KTR recipients who develop PTDM do not necessarily have these typical risk factors making risk stratification challenging. There is a paucity of research on preventative measures during the peri-operative period in the pediatric KTR population, however adult pilot studies exploring the use of early insulin initiation for post-operative

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hyperglycemia show promise. [34] We have used the results of our research to inform a quality improvement initiative that supports early involvement of pediatric endocrinologists in the care of children and youth who receive kidney transplant, allowing for timely insulin initiation to prevent post-operative dysglycemia. More research is needed to determine the impact of this approach on risk for PTDM, as well as graft survival and mortality in the pediatric KTR population.

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Table 1. Definitions of Post-transplant pre-diabetes mellitus (PTpreDM), Post-transplant diabetes mellitus (PTDM), and Dysglycemia

Definition & Criteria	**PTpreDM** (> 31 days PT*)	**PTDM** (> 31 days PT*)	**Dysglycemia** (any time PT*)
Fasting glucose 5.6-6.9 mmol/L (IFG)	✖		✖
Fasting glucose ≥ 7.0 mmol/L		✖	✖
OGTT or random glucose 7.8-11 mmol/L (IGT)	✖		✖
OGTT or random glucose ≥ 11.1 mmol/L		✖	✖

*PT, post-transplant

Table 2. Clinical characteristics of patients pre-transplant and with PTDM in Year-1 and Year-2

Variable	Pre-transplant	PTDM in Year-1	PTDM in Year-2
Number of patients	142	44	20
Recipients age			
Mean age at transplant (SD)	11.2 (5.45)	12.18 (5.21)	10.95 (5.88)
Recipients sex			
Percentage male (n)	58.5% (83)	63.6% (28)	70% (14)
Ethnicity			
Caucasian (n)	56.3% (80)	70.5% (31)	60% (12)
South/East Asian (n)	23.3% (33)	6.8% (3)	20% (4)
First Nations (n)	13.4% (19)	18.2% (8)	15% (3)
Other ethnicity (n)	7% (10)	4.6% (2)	5% (1)
BMI			
BMI z-score at transplant (SD)	0.44 (1.31)	0.45 (1.2)	0.39 (1.47)
BMI z-score 1 year post-transplant (SD)	0.56 (1.35)	0.86 (1.08)	0.77 (1.16)
BMI z-score 2 years post-transplant (SD)	0.73 (1.25)	0.87 (1.05)	0.98 (1.39)
Pre-transplant hypertension			
Use of antihypertensive medication (n)	81% (115)	86.3% (38)	90% (18)
Family history of diabetes			
Type 2 diabetes (n)	18.3% (26)	13.6% (6)	15% (3)
Type of kidney disease			
Congenital structural anomaly	37.4% (53)	43.2% (19)	45% (9)
Hereditary renal disorder	16.2% (23)	6.8% (3)	10% (2)
Glomerular disease	35.2% (50)	41% (18)	30% (6)
Systemic disease	4.2% (6)	2.2% (1)	15% (3)
Other conditions	7% (10)	6.8% (3)	.
Type of dialysis pre-transplant			
Pre-emptive (n)	32.4% (46)	29.5% (13)	40% (8)
Hemodialysis (n)	32.4% (46)	34.1% (15)	40% (8)
Peritoneal Dialysis (n)	34.5% (49)	36.4% (16)	20% (4)
Mixed Dialysis (n)	0.7 % (1)	.	.
Type of donor			
Deceased (n)	50% (71)	43.2% (19)	40% (8)
Hospitalizations days post-transplant			
Mean hospital days post-transplant (SD)	13.22 (5.58)	13.73(7.36)	12.35(4.92)
Magnesium levels (mmol/L)			
Mean magnesium levels (SD)	0.73(0.11)	0.73 (0.15)	0.77 (0.12)

Figure 1: Incidence of blood glucose dysregulation by days post-transplant

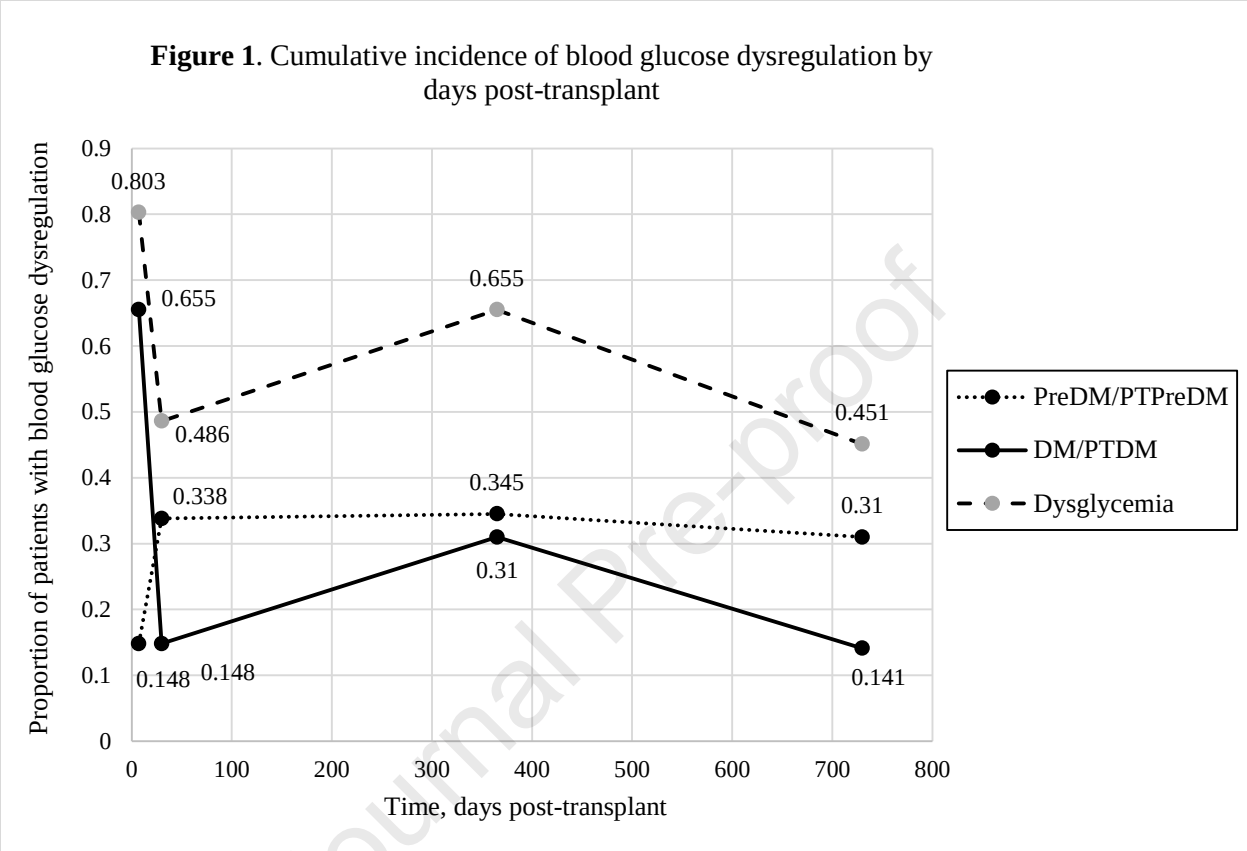
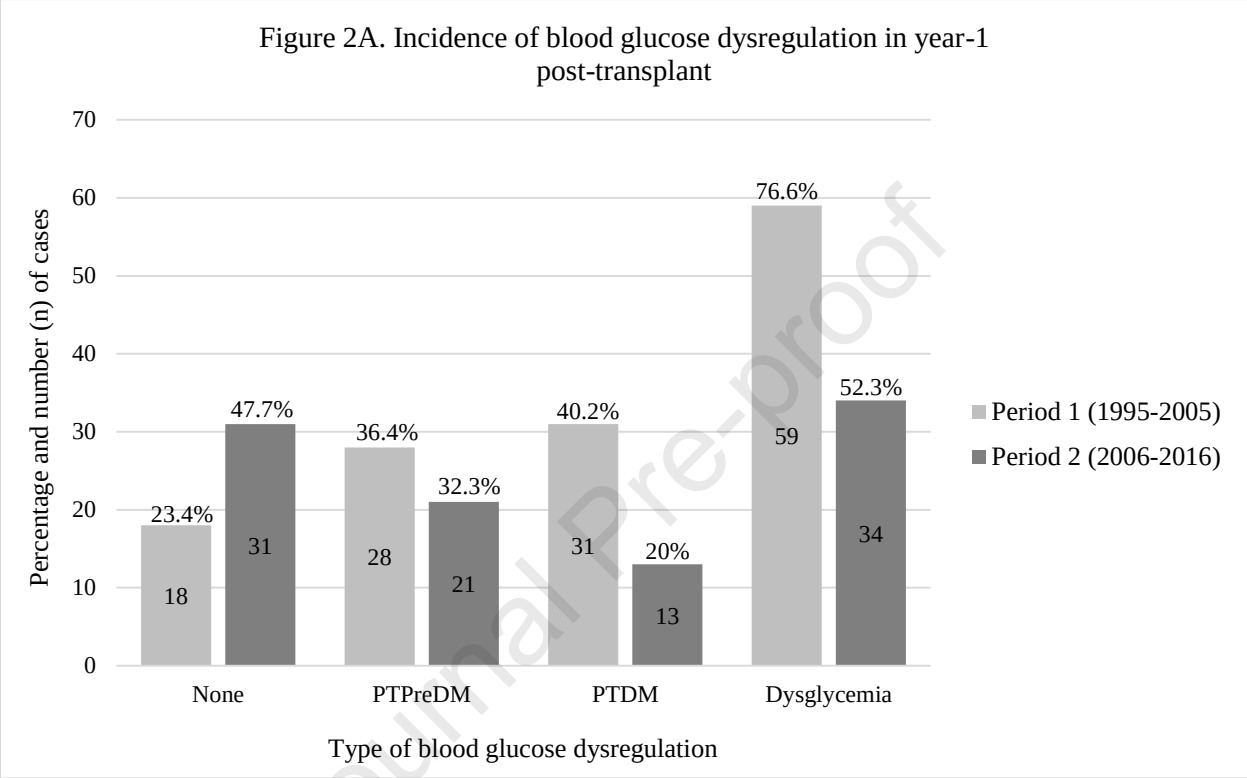


Figure 2: 2A – Incidence of blood glucose dysregulation in Year-1 post-transplant; 2B – Incidence of blood glucose dysregulation in Year-2 post-transplant



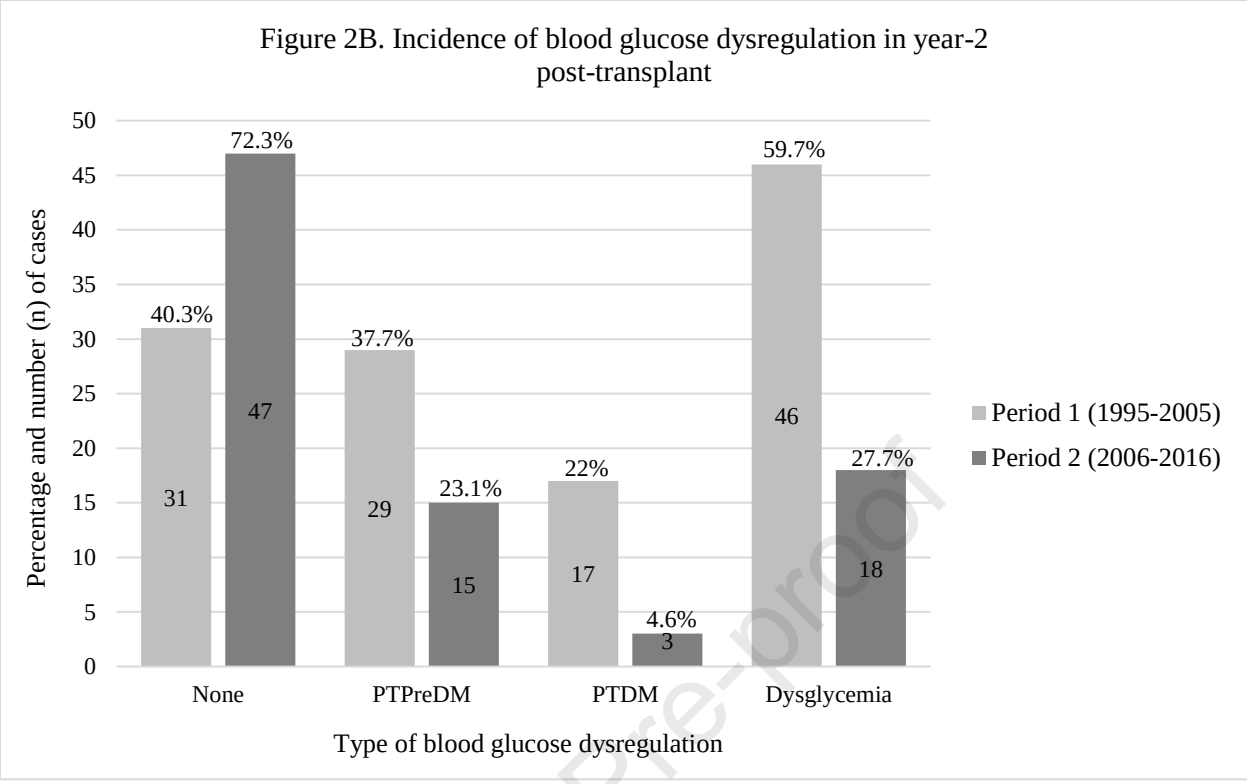


Figure 3: Probability of PTDM free survival with time post-transplant

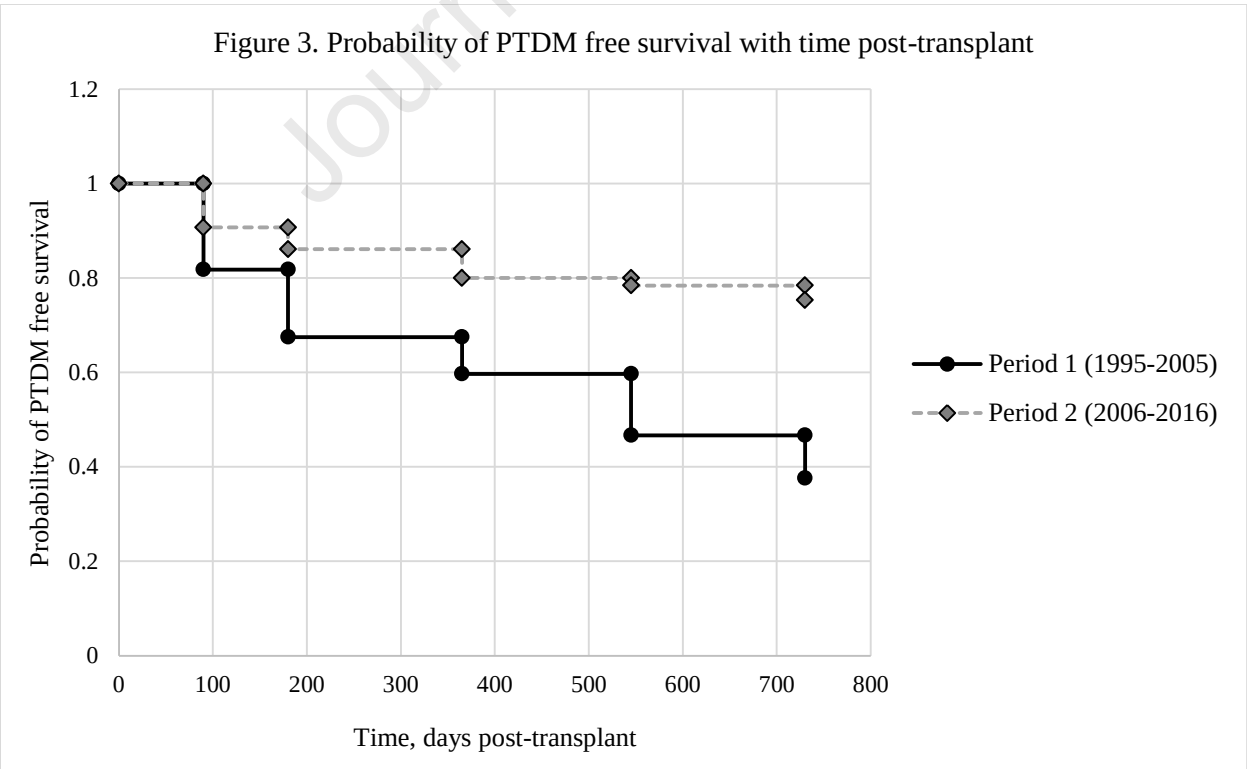


Figure 4: Immunosuppressive protocol in first month post-transplant in Period 1 (1995-2005) and Period 2 (2006-2016)

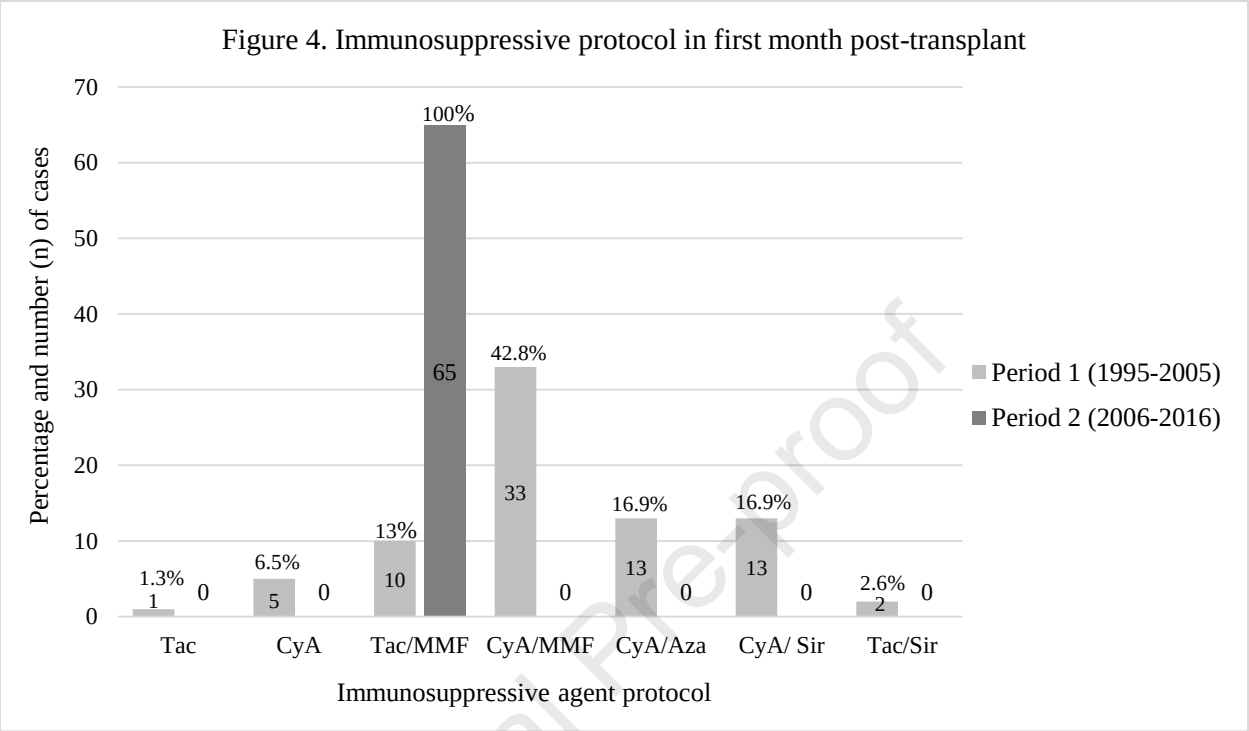


Table 3. Unadjusted and adjusted analysis of risk factors associated with PTDM

Variable	PTDM year 1 post-transplant [odds ratio (95% CI)]		PTDM year 2 post-transplant [odds ratio (95% CI)]	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Age				
Age at transplant	1.05 (0.98-1.12)	1.03 (0.93-1.13)	0.99 (0.90-1.08)	0.99 (0.88-1.14)
Sex				
Female	0.73 (0.35-1.51)	0.62 (0.25-1.49)	0.55 (0.20-1.54)	0.49 (0.16-1.48)
Ethnicity				
Caucasian	0.42 (0.19-0.89)†	0.48 (0.20-1.13)	0.84 (0.32-2.2)	1.07 (0.37-3.07)
Family history of diabetes				
Type 2 diabetes	0.58 (0.25-1.31)	0.63 (0.26-1.55)	0.74 (0.25-2.17)	0.78 (0.25-2.40)
BMI				
BMI z-score at transplant	1.01 (0.76-1.33)	0.89 (0.62-1.28)	0.97 (0.67-1.38)	0.95 (0.60-1.47)
Medication				
Cumulative dose steroids first 7 days PT	**2.63 (1.08-6.40)†**	2.36 (0.69-8.04)	0.76 (0.21,-2.73)	0.54 (0.11-2.67)
Tacrolimus use first 30 days PT	0.58 (0.28-1.18)	1.55 (0.5-4.82)	0.57 (0.21,-1.47)	0.87 (0.21-3.55)
Sirolimus use first 30 days PT	**2.89 (1.03-8.09)†**	**5.33 (1.16-24.35)†**	1.36 (0.35-5.24)	2.01 (0.30-13.37)
Blood glucose criteria				
Diabetes first 7 days PT	**8.21 (1.83-36.70)‡**	**.**	5.6 (0.71-44.33)	**.**
Diabetes 8-30 days PT	**7.73 (2.65-22.55)‡**	**.**	1.35 (0.32-5.63)	.
Dysglycemia first 7 days PT	**7.58 (1.71-33.57)‡**	.	5.4 (0.69-42.18)	.
Dysglycemia 8-30 days PT	**2.803 (1.33-5.88)‡**	**3.02 (1.21-7.53)†**	1.71 (0.65-4.47)	1.66 (0.54-5.01)

†significant at a $p \leq 0.05$; ‡ significant at a $p \leq 0.01$

Table 4. Unadjusted and adjusted analysis of risk factors associated with dysglycemia

Variable	Dysglycemia year-1 post-transplant [odds ratio (95% CI)]		Dysglycemia year-2 post-transplant [odds ratio (95% CI)]	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Age				
Age at transplant	1.05 (0.98-1.12)	1.06 (0.96-1.17)	1.00 (0.93-1.06)	1.03 (0.94-1.12)
Sex				
Female	0.55 (0.27-1.11)	0.40 (0.17-0.93)†	0.93 (0.47-1.82)	0.78 (0.35-1.72)
Ethnicity				
Caucasian	1.05 (0.52-2.11)	1.68 (0.73-3.87)	0.90 (0.46-1.74)	1.40 (0.64-3.03)
Family history of diabetes				
Type 2 diabetes	0.73 (0.34-1.53)	0.67 (0.28-1.58)	1.63 (0.79-3.34)	1.49 (0.67-3.30)
BMI				
BMI z score at transplant	1.21 (0.92-1.59)	1.22 (0.83-1.78)	1.28 (0.98-1.67)	1.29 (0.9-1.84)
Medications				
Cumulative dose steroids first 7 days PT	2.29 (0.94-5.54)	1.19 (0.35-4.03)	1.40 (0.61-3.19)	0.67 (0.21-2.14)
Tacrolimus use first 30 days PT	0.34 (0.15-0.71)‡	0.62 (0.19-1.98)	0.37 (0.18-0.72)‡	0.74 (0.26-2.06)
Sirolimus use first 30 days PT	1.83 (0.56-5.94)	2.84 (0.5-16.15)	**4.72 (1.45,15.28)‡**	**4.97 (1.12-21.90)†**
Blood glucose criteria				
Diabetes first 7 days PT	**5.30 (2.15-13.04)‡**	.	**7.95 (2.55-24.72)‡**	.
Diabetes 8-30 days PT	**5.84 (1.58-21.53)‡**	.	1.36 (0.50-3.64)	.
Dysglycemia first 7 days PT	**3.96 (1.67-9.37)‡**	.	**6.66 (2.17-20.43)‡**	.
Dysglycemia between 8-30 days PT	**4.19 (1.96-8.94)‡**	**4.50 (1.74-11.61)‡**	**2.22 (1.12-4.34)†**	2.10 (0.92-4.80)

†significant at a $p \leq 0.05$; ‡ significant at a $p \leq 0.01$