Nephrol Dial Transplant (2019) 34: 524–531
doi: 10.1093/ndt/gfy213
Advance Access publication 30 July 2018

ndt
Nephrology Dialysis Transplantation

ORIGINAL ARTICLE

Incidence of new-onset diabetes mellitus and association with mortality in childhood solid organ transplant recipients: a population-based study

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ABSTRACT

Background. Precise estimates of the long-term risk of new-onset diabetes and its impact on mortality among transplanted children are not known.

Methods. We conducted a cohort study comparing children undergoing solid organ (kidney, heart, liver, lung and multiple organ) transplant ($n = 1020$) between 1991 and 2014 with healthy non-transplanted children ($n = 7\,134\,067$) using Ontario health administrative data. Outcomes included incidence of diabetes among transplanted and non-transplanted children, the relative hazard of diabetes among solid organ transplant recipients, overall and at specific intervals posttransplant, and mortality among diabetic transplant recipients.

Results. During 56 019 824 person-years of follow-up, the incidence rate of diabetes was 17.8 [95% confidence interval (CI) 15–21] and 2.5 (95% CI 2.5–2.5) per 1000 person-years among transplanted and non-transplanted children, respectively. The transplant cohort had a 9-fold [hazard ratio (HR) 8.9; 95% CI 7.5–10.5] higher hazard of diabetes compared with those not transplanted. Risk was highest within the first year after transplant (HR 20.7; 95% CI 15.9–27.1), and remained elevated even at 5 and 10 years of follow-up. Lung and multiple organ recipients had a 5-fold (HR 5.4; 95% CI 3.0–9.8) higher hazard of developing diabetes compared with kidney transplant recipients. Transplant recipients with diabetes had a three times higher hazard of death compared with those who did not develop diabetes (HR 3.3; 95% CI 2.3–4.8).

Conclusions. The elevated risk of diabetes in transplant recipients persists even after a decade, highlighting the importance of ongoing surveillance. Diabetes after transplantation increases the risk of mortality among childhood transplant recipients.

Keywords: administrative databases, cohort study, death, incidence, outcomes

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Diabetes mellitus is an important public health issue due to its increasing burden, health resource utilization and long-term complications [1]. Over the last two decades, the incidence of diabetes has increased not only in adults but also in children and adolescents, primarily due to changes in the lifestyle, dietary habits and increase in the prevalence of obesity.

In addition to the general population, solid organ transplant (SOT) recipients are also at an increased risk of diabetes [2].

Although transplantation leads to significant improvements in quality of life and life expectancy, long-term exposure to the underlying cause of end-organ failure, transplant medications and chronic inflammation predisposes children to develop comorbidities after transplantation. Among the various complications, new-onset diabetes after transplantation is a major clinical problem that affects long-term graft and patient survival, at least partly due to cardiovascular and infectious complications [3, 4].

Data on the incidence of diabetes are scarce in pediatric SOT recipients and have been previously reported from small study populations with variably defined outcomes [4]. Diabetes after transplantation could be transient, related to medications and other factors. Only recently, we reported the incidence rates (IRs) of hyperglycemia and insulin-treated diabetes 3 years after transplantation [5]. Yet, there are few population-based studies with long-term follow-up as children age into adulthood. Although the first few years after transplantation confer the greatest risk of diabetes in SOT recipients, the magnitude and direction of the long-term risk up to 10 years in transplanted children is unknown. The incidence of diabetes in all children is rising, and it is also not known if rates are greater among those transplanted compared with the general pediatric population. Furthermore, the strong association of diabetes with mortality is known in adults [6–8], but there are conflicting results among children [4].

The objectives of our study were to determine the absolute risk of new-onset diabetes among children with SOT using a validated administrative data case definition, and to compare this risk with that observed among Ontarian children without a transplant. We also determined the risk of all-cause mortality associated with diabetes among the transplanted children. We hypothesized that the risk of diabetes in pediatric SOT recipients is higher as compared with those without a transplant, with the risk greatest early after transplantation and then rates becoming similar to the general population as children age. The universal health care system in Ontario provides a unique opportunity to study long-term outcomes among the pediatric population as they age into adulthood.

MATERIALS AND METHODS

Setting and participants

This is a cohort study of children who received their SOT at the Hospital for Sick Children (SickKids), in Toronto, Canada. Institutional ethics approval was obtained from the Research Ethics Boards at SickKids and Sunnybrook Health Science Centre, Toronto, Canada. The reporting of the results is in compliance with the Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) statement [9].

Study population

(i) Transplant cohort: children (0–18 years) with their first SOT (kidney, liver, lung, heart, multiple organs) between 1 January 1991 and 31 December 2014 at SickKids ($n = 1020$).

(ii) Non-transplanted cohort: children chosen from the general population born in Ontario (~7 million) during the same year as transplanted children. The rationale to include all children is that the incidence of diabetes mellitus in the general pediatric population is quite low, but the inclusion of only 'healthy' children may further inflate the relative risk of new-onset diabetes mellitus in transplant recipients.

We excluded children who were aged >18 years at the time of study entry, non-Ontario residents, those with an invalid Ontario health card and those with Ontario Health Insurance Plan (OHIP) eligibility gaps of >1 year. We excluded those with any history of SOT in the non-transplant group using a look-back window of 3 years from the index date.

Data sources and linkage

We identified all children with a SOT through clinical electronic medical records at the Hospital for Sick Children with data on all pediatric transplants from 1991 onwards. We used these electronic medical records to generate the list of patients and also validated the list with additional electronic and paper sources. Data from this cohort were linked to health administrative databases at the Institute for Clinical Evaluative Sciences (ICES) to determine the study outcomes. ICES Databases used in this study were the Ontario Registered Persons Database (contains information on date of birth, death, sex, location of residence and vital status), the OHIP Claims Database (contains all physician billings claims, including type and date of service and primary diagnosis), the Canadian Institute for Health Information Discharge Abstract Database (captures procedural and diagnostic information on all inpatient hospitalizations) and the Canadian Organ Replacement Register (used to determine patients' history of transplantation).

Outcome assessment and classification

We used a validated definition of diabetes based on International Classification of Disease and OHIP codes: four OHIP claims and no hospital records within 2 years for children, that is, aged <18 years (83% sensitivity, 99% specificity) [10] and one hospital or two OHIP claims within a 2-year period for adults (86% sensitivity, 97% specificity, 80% positive predictive value) [11] (Supplementary data, Table S1). Children were followed from the index date until the development of diabetes mellitus. They were censored at death, transfer out of province, loss of OHIP coverage or 31 March 2015.

Covariates

We included covariates available in administrative data in both transplanted and general population that could influence development of diabetes. These included age, sex, neighborhood income quintile, rural residence, donor status (living or deceased) and era (1991–2002 versus 2003–14). The index date was defined as the date of transplant in the transplant cohort. Children in the non-transplant cohort were born in the same birth year as the transplant cohort and survived until inception to the study. An index date was randomly assigned to each member of the non-transplant cohort based on the distribution of transplant dates in the transplant cohort, stratified by birth year and sex using methodology from previous ICES-based studies [12]. Socioeconomic status was defined by

neighborhood income as determined by the first three digits of the postal code from the census data by Statistics Canada [13]. The average neighborhood income was categorized into quintiles based on the average neighborhood income for all persons in Ontario, quintile 1 was the lowest income category of <$40 000, and quintile 5 >$125 000. The income quintile is based on the average neighborhood household income, adjusted for household size and housing costs. Rurality was defined by a community size of fewer than 10 000 persons. The study period was divided into two eras, Era 1 (1991–2002) and Era 2 (2003–14), to determine whether the risk of diabetes differed in these two periods.

Statistical analysis

Continuous variables were reported as means (±SD) or medians [interquartile range (IQR)], depending on the data distribution. Categorical variables were reported as frequencies and percentages. We assessed all continuous variables for distribution using both graphical and numerical methods.

For absolute risk of diabetes, IRs (per 1000 person-years) were calculated overall and at specific time intervals after study entry (0–1, 1–5, 5–10 and >10 years). Stratified analyses were performed to determine the IRs of diabetes across eras and various organ-specific groups.

The Kaplan–Meier product-limit method was used to calculate the cumulative incidence of diabetes mellitus. The proportional hazards assumption was graphically examined using log-log plots and scaled Schöenfeld residuals. Due to violations of the proportional hazards assumption, time-dependent Cox proportional hazards models were fitted by dividing follow-up time into periods during which the assumption was not violated (i.e. 0–1, 1–5, 5–10 and >10 years). Three sequentially nested Cox proportional hazards models were fitted to estimate the relative hazard of diabetes: Model 1 was the univariable association for transplant versus non-transplant cohorts. Model 2 adjusted for the demographics of age at index date and sex. Model 3 adjusted for variables in Model 2 along with rural status, income quintile, era and donor status. Subgroup analyses were performed to determine if the relative hazard of diabetes differed by era and across various organ-specific groups.

We also examined the effect of posttransplant diabetes on mortality using Cox proportional hazards model treating diabetes as a time-dependent exposure.

Sensitivity analyses

We performed sensitivity analyses to assess the robustness of the findings. As lung and multiple organ transplant recipients commonly have cystic fibrosis, we determined the risk of diabetes after exclusion of the lung and multiple organ transplant recipients. We also determined the effect of the first transplant on the risk of diabetes, censoring transplant individuals at time of receipt of a subsequent organ transplant and non-transplant individuals on receipt of a SOT.

Analyses yielding a cell count of five or fewer study participants were reported as '<6' in accordance with ICES privacy policies. Analyses were performed using Stata/MP, version 13 (StataCorp, College Station, TX, USA). A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Based on the inclusion and exclusion (Supplementary data, Table S2) criteria, 988 individuals were retained in the transplant cohort and 5 281 978 in the non-transplant cohort (Supplementary data, Figure S1).

Baseline features were comparably distributed across both cohorts (Table 1). The median follow-up duration was 9.2 (IQR 3.9–15.9) years for the entire cohort. Kidney, lung and multiple organ recipients were older compared with liver and heart recipients at the time of transplant.

IRs of diabetes

During 56 019 824 person-years of follow-up, the IR of diabetes in the transplant cohort [IR 17.8 per 1000 person-years; 95% confidence interval (CI) 15–21] was significantly higher than in the non-transplant cohort (IR 2.5 per 1000 person-years; 95% CI 2.5–2.5) (Table 2). The median age at onset of diabetes also was lower in the transplant group: 15.7 years (IQR 13.3–19.9) versus 21.4 years (IQR 15.6–27.8) among the non-transplant group. Moreover, transplanted children developed diabetes much earlier (1.9 years; IQR 0.3–8.6) than non-transplanted children (8.7 years; IQR 3.6–14). In all, 98 (71%) individuals in the transplant cohort developed diabetes at <18 years of age compared with 49 635 (35%) in the non-transplant cohort.

The IR of diabetes (61.6 per 1000 person-years; 95% CI 47.2–80.4) was the highest within the first year after transplantation. After the first year, the IR declined to one-fifth but remained consistently five to six times greater than those in the non-transplant cohort even after a decade of follow-up (Table 2).

Among the children in the individual organ groups, the IR of diabetes per 1000 person-years was highest in the lung and multiple organ transplant recipients (IR 111.3; 95% CI 70.7–178.2). The risk was also highest within the first year of transplant and was 5–20 times higher compared with other SOT recipients. Risk declined after the first year but remained two to four times higher compared with other organ recipients until a decade after transplant (Table 3).

In stratified analysis by era (Supplementary data, Table S3), in the first year, the IR (69.1 per 1000 person-years; 95% CI 49.9–95.8) of diabetes was higher in Era 2 for the transplant group as compared with Era 1 (50.5 per 1000 person-years; 95% CI 31.8–80.2). This trend continued until 5 years after the index date.

Risk of diabetes

The cumulative incidence of diabetes at 1, 5, 10 and >10 years in the transplant cohort was 5.8%, 10.3%, 14.8% and 36.0% compared with 0.3%, 0.9%, 2.0% and 6.7%, respectively, in the non-transplant cohort. Overall, the transplant cohort had seven times [hazard ratio (HR) 7.4; 95% CI 6.2–8.7] higher relative hazard of diabetes as compared with the non-transplant cohort (Table 2). After adjusting for potential confounders, there was no significant change in the relative hazard (HR 8.9; 95% CI 7.5–10.5). The adjusted relative hazard of diabetes was highest in the first year (HR 20.7; 95% CI 15.9–27.1) after study

Table 1. Baseline demographic, organ type and donor status of the transplanted and healthy children in Ontario from 1991 to 2014

Characteristics	Transplant cohort				Non-transplant cohort	Overall
	Kidney $n=406$	Heart $n=221$	Liver $n=310$	Lung and multiple[a] $n=51$	$n=5\,281\,978$	$n=988$
Mean ± SD age at transplant (years)	10.7 ± 5.0	5.7 ± 6.3	4.9 ± 5.7	10.4 ± 5.7	8.2 ± 6.4	7.8 ± 6.2
Males, *n* (%)	239 (58.9)	121 (54.7)	155 (50.0)	21 (41.2)	2 632 984 (49.8)	536 (54.2)
Era of transplant, *n* (%)						
1991–2002	182 (44.8)	89 (40.3)	115 (37.1)	12 (23.5)	2 224 510 (42.1)	398 (40.3)
2003–14	224 (55.2)	132 (59.7)	195 (62.9)	39 (76.5)	3 057 468 (57.9)	590 (59.7)
Living donation, *n* (%)	178 (43.8)	0	97 (31.4)	0	NA[b]	275 (27.9)
Income quintile, *n* (%)						
1	78 (19.2)	49 (22.2)	81 (26.1)	8 (15.7)	1 077 103 (20.4)	216 (21.9)
2	90 (22.2)	40 (18.1)	57 (18.4)	8 (15.7)	1 012 407 (19.2)	195 (19.7)
3	82 (20.2)	51 (23.1)	52 (16.8)	14 (27.4)	1 047 173 (19.8)	199 (20.1)
4	84 (20.7)	40 (18.1)	72 (23.2)	11 (21.6)	1 091 174 (20.7)	207 (20.9)
5	72 (17.7)	41 (18.5)	48 (15.5)	10 (19.6)	1 016 244 (19.2)	171 (17.3)
Rural status					688 941 (13.1)	137 (13.9)[c]

[a]Due to small number of transplant recipients in the lung and multiple organ recipients, they were combined and studied as a single group.
[b]NA, not applicable.
[c]Individual data in organ groups not shown due to small cell sizes <6.

Table 2. Incidence and risk of diabetes in the transplant and non-transplant cohorts, overall and at specific time intervals from 1991 to 2014

Results	Transplant cohort	Non-transplant cohort
Overall		
Number with diabetes, *n*	138	141 108
IR per 1000 person-years (95% CI)	17.8 (15.0–21.0)	2.5 (2.5–2.5)
Incidence rate ratio (95% CI)	7.0 (5.9–8.3)	Ref.
Model 1[a] (HR; 95% CI)	7.4 (6.2–8.7)	Ref.
Model 2[b]	8.9 (7.5–10.5)	Ref.
Model 3[c]	8.9 (7.5–10.5)	Ref.
0–1 years		
Number with diabetes	54	15 844
IR per 1000 person-years (95% CI)	61.6 (47.2–80.4)	3.1 (3.0–3.1)
Incidence rate ratio (95% CI)	11.9 (9.0–15.6)	Ref.
Model 1(HR; 95% CI)	19.7 (15.1–25.7)	Ref.
Model 2	20.9 (15.9–27.2)	Ref.
Model 3	20.7 (15.9–27.1)	Ref.
1–5 years		
Number with diabetes	35	29 069
IR per 1000 person-years (95% CI)	12.8 (9.2–17.8)	1.7 (1.7–1.7)
Incidence rate ratio (95% CI)	5.8 (4.1–8.1)	Ref.
Model 1(HR; 95% CI)	7.6 (5.4–10.6)	Ref.
Model 2	8.3 (6.0–11.6)	Ref.
Model 3	8.4 (6.0–11.7)	Ref.
5–10 years		
Number with diabetes	22	34 538
IR per 1000 person-years (95% CI)	9.7 (6.4–14.8)	2.1 (2.1–2.2)
Incidence rate ratio (95% CI)	3.2 (2.0–4.8)	Ref.
Model 1(HR; 95% CI)	4.5 (2.9–6.9)	Ref.
Model 2	5.5 (3.6–8.4)	Ref.
Model 3	5.6 (3.7–8.4)	Ref.
>10 years		
Number with diabetes	27	61 657
IR (per 1000 person-years)	14.3 (9.8–20.8)	3.5 (3.5–3.5)
Incidence rate ratio (95% CI)	3.6 (2.4–5.3)	Ref.
Model 1 (HR; 95% CI)	4.2 (2.9–6.1)	Ref.
Model 2	5.6 (3.8–8.2)	Ref.
Model 3	5.6 (3.8–8.2)	Ref.

[a]Model 1, unadjusted model.
[b]Model 2, adjusted for age at study entry and sex.
[c]Model 3, adjusted for age, sex, income quintile, rural status, era of transplant.

Table 3. Incidence and risk of diabetes in the individual organ groups, overall and at specific time intervals from 1991 to 2014

Results	Kidney	Heart	Liver	Lung and multiple
Overall				
Number with diabetes	70	26	24	18
IR per 1000 person-years (95% CI)	18.8 (14.9–23.8)	17.3 (11.8–25.4)	10.0 (6.7–15.0)	111.3 (70.7–178.2)
Model 1[a] (HR; 95% CI)	Ref.	0.9 (0.6–1.4)	0.5 (0.3–0.8)	4.4 (2.6–7.5)
Model 2[b]	Ref.	1.5 (0.9–2.4)	0.9 (0.6–1.5)	5.1 (3.0–8.7)
Model 3[c]	Ref.	1.6 (0.9–2.6)	0.9 (0.6–1.6)	5.4 (3.0–9.8)
0–1 years				
Number with diabetes	28	6	6	14
IR per 1000 person-years (95% CI)	74.4 (51.4–107.8)	32.0 (14.4–71.2)	21.5 (9.6–47.8)	412.2 (244.1–696.1)
Model 1 (HR; 95% CI)	Ref.	0.4 (0.2–1.0)	0.3 (0.1–0.7)	4.9 (2.6–9.3)
Model 2	Ref.	0.8 (0.3–2.0)	0.6 (0.2–1.5)	5.1 (2.7–9.9)
Model 3	Ref.	1.0 (0.4–2.5)	0.7 (0.3–1.7)	5.6 (2.6–12.3)
1–5 years				
IR per 1000 person-years (95% CI)	12.3 (7.4–20.3)	14.9 (7.8–28.7)	9.4 (4.7–18.7)	48.0 (15.5–148.8)
Model 1 (HR; 95% CI)	Ref.	1.2 (0.5–2.8)	0.7 (0.3–1.8)	3.8 (1.1–13.0)
Model 2	Ref.	2.1 (0.9–4.8)	1.5 (0.6–3.7)	5.0 (1.4–17.5)
Model 3	Ref.	2.2 (0.8–5.8)	1.6 (0.6–3.9)	5.3 (1.4–20.2)
5–10 years				
IR per 1000 person-years (95% CI)	11.9 (6.9–20.6)	6.6 (2.1–20.5)	7.4 (3.1–17.8)	23.3 (3.3–165.6)
Model 1 (HR; 95% CI)	Ref.	0.6 (0.2–2.0)	0.6 (0.2–1.8)	2.1 (0.3–15.8)
Model 2	Ref.	0.9 (0.2–3.5)	1.1 (0.3–3.2)	2.8 (0.4–22.0)
Model 3	Ref.	0.7 (0.2–2.9)	0.9 (0.3–2.7)	2.0 (0.2–17.3)
>10 years				
IR per 1000 person-years (95% CI)	13.6 (8.0–22.9)	30.8 (15.4–61.6)	8.6 (3.6–20.7)	–
Model 1 (HR; 95% CI)	Ref.	2.7 (1.1–6.6)	0.7 (0.2–2.0)	–
Model 2	Ref.	3.2 (1.2–8.4)	0.8 (0.3–2.4)	–
Model 3	Ref.	3.6 (1.2–10.6)	0.7 (0.2–2.3)	–

[a]Model 1, unadjusted model.
[b]Model 2, adjusted for age at study entry and sex.
[c]Model 3, adjusted for age, sex, income quintile, rural status, era of transplant.

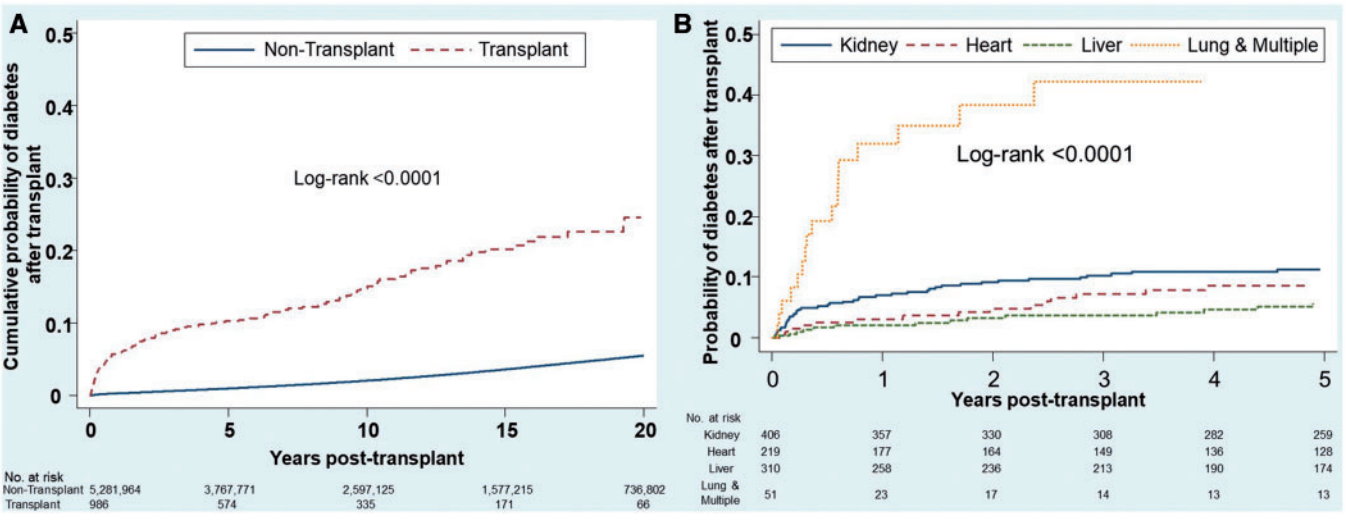

FIGURE 1: **(A)** Cumulative risk of diabetes in the transplant and non-transplant cohort. Children with SOT are compared with non-transplanted children in Ontario. **(B)** Cumulative risk of diabetes among individual organ transplant groups. Cumulative risk of diabetes is compared among individual SOT groups. P-values are calculated by univariate log-rank test.

entry. Later, the relative hazard of diabetes reduced but remained approximately five to eight times higher in the transplant cohort as compared with the non-transplant cohort (Table 2 and Figure 1A).

Among the individual organ groups, lung and multiple organ recipients were at highest risk of developing diabetes. The relative hazard of diabetes was five times higher (HR 5.4; 95% CI 3.0–9.8) compared with kidney transplant recipients during the entire study period (Table 3 and Figure 1B). The risk of developing diabetes in lung and multiple organ recipients was highest within the first year after transplant (HR 5.6; 95% CI 2.6–12.3). After the first year, the risk in the lung and

multiple organ groups was attenuated but remained two to five times higher compared with kidney transplant recipients.

The relative hazard of diabetes was higher in the transplant cohort during Era 2 (HR 12.6; 95% CI 9.8–16.3) compared with Era 1 (HR 7.3; 95% CI 5.8–9.1) (Supplementary data, Table S4). The results of sensitivity analyses were similar to the main analyses. After excluding the lung and multiple organ transplant recipients, the risk of diabetes in the transplant cohort was eight times (HR 7.9; 95% CI 6.6–9.5) higher than the non-transplant cohort (Supplementary data, Table S5). The risk of diabetes did not change significantly after censoring individuals who received a transplant after the index date (Supplementary data, Tables S6 and S7).

Association of diabetes with mortality

We found a strong association of post-transplant diabetes with mortality among the transplant recipients. In the unadjusted model, there was a three times higher hazard of mortality among transplant recipients with diabetes compared with those without diabetes (HR 3.4; 95% CI 2.3–4.9). After adjusting for sex, the relative hazard of mortality was not attenuated (HR 3.3; 95% CI 2.3–4.8).

DISCUSSION

This is the first study to determine the long-term risk of new-onset diabetes in a population-based cohort of pediatric SOT recipients compared with healthy children. We demonstrate that there is a considerable burden of diabetes in children after transplantation, and risk of diabetes remains an issue as children age into young adults. Our results show that, among transplant recipients who develop diabetes, most do so during childhood, and the greatest risk of diabetes is in the first year of transplant. The overall risk of diabetes is nine times higher in SOT recipients compared with non-transplanted children. Within the first year, however, the relative risk is 20 times greater in children with a SOT compared with healthy children. After the first year, the risk of diabetes declines but remains at least five times higher even a decade after transplant compared with non-transplanted individuals. Among the individual organ groups, lung and multiple organ transplant recipients have the highest risk of developing diabetes compared with heart, kidney or liver transplant recipients. New-onset diabetes is also associated with a three times higher risk of mortality among the transplant recipients.

No prior studies have compared the risk of diabetes post-transplant with a healthy pediatric cohort, nor followed children after age 18 years to determine the risk as young adults. Several study findings deserve emphasis. First, a majority of transplanted individuals developed diabetes during their childhood in their mid-teens when they were transitioning to adult care. Hence, it is important to consider routine screening in these children for diabetes, especially during the peri-transition period. This is a time associated with increased graft loss and concerns for non-adherence [14]. Second, transplant recipients remain at a five times higher risk of diabetes compared with non-transplanted individuals, even after 10 years of follow-up. This suggests that other transplant factors in addition to immunosuppressive medications (which are typically reduced after the first year) are important in the development of diabetes, and that regular monitoring for diabetes after the first year is critical. Previously, we demonstrated that hyperglycemia and insulin-treated diabetes occurred in 14.8% and 6% of children, respectively, within a median of 52 days after transplant. Those with hyperglycemia were at risk for diabetes, and more than 50% required insulin for >1 year, thus transient diabetes from corticosteroids was unlikely [5]. We now extend these findings, as risk for diabetes is persistent after the first year of transplantation. Importantly, our findings are in contrast to the current understanding that risk of diabetes in organ recipients achieves similar rates as wait-listed candidates after a few years of transplant [15, 16].

There is significant variation among previously reported rates of diabetes in children with SOT, ranging from 3% to 20% for kidney [17, 18], 8% to 14% for liver [19, 20] and 4% to 40% [21] for heart and heart/lung transplant recipients. Several factors could explain the significant differences in diabetes risk among organ groups. The definition of diabetes has not been consistent across studies, nor has the timing of diagnosis of diabetes after transplant [22]. Variable follow-up after transplant also contributes to differences in the reported incidence of diabetes among various organ groups. To help address these limitations, we used validated algorithms to define diabetes across a large, diverse cohort of transplant recipients from the time of transplant to last available follow-up as children age.

Prior studies have shown a strong impact of diabetes on mortality in adult transplant recipients [6–8, 23]. However, the association of diabetes with mortality is not clear among pediatric transplant recipients. As previously reported in a study on 2168 pediatric renal transplant recipients, there was no significant association between diabetes and mortality (HR 1.51; 95% CI 0.57–3.99) during a 3 years follow-up [24]. On the contrary, a study in Canada demonstrated a 2.7-fold higher risk of mortality [25] with diabetes among 274 pediatric renal transplant recipients (HR 2.79; 95% CI 1.04–7.44). In our study, we report that SOT recipients who develop diabetes have three times greater risk of mortality than those children who did not develop diabetes. However, we could not ascertain the cause of death as it is not well characterized in the provincial administrative data.

We compared the risk of diabetes across different eras to explore variations in immunosuppressive therapy practices, and revealed that the relative risk of diabetes was greater in the more recent era. This finding has several possible explanations, including the increasing burden of obesity [26], poor dietary habits and sedentary lifestyle, as well as temporal trends in post-transplant care and choice of immunosuppressive medications. In particular, use of tacrolimus has increased over the last decade across all SOT groups, which is more diabetogenic than cyclosporine. Also, a concomitant increase in the obesity both in general and the transplant population [27] may be responsible for the higher incidence of diabetes in the recent time periods. Finally, the higher incidence of diabetes may be due to greater awareness of diabetes and increased recognition by physicians over the last decade. Our study has provided more precise estimates of the incidence of diabetes, thus providing

information to families on long-term risk and the need for continued lifestyle modifications to decrease risk as they age.

We utilized the strengths of a single large regional referral center and universal health care system that captures data on all patients with eligible health care coverage and access to health care and medications. Use of health administrative data also permit unobtrusive follow-up of patients over a prolonged period. This study addresses prior concerns of predominantly cross-sectional studies, small sample sizes and short follow-up. It is novel as there are few studies among liver, lung and heart recipients with outcomes beyond age 18.

Our study also has several important limitations. Health administrative data in Ontario do not contain information on clinically relevant risk factors for diabetes, such as type and dose of immunosuppressive medications, family history of diabetes, lifestyle and dietary habits, all of which could potentially contribute to the development of diabetes. A potential source of misclassification bias is the increased surveillance of the transplant recipients. Children with a transplant have more frequent contacts with the health care system than non-transplanted children and are, therefore, at greater risk for diabetes detection. Additionally, validation algorithms were initially based on coding for hospitalized persons whereas transplant recipients may have a combination of inpatient and outpatient visits, thus we may have underestimated the incidence of diabetes. Also, health administrative data prevent differentiation between Type 1 and Type 2 diabetes. Finally, some children with stem cell transplantation may be included in the unexposed cohort, which if not present, would have lowered the incidence of diabetes.

To conclude, children with organ transplantation are at a higher risk of diabetes compared with non-transplanted individuals. The risk is highest, about 20 times, in the first year of transplant but remains 5 times elevated even a decade after transplantation. Although many recipients develop diabetes within the first year of transplantation, clinicians need to remain vigilant to monitor even as young adults. Lung and multiple organ recipients are at greatest risk thereby alerting physicians to the risk based on underlying chronic disease leading to end organ damage. Finally, post-transplant diabetes significantly increases the risk of mortality among children.

SUPLEMENTARY DATA

Supplementary data are available at ndt online.

FUNDING

We gratefully acknowledge funding from the Transplant & Regenerative Medicine Centre (TRMC) Catalyst Grant at The Hospital for Sick Children, and Canadian Institutes of Health Research (CIHR). These funding agencies had no role in the study design, collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

This study was supported by the ICES, a non-profit research institute sponsored by the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the authors and not necessarily those of CIHI.

AUTHORS' CONTRIBUTIONS

R.C. wrote the manuscript and researched data. S.J.K., S.N.D., V.J., J.V.-R., T.B., K.B., A.D., M.S., D.H., J.M.P. and V.N. reviewed/edited the manuscript and contributed to discussion. R.S.P. reviewed/edited the manuscript, researched data and contributed to discussion.

CONFLICT OF INTEREST STATEMENT

None declared.

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Received: 8.2.2018; Editorial decision: 11.6.2018

Nephrol Dial Transplant (2019) 34: 531–538
doi: 10.1093/ndt/gfy241
Advance Access publication 6 August 2018

The development of a predictive model of graft function in uncontrolled donors after circulatory death: validity of a pulsatile renal preservation machine cut-off value for kidney acceptance

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ABSTRACT

Background. The criteria for kidney suitability in uncontrolled donors after circulatory death (uDCD) procured after regional normothermic perfusion are based on macroscopic appearance and renal haemodynamic values with final renal resistance (FRR). However, these criteria have not been analysed to predict the future graft function. This study presents a model to predict the outcome in uDCD kidneys and define the predictive FRR value.

Methods. All uDCD kidney transplants performed in our hospital from 2004 to 2016 were included. Donors and recipients and pre-transplantation data are described. The endpoint was glomerular filtration rate (GFR) $\geq$30 mL/min at 6 months after transplantation.

Results. A total of 194 recipients were included. FRR in donors $\geq$60 years old was (mean $\pm$ SD) 0.27 $\pm$ 0.11 versus 0.22 $\pm$ 0.09 mmHg/mL/min in donors <60 years ($P = 0.042$). Kidney survival was 88.2% versus 84% at 12 months and 60.7% versus 30.8% at 120 months ($P = 0.067$). For the group of recipients from donors $\geq$60 years, the FRR was 0.37 $\pm$ 0.08 mmHg/mL/min in the GFR <30 mL/min group versus 0.18 $\pm$ 0.06 mmHg/mL/min in the GFR $\geq$30 mL/min group ($P < 0.001$). The value FRR $\geq$0.3 mmHg/mL/min predicts 59–79% of GFR <30 mL/min [odds ratio = 2.16, 95% confidence interval (CI) 1.80–6.40; $P < 0.001$]. The predictive accuracy of FRR for GFR by ROC curve was 0.968 (95% CI). The best cut-off for FRR was 0.3 mmHg/mL/min to predict GFR at 6 months with a sensitivity of 67%, specificity of 100%, positive predictive value of 83% and negative predictive value of 92%.

Conclusions. Our results suggest that in uDCD donors the combination of donor age $\geq$60 years together with FRR $\geq$0.3 mmHg/mL/min could predict poor outcome at 6 months after transplantation in low immunological risk recipients.

Keywords: delayed graft function, GFR, graft survival, kidney biopsy, kidney transplantation

INTRODUCTION

The growing demand for organs for transplantation has promoted a recent development of donors after circulatory death