ORIGINAL ARTICLE

Risk of post-transplantation diabetes mellitus is greater in South Asian versus Caucasian kidney allograft recipients

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SUMMARY

South Asians have increased risk for type 2 diabetes mellitus compared with Caucasians in the general population, but data for the development of post-transplantation diabetes mellitus (PTDM) is scarce. In this retrospective analysis, data was extracted from electronic patient records at a single centre (2004–2014). Caucasians were more likely to be male, with higher age and BMI than South Asians. Case–control matching was therefore undertaken to remove this bias, resulting in 102 recipient pairs. Median follow-up was 50 months (range 4–127 months). Matched groups had similar baseline characteristics, although South Asians compared with Caucasians received more deceased-donor kidneys (74% vs. 43%, respectively, $P < 0.001$) and were more likely to be CMV positive (77% vs. 43%, respectively, $P < 0.001$). PTDM incidence was significantly higher in South Asians versus Caucasians (35% vs. 10%, respectively, subhazard ratio 4.2 [95% CI: 2.1–8.5, $P < 0.001$]). Donor type had significant interaction with ethnicity, with the observed difference in PTDM rates between ethnicities most visible with receipt of deceased-donor kidneys. No significant difference was detected in allograft function, rejection episodes, adverse cardiovascular events or patient/graft survival. South Asians have increased risk of PTDM, especially recipients of deceased kidneys, and recognition of this allows appropriate patient counselling and development of targeted strategies.

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Introduction

Post-transplantation diabetes mellitus (PTDM) is a common medical complication arising after kidney transplantation and is associated with increased morbidity, mortality and cost [1]. Risk factors for PTDM are well described, and one of the most important nonmodifiable risk factors for PTDM is ethnicity [2]. However, literature regarding ethnicity risk for PTDM has predominantly focused on data relating to African Americans and Hispanics [2]. In the context of South Asian (or Indo-Asian) ethnicity, data relating to risk for PTDM is contradictory. Dooldeniya and colleagues described an increased risk of PTDM among South Asians compared with Caucasians nearly 10 years ago in an English cohort [3], but a subsequent analysis by

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Prasad and colleagues identified no difference between the ethnic groups for the development of PTDM in a Canadian cohort [4]. These differences can be largely explained by different eras, immunosuppression and diagnostic criteria applied for PTDM, rendering a direct comparison between the studies difficult.

These conflicting results expose an important gap in our literature. Firstly, residents of South Asia (incorporating India, Pakistan, Bangladesh, Sri Lanka, Nepal and Bhutan) comprise nearly a quarter of the total global population (1.7 billion persons) [5]. Migration has made South Asians a growing minority ethnic group in Western countries. For example, they are the largest minority ethnic group in both the UK (4.9%, 3 078 374 persons) and Canada (4.8%, 1 567 400 persons) [6,7]. From a transplantation perspective, they are important as in the UK they comprised 13.1% of the incident kidney transplant cohort last year and they constitute 18.0% of the kidney transplant waiting list, due to increased risk for end-stage kidney disease requiring renal replacement therapy [8]. The second important observation is that South Asians have significantly greater risk for type 2 diabetes mellitus compared with Caucasians in the general population, due to both genetic and environmental factors [9], which contributes to their increased cardiovascular risk profile [10]. Indeed, South Asians are estimated to have a four- to sixfold increased risk for developing diabetes in the general population (approximate prevalence of 20% in South Asians versus 4% prevalence in Caucasians), with a younger age of onset and a greater proportion with undiagnosed diabetes [10]. As incidence of both PTDM and cardiovascular events is increased in the context of kidney transplantation, South Asian kidney allograft recipients are intuitively thought to be more susceptible to these medical complications, but existing data does not support this assumption. One of the key recommendations from a recent PTDM consensus meeting of international experts is to clearly identify patients at risk for PTDM [11], and it is therefore important to quantify PTDM risk for South Asian kidney allograft recipients to improve clinical management and patient counselling.

Therefore, we aimed to analyse the incidence of PTDM after kidney transplantation, using a matched-pair cohort comparing South Asian to Caucasian nondiabetic kidney allograft recipients. In addition, we sought to extract information relating to adverse cardiovascular events, allograft outcomes and mortality to determine any difference in hard outcomes between South Asians and Caucasians after kidney transplantation.

Patients and methods

Patient cohort

Our centre caters for an ethnically diverse English city and region – we perform kidney transplants for a Birmingham city population of 1 073 045 residents (25.4% South Asian) and a wider West Midlands regional population of 5 601 847 residents (10.2% South Asian) [6]. Our hypothesis was that South Asians would have significantly greater incidence of PTDM compared with Caucasians. To investigate this, we retrospectively extracted patient-level data from electronic patient records at a single centre for all adult South Asian and Caucasian kidney allograft recipients between April 2004 and April 2014. Patients were excluded from further analysis if they fulfilled any of the following criteria: history of pretransplant diabetes, repeat kidney transplant, multi-organ recipient and whether long-term follow-up was repatriated to original referral centre. Adverse cardiovascular events were defined as the following: acute coronary syndrome (including unstable angina, abnormal cardiac stress test or significant disease on coronary angiogram requiring intervention), coronary artery bypass surgery or death from cardiac cause. The study was conducted in accordance with the principles of the Declaration of Helsinki, received institutional approval (CARMS-11303) and was conducted in line with STROBE guidance for reporting of observational cohort studies (http://www.strobe-statement.org/).

Centre protocol

During the time period encompassing data collection, our immunosuppression protocols remained relatively static. Every kidney allograft recipient received induction therapy with basiliximab. All patients received a calcineurin inhibitor (CNI) as primary immunosuppressant; prior to 2007, the standard was cyclosporine (aiming for 12-h trough levels between 100 and 200 ng/l), with tacrolimus standard of care thereafter (achieving target 12-h trough levels of 5–8 ng/l). Mycophenolate mofetil (MMF) was commenced at a dose of 1 g twice daily. Every recipient received an intra-operatic dose of intravenous methylprednisolone at the time of transplantation (500 mg) followed by 10 mg twice-daily prednisolone, which is subsequently weaned down to a maintenance low-dose 5 mg once daily by 3 months post-transplantation in the absence of any rejection. Episodes of acute cellular rejection were treated with a

bolus of corticosteroids, with T-cell depletion therapy for steroid-resistant rejection. Antibody-mediated rejection was treated with antibody removal by plasmapheresis +/− intravenous immunoglobulin. Standard antibiotic prophylaxis after kidney transplantation was nystatin (3 months), co-trimoxazole (12 months), valganciclovir (3 months if deemed high risk [donor CMV+/recipient CMV−]) and isoniazid/pyridoxine (12 months if high risk for TB [previous TB, minority ethnic]). Cardiac assessment pretransplantation was standard for all kidney allograft recipients and included 3-yearly echocardiogram and 5-yearly noninvasive cardiac imaging. Any abnormalities, or cardiac symptoms, led to cardiology referral and formal coronary angiogram if indicated.

Diagnosis of PTDM

PTDM was diagnosed in line with the latest consensus recommendations [11]: symptoms of diabetes plus random plasma glucose ≥200 mg/dl (11.1 mmol/l), fasting plasma glucose ≥126 mg/dl (7.0 mmol/l), 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test or HbA1c ≥6.5% (48 mmol/mol). Patients were diagnosed with PTDM if any of the above criteria were present on at least two occasions, at least 3 months apart. PTDM was not diagnosed for recipients if only present during the immediate 3 months following transplant. All patients would get glucose levels checked with every clinic appointment, and HbA1c was routinely checked on all patients every 3 months indefinitely.

Statistical analysis

An initial comparison between patient demographics comparing South Asians and Caucasians was performed using independent samples *t*-tests and Fisher's exact tests, as applicable. Patients were then paired using 1:1 matching without replacement. The resulting groups were then compared to test the accuracy of the matching. The distributions of continuous variables were assessed prior to the analysis using graphical methods. Normally distributed variables were compared between groups using paired *t*-tests (after log-transformation where skew was observed), with Wilcoxon's test used for non-normal variables. Categorical variables with two categories were compared between the groups using McNemar's test, with Fisher's exact test used where there were more than two categories. Survival outcomes were analysed using a Kaplan–Meier approach, with log-rank tests used to make comparisons between the ethnicities.

Analyses of PTDM rates were performed using competing risks regression models, using the 'stcrreg' command in Stata 14 (StataCorp LP, Lakeway Drive, TX, USA), with death and transplant treated as the competing events. Based on these models, cumulative incidence curves were generated, and subhazard ratios for PTDM were calculated. Factors found to differ significantly between the groups were then considered in multivariable models Cox regression models. These models initially included interaction terms, which were excluded where nonsignificant.

A sensitivity analysis was also performed on the full cohort (prematching), using a multivariable Cox regression model, to test the association between ethnicity and PTDM after accounting for patient age, sex and BMI.

With the exception of the competing risks regression modelling, all analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA), with $P < 0.05$ deemed to be indicative of statistical significance. Patients with missing data were excluded on a per analysis basis.

Results

A total of 354 Caucasian and 121 South Asian kidney allograft recipients met the inclusion/exclusion criteria of the study. Comparison of the demographics of the two groups found Caucasians to be significantly older than South Asians (mean: 46.8 vs. 43.2, respectively, $P = 0.017$), more likely to be male (59% vs. 46%, respectively, $P = 0.011$) and with higher BMIs (mean: 26.4 kg/m^2 vs. 24.9 kg/m^2, respectively, $P = 0.002$). To remove the effects of these biases from the analysis, the patients were matched. Exact matches were used for gender and calliper matches for the continuous variables, within ±5 years of age, ±2.5 kg/m^2 of BMI and ±2 years of transplant date. This resulted in 102 pairs of patients, which were well matched on all of these variables (Table 1).

A range of factors were then compared between these two matched groups (Table 2). Rates of ABO-incompatible transplantation, hepatitis C, modes of renal replacement therapy prior to transplant, primary immunosuppression and smoking status were similar in the two ethnic groups. However, South Asian patients were found to be significantly more likely to receive deceased-donor kidneys (74% vs. 43%, respectively, $P < 0.001$) and to be CMV serostatus positive (77% vs.

Table 1. Demographic of the cohort before and after matching.

	All patients			Matched patients			
	Caucasian (*N* = 354)	South Asian (*N* = 121)	*P*-value	Caucasian (*N* = 102)	South Asian (*N* = 102)	*P*-value	Std. Diff.
Age (years)	46.8 (14.7)	43.2 (14.0)	0.017*	45.1 (13.4)	45.2 (13.3)	0.660	−0.009
Body mass index (kg/m^2)	26.4 (4.6)	24.9 (4.2)	0.002*	25.4 (3.7)	25.4 (3.8)	0.946	0.003
Gender (male)	210 (59.3%)	55 (45.5%)	0.011*	51 (50.0%)	51 (50.0%)	1.000	0.000

Continuous data reported as: 'mean (SD)', with *P*-values from independent/paired sample *t*-tests, as applicable. Dichotomous data reported as: '*N* (%)', with *P*-values from Fisher's exact/McNemar's tests, as applicable. Std. Diff = Standardized difference.
*Significant at $P < 0.05$.

Table 2. Comparison of factors between paired groups.

	N pairs	Caucasian	South Asian	*P*-value
Received deceased-donor kidney	102	44 (43%)	75 (74%)	<0.001†
ABO-incompatible transplant	102	5 (5%)	2 (2%)	0.453
Recipient hepatitis C+ status	102	0 (0%)	2 (2%)	0.480
Recipient CMV positive	87	37 (43%)	67 (77%)	<0.001†
CMV infection/viraemia	102	6 (6%)	8 (8%)	0.791
Nonsmoker	76	55 (72%)	64 (84%)	0.122
Cause of renal failure	62			0.117*
Polycystic kidney disease		19 (31%)	10 (16%)	
Inflammatory renal/IgA		19 (31%)	27 (44%)	
Other		24 (39%)	25 (40%)	
Mode of renal replacement therapy	102			0.419*
Pre-emptive		22 (22%)	17 (17%)	
Haemodialysis		43 (42%)	53 (52%)	
Peritoneal dialysis		30 (29%)	23 (23%)	
Both therapies		7 (7%)	9 (9%)	
Primary immunosuppression	102			1.000*
Tacrolimus		86 (84%)	86 (84%)	
Cyclosporine		13 (13%)	14 (14%)	
Sirolimus		3 (3%)	2 (2%)	

N Pairs: the number of pairs of patients included in each analysis, after excluding cases where one patient in the pair had missing data. Dichotomous factors are compared between groups by McNemar's test.
*Categorical variables compared using Fisher's exact test.
†Significant at $P < 0.05$.

43%, respectively, $P < 0.001$) compared with Caucasian patients (Appendices A–C).

Incidence of post-transplantation diabetes mellitus

A large difference in the rate of PTDM was observed (Fig. 1), with a cumulative incidence at 5 years of 35% in South Asians compared with 10% in Caucasians ($P < 0.001$). This resulted in a subhazard ratio for PTDM of 4.2 (95% CI: 2.1–8.5, $P < 0.001$).

In our cohort, PTDM was diagnosed in 20% of patients on the basis of HbA1c values alone. A further 16% were diagnosed on the basis of high random or fasting blood glucose levels. The majority (64% of patients) were diagnosed using a combination of high HbA1c and random blood sugar values. None of the patients included in this analysis had been diagnosed with an oral glucose tolerance test.

Since the rates of deceased-donor kidneys and CMV positivity had been found to differ between the two

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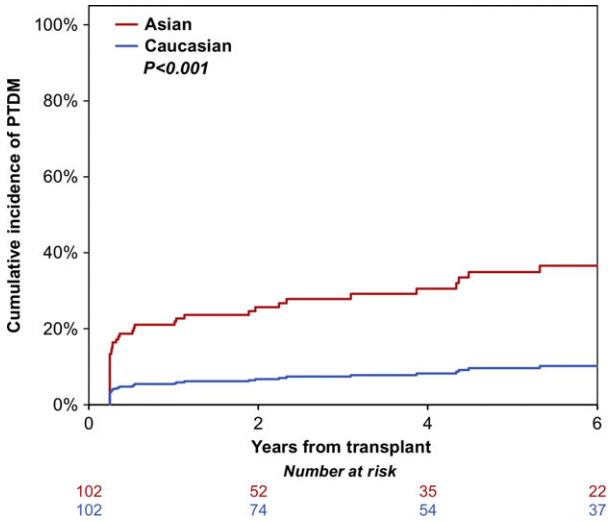

Figure 1 Cumulative incidence curve of PTDM risk by ethnicity.

ethnic groups, and their relationship with PTDM was also assessed. A competing risks regression analysis (Fig. S1a and b) found both of these factors to be significantly associated with PTDM ($P = 0.005$ and 0.004, respectively). Multivariable stratified Cox regression analyses were then performed on these factors, to test whether either was a confounder in the comparison of ethnicity against PTDM.

When considering the effect of organ type, both the effects of ethnicity ($P = 0.263$) and organ type ($P = 0.178$) were found to be nonsignificant. However, a significant interaction term between the factors was observed ($P = 0.035$). This indicated that the relationship between ethnicity and PTDM was dependent on the type of kidney a patient had received, which is demonstrated on the cumulative incidence curves in Fig. 2a and b. In patients who received live-donor kidneys, there was no evidence of a significant difference in PTDM rates between South Asian and Caucasian recipients ($P = 0.723$). However, when deceased-donor kidneys were used, South Asian recipients did significantly worse, with cumulative PTDM incidence at 5 years of 40% versus 4% in Caucasian recipients ($P < 0.001$).

A similar analysis was performed for recipient CMV. It was not possible to produce a convergent Cox regression model, on account of the smaller sample size ($n = 87$) resulting from missing data. However, the cumulative incidence curves (Fig. S2a and b) gave no reason to suggest that recipient CMV was a confounding factor in the relationship between ethnicity and PTDM, with South Asian patients having consistently higher rates of PTDM whether CMV negative ($P = 0.044$) or positive ($P = 0.003$).

Other cardio-metabolic risks

No significant difference was observed after kidney transplantation in the treatment of cardio-metabolic risk factors (see Table 3). Both groups saw a significant ($P < 0.001$) increase in BMI after surgery, with a mean increase from pre- to 1 year post-transplant of 0.9 (SD = 2.5) in Caucasian and 1.5 (SD = 3.5) in South Asian patients. This increase in BMI was not found to differ significantly between the ethnic groups ($P = 0.084$) and was maintained for up to 5 years, for the patients with sufficient follow-up (Table 4).

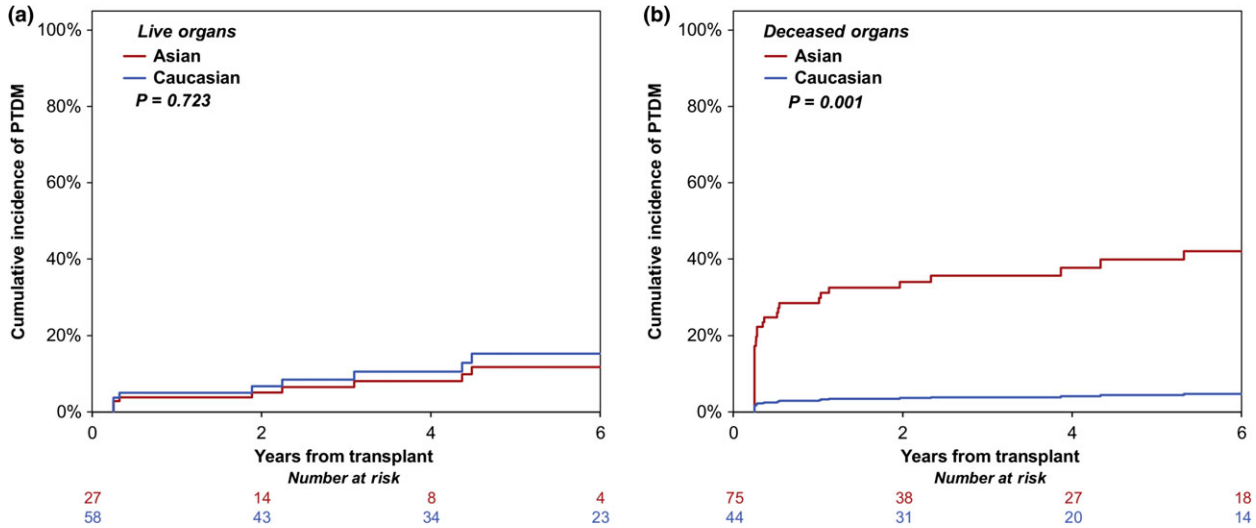

Figure 2 Cumulative incidence curve of PTDM risk by ethnicity for (a) live and (b) deceased organs.

Table 3. Comparison of cardio-metabolic outcomes between paired groups.

	Caucasian	South Asian	*P*-value
Adverse cardiovascular events	4 (4%)	4 (4%)	1.000
Antihypertensive therapy	81 (79%)	78 (77%)	0.368
Lipid-lowering therapy	50 (49%)	40 (39%)	0.102
Magnesium supplementation	8 (8%)	4 (4%)	0.431
Hyperuricaemia	38 (37%)	43 (43%)	0.592
PTDM*			
5-Year cumulative incidence	10%	35%	<0.001†
Subhazard ratio	–	4.2 (2.1–8.5)	

Data reported as the numbers and percentages of patients that experienced at least one event, with *P*-values from McNemar's test, unless stated otherwise.

*PTDM was assessed using a competing risks regression model.

†Significant at $P < 0.05$.

Table 4. Comparison of post-transplant BMI between paired groups.

	1 Year	3 Years	5 Years
BMI			
N (pairs)	91	55	35
Caucasian	26.2 (4.0)	26.2 (4.3)	26.1 (4.8)
South Asian	27.0 (4.9)	27.1 (4.5)	26.7 (3.7)
P-value*	0.080	0.085	0.273
Increase in BMI from pretransplant			
Caucasian			
N	96	62	48
Increase	0.9 (2.5)	1.3 (3.1)	0.8 (3.4)
P-value†	<0.001‡	<0.001‡	0.093
South Asian			
N	95	58	40
Increase	1.5 (3.5)	2.1 (3.0)	2.0 (3.7)
P-value†	<0.001‡	<0.001‡	0.002‡

Data reported as means and standard deviations, with *P*-values from paired *t*-tests.

*Comparing Caucasian versus South Asian at each year post-transplant.

†Testing whether BMI has increased significantly from the pretransplant measurement in the years post-transplant.

‡Significant at $P < 0.05$.

Adverse cardiovascular events, allograft outcomes and mortality

Analysis of hard patient outcomes (including adverse cardiovascular events, mortality and allograft function/survival) found no evidence of a significant difference between South Asians and Caucasians after kidney transplantation (see Table 5). Graft function was similar in the two groups at 1, 3 and 5 years after kidney transplantation, as were the rates of rejection. Survival rates were also similar, with Caucasian recipients having Kaplan–Meier estimates of 95% and 94% for patient survival and overall graft survival, respectively, compared with 96% and 90% in South Asian recipients (Fig. 3a and b).

Immunosuppression

Caucasian and Asian patients were matched (within 2 years) for date of transplant and were on our standard centre immunosuppression regimen (see methods). There was no significant difference in number of episodes of acute rejection (requiring high dose steroids) between the two groups. Cumulative exposure to steroids between both groups therefore should not vary considerably; 84% of patients in both ethnic groups received tacrolimus-based immunosuppression. Median 12-h trough tacrolimus levels did not differ significantly between the groups (Caucasians – 7.6 ng/l (IQR: 7.1–8.2) vs. Asians – 7.6 ng/l (IQR: 7.1–8.1), $P = 0.602$).

Sensitivity analysis

A secondary analysis of PTDM was performed using the whole patient cohort from before matching (i.e. 354 Caucasian and 121 South Asian patients, see Table 6). A multivariable Cox regression analysis was used, to account for the baseline differences in age, gender and BMI between the ethnicities. This analysis found increasing age ($P < 0.001$) and BMI ($P = 0.008$) to be significantly associated with higher rates of PTDM. After accounting for these factors, a significant difference in rates of PTDM

Table 5. Comparison of patient and allograft outcomes between paired groups.

	Caucasian	South Asian	*P*-value
1-year Creatinine (*N* pairs = 92)*	124 (117–131)	121 (113–130)	0.625
3-year Creatinine (*N* pairs = 54)*	116 (109–123)	126 (113–142)	0.116
5-year Creatinine (*N* pairs = 35)*	118 (106–131)	122 (105–140)	0.669
Episodes of rejection†	13 (13%)	8 (8%)	0.359
Patient survival			
5-Year rate‡	95% (±3%)	96% (±2%)	0.582
Hazard ratio§	–	1.3 (0.3–4.7)	0.739
Overall graft survival			
5-Year rate‡	94% (±3%)	90% (±4%)	0.383
Hazard ratio§	–	2.2 (0.8–6.3)	0.144

*Data reported as geometric means and 95% confidence intervals, with *P*-values from paired *t*-tests on log-transformed data. Pairs with missing data for the stated year were excluded.

†Data reported as the numbers and percentages of patients that experienced at least one event, with *P*-values from McNemar's test.

‡Data reported as Kaplan–Meier estimated rates and standard errors, with *P*-values from log-rank tests.

§Data reported as hazard ratios and 95% confidence intervals, from stratified Cox regression models, accounting for the pairing.

¶Significant at $P < 0.05$.

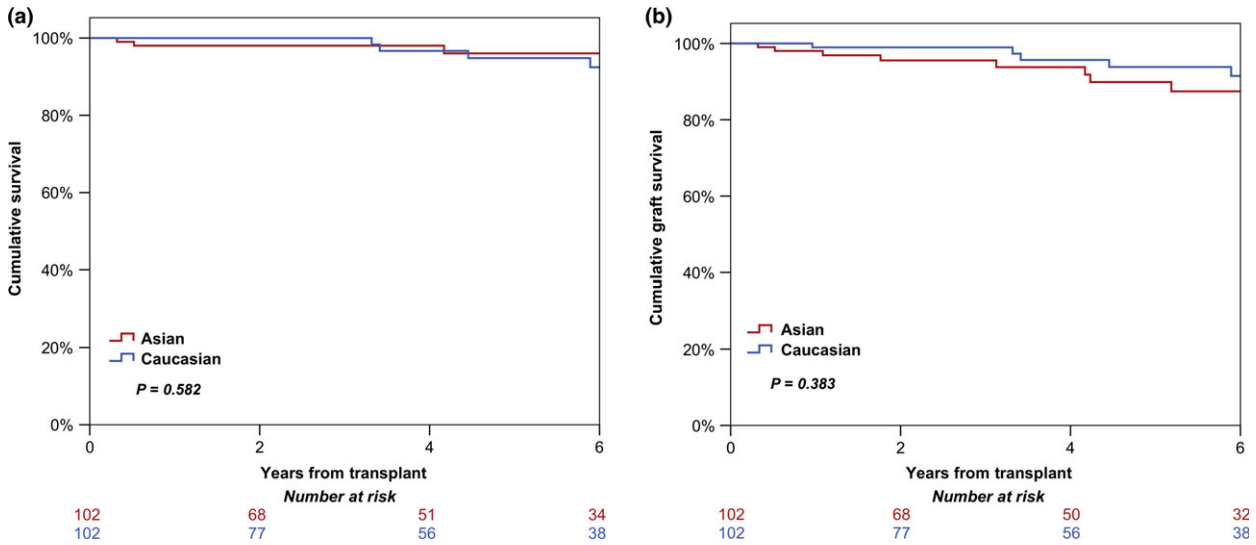

Figure 3 Kaplan–Meier curve of (a) patient survival and (b) graft survival, stratified by ethnicity.

between the ethnicities persisted ($P < 0.001$), with a hazard ratio of 2.59 (95% CI: 1.67–4.01) for South Asian patients, relative to Caucasians.

Discussion

In our matched-pair analysis, we identified nondiabetic kidney allograft recipients of South Asian ethnicity were at significantly higher risk for the development of PTDM compared with Caucasian kidney allograft recipients. Much of this elevated risk for South Asians was associated with receipt of deceased-donor rather than live-donor kidneys. Other cardio-metabolic risk factors were similar between South Asians and Caucasians, and there was no difference in rates of admission to hospital with an adverse cardiovascular event. Importantly, despite significantly higher rates of PTDM in South Asians versus Caucasians, no difference was observed with regard to mortality, allograft function, rejection or survival after kidney transplantation.

Table 6. Multivariable analysis of PTDM using the whole cohort.

Factor	Hazard ratio (95% CI)	*P*-value
Ethnicity (Asian)	2.59 (1.67–4.01)	<0.001*
Sex (female)	1.37 (0.89–2.09)	0.151
Age		<0.001*
<30	–	–
30–39	0.67 (0.18–2.53)	0.554
40–49	3.42 (1.27–9.23)	0.015*
50–59	4.39 (1.69–11.41)	0.002*
60–69	6.37 (2.38–17.04)	<0.001*
BMI		0.008*
≤25	–	–
26–30	1.53 (0.93–2.52)	0.097
>30	2.36 (1.38–4.07)	0.002*

Results from a multivariable Cox regression model, with PTDM as the outcome.

*Significant at $P < 0.05$.

South Asians are well known to be at higher risk for diabetes mellitus than Caucasians in the general population, but this risk is predominantly excess type 2 diabetes mellitus [9]. While this has been attributed to lifestyle and metabolic differences, increased susceptibility due to genetic associations has also been identified in genomewide association studies [12]. The pathophysiology of PTDM is distinct, with interplay from both type 1 and type 2 diabetes mellitus features [13]. Therefore, we cannot simply translate presumed risk from the general to transplant population cohort. Unfortunately, our current evidence base regarding PTDM risk for South Asian kidney allograft recipients is both limited and conflicting. Dooldeniya and colleagues explored PTDM rates among South Asian ($n = 46$) versus Caucasian ($n = 90$) kidney allograft recipients in an English cohort and observed a PTDM risk of 10.9% versus 3.3%, respectively ($P = 0.02$) [3]. The authors corroborated their data with the larger LOTESS (Long-Term Efficacy and Safety Surveillance) registry, which was a Novartis-funded project collecting data on kidney allograft recipients (recruited between 1995 and 1998 in the UK) treated with cyclosporine microemulsion. The rate of PTDM in the LOTESS data set for South Asians versus Caucasians was 5.5% versus 1.6%, respectively ($P < 0.001$), confirming increased PTDM risk for South Asians to support their single-centre observations. Reassuringly, 5-year patient and allograft outcomes were equivalent (as per our analysis), which contrasted with earlier data suggesting inferior allograft outcomes among South Asians compared with Caucasians in the UK [14]. The major limitation of the data from Dooldeniya and colleagues was the archaic definition of PTDM (diagnosed by treatment only) and being representative of a different era of immunosuppression and clinical practice. In contrast, Prasad and colleagues have more recently explored South Asian ethnicity as a risk factor for major adverse cardiovascular events (MACE) after kidney transplantation in a Canadian cohort of 864 patients [4]. South Asian ethnicity was an independent risk factor for post-transplant cardiac events, with MACE rate of 4.4/100 patient-years (compared with 1.2/100 patient-years for Caucasians), but no significant difference in PTDM was observed between South Asians (7%) and Caucasians (5%). This analysis utilized contemporaneous Canadian Diabetes Association guidelines, which mirror current consensus recommendations (with the exception of glycated haemoglobin incorporation) [11].

We can speculate why our results contrast with the findings from Prasad and colleagues [4], considering both utilized more robust diagnostic criteria compared with the historical Dooldeniya publication [3]. We included HbA1c as part of our diagnostic criterion, in line with latest consensus recommendations, which was not previously standard practice and not utilized by Prasad and colleagues. It is possible this approach captured more South Asians as having PTDM because data from the general population suggest glycated haemoglobin is higher among South Asians compared with Caucasians [15]. For example, 20% of our PTDM patients were diagnosed on the basis of HbA1c alone. In addition, the study from Prasad and colleagues tailored immunosuppression based on diabetes risk, and therefore, many high-risk South Asian patients may have received cyclosporine rather than tacrolimus as per centre protocol [16]. No immunosuppression tailoring is performed at our centre on the basis of PTDM risk alone, and this may have potentiated risk among South Asians (versus attenuated any risk in the study from Prasad and colleagues).

However, we would caution any interpretation of our data to suggest we should attenuate risk of PTDM among South Asians by modification of immunosuppression. While the complications associated with the development of PTDM are well documented [1], reassuringly short- to medium-term 'hard' patient outcomes relating to survival are comparable between South Asians and Caucasians. Therefore, pre-emptive modification of immunosuppression based upon PTDM risk alone may be premature and a careful risk versus

benefit calculation would be warranted on an individual patient basis. Supportive evidence for modification comes from the DIRECT study, which demonstrated cyclosporine led to less abnormal glucose metabolism than tacrolimus with equivalent 6-month allograft outcomes [17]. In addition, a preliminary report of the prospective, randomized controlled study entitled REVERSE observed tacrolimus conversion to cyclosporine in the context of persistent PTDM (duration >6 months) attenuated abnormal glucose metabolism, and frequently reversed PTDM, with no negative allograft effects within the first year [18]. However, the landmark SYMPHONY study clearly demonstrated superior allograft outcomes for tacrolimus compared with cyclosporine at 1 year and 3 years after kidney transplantation [19,20], and balancing PTDM risk against these more important 'hard' outcomes should remain the priority for patients. In addition, other side effects may have more deleterious impact among South Asians. For example, hirsutism is more common with cyclosporine [21] and South Asians are more prone to hirsutism (possibly due to an increase in peripheral 5α-reductase activity and/or androgen disturbances) [22]. These cosmetic side effects may be considered unacceptable by South Asians (especially women). An alternative approach could be corticosteroid avoidance or withdrawal, but the evidence base for such strategies remains equivocal. Systematic reviews and meta-analyses of steroid avoidance/withdrawal have demonstrated some improvement of cardio-metabolic parameters (including hyperglycaemia) but increased risk for rejection [23,24]. However, recently published data suggests no difference in PTDM incidence 5 years after kidney transplantation comparing early steroid withdrawal (35.9%) versus low-dose steroid maintenance (36.3%) in the context of a randomized controlled trial [25]. While short-term patient and allograft survival is equivalent, long-term evaluation of 'hard' outcomes is currently lacking for steroid avoidance/withdrawal regimens. Finally, belatacept may have a more favourable cardio-metabolic risk profile compared with calcineurin inhibitors (with increased risk for rejection), although this does not currently translate into any difference in patient and/or allograft survival [26]. No specific data exists in relation to belatacept use in South Asian kidney allograft recipients. Therefore, choice of immunosuppression post-transplantation should be tailored to optimization of long-term patient and allograft outcomes, rather than attenuation of PTDM risk alone, and this is aligned with the latest consensus recommendations [11]. Lifestyle modification should be advocated to all kidney allograft recipients based on potential benefit [27], but for South Asians likely needs tailoring to their unique cultural and dietary behaviour as they have a distinct cardio-metabolic risk profile compared with Caucasians [28].

Our analysis identified a significant statistical interaction of deceased-donor effect on PTDM risk for South Asians. Inclusion of the interaction term in the multivariable models was prespecified, but there was the potential for any one of the nine confounding factors considered to be included in this analysis, had they differed significantly between the ethnicities. As such, there is an increased likelihood of the observed interaction effect being a result of a false positive error. However, the striking differences observed between the cumulative incidence curves of the donor type subgroups do appear to support this finding. Despite this, we concede that this result should be interpreted with caution, and further studies would be warranted to validate this result.

The evidence linking deceased organ donation and PTDM was originally observed in a historical cohort of kidney allograft recipients [29], but subsequent data has been conflicting with no clear link identified. For example, Kasiske *et al.* did not identify any link between donor source and PTDM in a large multivariate analysis of registry data exploring 11 659 kidney allograft recipients in the United States [30]. By contrast, Gourishankar *et al.* did find deceased-donor kidney recipients to have an independently higher risk for the development of PTDM in a retrospective analysis of predominantly Caucasian kidney allograft recipients in Canada (n = 386, hazard ratio 3.7 [CI 1.4–9.7], P = 0.008) [31]. In a retrospective analysis of 490 kidney allograft recipients, Cosio *et al.* observed receiving a deceased-donor kidney was statistically the strongest predictor of PTDM at 1 week post-transplantation but was no longer a significant predictor on multivariate analysis at 1 year post-transplantation [32]. However, this effect may have been masked by glycaemia at 1 week post-transplant emerging as the strongest predictor of PTDM at 1 year [32]. Similar observations linking risk for PTDM with receipt of a deceased-donor allograft have also been observed after liver transplantation [33]. No definitive link justifying an increased risk of PTDM after deceased donation has been proposed. However, we can postulate on theories that focus on pathophysiologic alterations to glycaemic metabolism associated with either brain or cardio-respiratory death being a contributory factor. For example, donor hyperglycaemia is common after brain death due to stress response to injury, depressed insulin levels, electrolyte disturbances (e.g. hypomagnesaemia)

and catecholamine release [34]. This hyperglycaemic donor state may potentiate peri-transplant ischaemia–reperfusion injury [35], which could trigger recipient hyperglycaemia mediated via advanced glycation end products and their receptor RAGE [36]. More speculative is the theory that transplant-associated hyperglycaemia in the immediate postoperative setting is an evolutionarily preserved adaptive response designed to increase survival of the host in situations of stress [37]. Therefore, we can postulate that activation of the immune system in the context of profound ischaemia–reperfusion injury may lead to a state of insulin resistance which, in the context of calcineurin inhibitor-induced pancreatic beta-cell dysfunction [38], leads to increased risk for the development of PTDM. Further work in this area is warranted to shed light on these speculations.

One of the strengths of this study is a sizable South Asian cohort to adequately address our hypothesis and comprehensive electronic patient records to evaluate patient-level data. However, electronic patient records may be susceptible to missing data and would not capture admissions to different hospitals, thereby underestimating hospitalization for adverse cardiac events. Our study was also likely to be underpowered, and of short duration, to robustly assess difference in cardiovascular and mortality outcomes between South Asian and Caucasian kidney allograft recipients. We also undertook case–control matching to remove the bias of age, gender, BMI and era effect from the analysis. While case–control matching is advantageous to control for confounding, it only accounts for observed covariates and residual unmeasured confounders cannot be factored for. Hidden bias may therefore increase, as matching on observed variables may unleash bias from dormant unobserved confounders [39]. Finally, we are unable to speculate on whether risk for PTDM for South Asian kidney allograft recipients was *over and above* their risk for the development of type 2 diabetes mellitus had they not been transplanted – determining the additive risk from transplantation should be the focus of further research.

To conclude, our matched-pair cohort analysis identified South Asian kidney allograft recipients had a greater than fourfold increase in the hazard of developing PTDM compared with Caucasian kidney allograft recipients post-transplantation. Despite this significant difference, there was no evidence of significant difference in hard outcomes including serious cardiovascular events, mortality or adverse allograft events (function, rejection and failure). Nondiabetic South Asian kidney allograft recipients should be appropriately counselled and closely monitored for the development of abnormal glucose metabolism after kidney transplantation. However, in line with International Consensus Recommendations, tailoring of immunosuppression is not recommended to solely attenuate risk for PTDM in the absence of clinical trials suggesting benefits outweigh any potential risk. While short- to medium-term outcomes are equivalent between South Asian and Caucasian kidney allograft recipients, further studies will be warranted to ascertain whether the development of PTDM translates into adverse outcomes in the long term. In addition, the tenuous link between deceased organ donation and development of PTDM requires further investigation. In the interim, tailored strategies to target abnormal glucose metabolism in South Asian kidney allograft recipients are necessary to attenuate high PTDM risk and we require targeted clinical studies to better inform clinical practise.

Authorship

All authors made substantial contributions to conception and design. JP, JN, ST and KP: classified data. JN, CF, RB and AS: analysed and interpreted data. JP, JN, AR, KP and AS: draft manuscript. CF, RB and AS: revised the article. All authors approved the final version.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Cumulative incidence curve of PTDM risk by (a) organ type and (b) recipient CMV serostatus.

Figure S2. Cumulative incidence curve of PTDM risk by ethnicity for recipient CMV serostatus (a) negative and (b) positive.

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APPENDIX A

Comparison of factors between paired groups receiving deceased donor organs.

	N pairs	Caucasian	South Asian	*P*-value
ABO-incompatible transplant	33	0 (0%)	0 (0%)	1.000
Recipient hepatitis C+ status	33	0 (0%)	0 (0%)	1.000
Recipient CMV positive	27	10 (37%)	22 (81%)	0.004†
CMV infection/viremia	33	2 (6%)	3 (9%)	1.000
Non-smoker	23	14 (61%)	20 (87%)	0.109
Cause of renal failure	16			0.538*
Polycystic kidney disease		5 (31%)	2 (13%)	
Inflammatory renal/IgA		6 (38%)	8 (50%)	
Other		5 (31%)	6 (38%)	
Mode of renal replacement therapy	33			0.413 *
Pre-emptive		2 (6%)	4 (12%)	
Haemodialysis		15 (45%)	15 (45%)	
Peritoneal dialysis		14 (42%)	9 (27%)	
Both therapies		2 (6%)	5 (15%)	
Primary immunosuppression	33			0.337*
Tacrolimus		27 (82%)	23 (70%)	
Ciclosporin		6 (18%)	8 (24%)	
Sirolimus		0 (0%)	2 (6%)	

N pairs: the number of pairs of patients included in each analysis, after excluding cases where one patient in the pair had missing data. Dichotomous factors are compared between groups by McNemar's test.

*Categorical variables compared using Fisher's exact test.

†Significant at $P < 0.05$

APPENDIX B

Comparison of survival outcomes between ethnicities, within the PTDM subgroups.

	Ethnicity		
	Caucasian	Asian	*P*-value
Overall survival			
PTDM			
No	94% (3%)	99% (2%)	0.368
Yes	100%	92% (5%)	0.568
Graft survival			
PTDM			
No	93% (3%)	94% (4%)	0.316
Yes	100%	84% (7%)	0.984

Data reported as Kaplan–Meier estimated rates at 5 years, with standard errors.

P-values are from log-rank tests on all available follow up.

APPENDIX C

Comparison of survival outcomes by PTDM group, within the ethnicity subgroups.

	PTDM		
	No	Yes	*P*-value
Overall survival			
Ethnicity			
Caucasian	94% (3%)	100%	0.34
Asian	98% (2%)	92% (5%)	0.754
Graft survival			
Ethnicity			
Caucasian	93% (3%)	100%	0.556
Asian	94% (4%)	84% (7%)	0.802

Data reported as Kaplan–Meier estimated rates at 5 years, with standard errors.

P-values are from log-rank tests on all available follow up.