The Association of Pre-Transplant C-Peptide Level with the Development of Post-Transplant Diabetes: A Cohort Study

Amanda J. Vinson,1 Aran Thanamayooran,1 Bryce A. Kiberd,1 Kenneth West,2 Ferhan S. Siddiqi,2 Lakshman Gunaratnam3,4 and Karthik K. Tennankore1

Key Points
• A pretransplant fasting C-peptide level ≥3000 pmol/L was associated with a nearly 20-fold increased odds of post-transplant diabetes mellitus at 1 year post kidney transplantation.
• In a restricted cohort with a body mass index between 20 and 35 kg/m², a pretransplant C-peptide ≥3000 pmol/L was the only factor independently associated with post-transplant diabetes mellitus.
• Hemoglobin A1c at 1 year post kidney transplant was significantly higher (5.9% versus 5.5%, [P<0.02]) in those with a high versus low pretransplant C-peptide levels.

Abstract
Background Post-transplant diabetes mellitus (PTDM) is an important complication after kidney transplantation that results in reduced patient and allograft survival. Although there are established risk factors for PTDM, whether pretransplant C-peptide levels associate with PTDM is unknown. Therefore, in this study, we aimed to examine the association of pretransplant C-peptide levels with PTDM.

Methods This was a cohort study of nondiabetic adult patients who underwent kidney transplant in Nova Scotia, Canada, between January 1, 2016, and March 31, 2021, with fasting C-peptide levels measured before transplant. Multivariable logistic regression was used to determine the association of pretransplant C-peptide (dichotomized around the median) with PTDM at 1 year post transplant. Given the known association between pretransplant obesity and PTDM, we repeated our primary analysis in a cohort restricted to a BMI of 20–35 kg/m².

Results The median C-peptide value was 3251 (Q1 2480, Q3 4724); pretransplant C-peptide level was dichotomized at 3000 pmol/L. PTDM occurred in 25 (19%) individuals. Thirty percent of patients in the high and only 2% of patients in the low C-peptide groups developed PTDM (P<0.001). A C-peptide level ≥3000 pmol/L was strongly associated with PTDM in multivariable analysis (OR=18.9, 95% CI, 2.06 to 174.2). In a restricted cohort with a BMI of 20–35 kg/m², an elevated pretransplant C-peptide remained independently associated with the risk of PTDM (OR=15.7, 95% CI, 1.64 to 150.3). C-peptide was the only factor independently associated with PTDM in this restricted BMI cohort.

Conclusions A pretransplant C-peptide level ≥3000 pmol/L was associated with a nearly 20-fold increased odds of PTDM at 1 year post kidney transplantation. Identifying patients with high pretransplant C-peptide levels may therefore help identify those at risk for PTDM who may benefit from focused preventative and therapeutic interventions and support.

Introduction
Kidney transplantation is the most effective therapy for patients with end-stage kidney disease (ESKD) because it is associated with better recipient survival and quality of life, and improved cost-effectiveness (1,2). However, there are risks associated with kidney transplantation, including the potential development of post-transplant diabetes mellitus (PTDM) (3). The implications of PTDM are significant and include increased cardiovascular disease, infectious risk, and health care expenditure, in addition to reduced patient and kidney graft survival (4,5).

Several risk factors for the development of PTDM have been identified, including those that are known to cause diabetes in the general population such as obesity, older age, and family history. However, additional
transplant-specific risk factors are also associated with the development of diabetes after transplant (4). These include immunosuppressive therapies, hyperglycemia in the early post-transplant period, cytomegalovirus infection, human leukocyte antigen (HLA) mismatch, rejection episodes, and hypomagnesemia (4,6).

The pathogenesis of PTDM is proposed to consist of both β cell dysfunction and insulin resistance (7). Insulin is produced by pancreatic β cells by cleavage of a prohormone precursor, proinsulin, to equal parts insulin and C-peptide (8). C-peptide has a longer half-life than insulin and thus provides a more stable test window than insulin does for β cell function (8). In the nondiabetic population, abnormalities in fasting C-peptide levels may herald an impending diabetes diagnosis; elevated levels may suggest insulin resistance, and suppressed levels may reflect β cell dysfunction (9). However, the association of pretransplant C-peptide levels with the development of PTDM has not been explored. If pretransplant C-peptide levels can reliably predict patients likely to develop PTDM, strategies may be employed to minimize risk to specific transplant-eligible patients. These may include more aggressive health promotion programs directed at weight loss through diet and exercise (10) and potential tailoring of immunosuppressive regimens to minimize diabetogenic steroid or tacrolimus exposure (11–14).

Therefore, the purpose of this study was to determine if pretransplant C-peptide levels associate with the risk of developing PTDM in the first year after kidney transplantation.

### Materials and Methods

#### Study Design and Population

We conducted a retrospective cohort study of all adult patients (≥18 years) without diabetes who underwent a solitary kidney transplant in Halifax, Nova Scotia, Canada, between January 1, 2016, and March 31, 2021, who had post-transplant follow-up in Nova Scotia or select sites in New Brunswick with available data. We excluded anyone <18 years of age and those who were already diagnosed with diabetes at the time of kidney transplant. Maintenance immunosuppression at our center after the first 3 months includes prednisone 5 mg daily, tacrolimus to target a level of 5–8 ng/ml, and mycophenolic acid 1000 mg twice a day.

Diabetes status was defined as taking any diabetic medications (oral hypoglycemics or insulin), having a fasting blood glucose ≥7 mmol/L, a hemoglobin A1c (HbA1c) ≥7%, or a 2-hour oral glucose tolerance test (OGTT) or random glucose of ≥11.1 mmol/L with confirmatory testing, consistent with the Diabetes Canada guidelines for the diagnosis of diabetes (15).

#### Exposure

The exposure of interest was a fasting C-peptide level (pmol/L) from routine admission bloodwork at the time of kidney transplant.

Given C-peptide levels may be reduced by up to 40% after a session of hemodialysis (16), we aimed to use post-hemodialysis C-peptide levels where available. In a subsequent analysis, we included a correction factor for the subset of patients who had their C-peptide level sent before their last pretransplant hemodialysis session.

#### Outcome

The primary outcome was a diagnosis of PTDM in the first year post kidney transplant (as per the diabetes definition above) (15). Secondary outcomes included HbA1c at 1 year post transplant, maximum blood glucose in the first 2 weeks post transplant, and nadir magnesium in the first 2 weeks post transplant because both early hyperglycemia and hypomagnesemia post transplant have been associated with PTDM (6,17,18).

### Potential Confounding Variables

In addition to pretransplant fasting C-peptide, known literature predictors of PTDM and graft outcomes, including recipient age, race, sex, body mass index (BMI), cause of ESKD, live or deceased donor, dialysis vintage, cold ischemia time, previous kidney transplant, HLA mismatch, peak panel reactive antibody, cytomegalovirus serostatus of donor and recipient, recipient medical comorbidities including hypertension, coronary artery disease, and peripheral vascular disease, and pretransplant HbA1c level, were collected.

#### Analysis

Descriptive statistics were used to report baseline characteristics, including pretransplant C-peptide levels for all patients enrolled in the study. Medians and interquartile ranges were used for continuous variables, and counts and percentages were used for categorical variables (with significant differences determined using the Wilcoxon rank sum or chi-squared test, as appropriate). Pretransplant C-peptide levels were also displayed graphically using a histogram.

For the primary analysis, C-peptide was dichotomized around the cohort median value (defined as high and low groups).

#### Primary Analysis

Uni- and multivariable logistic regression models adjusting for the confounders listed above were used to determine the independent association of high versus low pretransplant C-peptide levels with PTDM at 1 year post transplant. Given a relatively small anticipated number of events, we selected variables for inclusion in our multivariable model a priori to avoid statistical overfitting.

#### Secondary Analyses

We determined if pretransplant fasting C-peptide level (dichotomized around the median value, as above) was associated with a difference in median HbA1c value at 1 year post transplant, median random peak glucose achieved in the first 2 weeks post transplant, or nadir magnesium in the first 2 weeks post transplant, using the Wilcoxon rank sum test.

#### Sensitivity Analyses

In sensitivity analyses, pretransplant C-peptide levels were treated as a continuous variable.

We repeated the primary analysis using exact logistic regression rather than the standard logistic regression approach. Exact logistic regression provides more reliable statistical inferences with small sample datasets compared with the usual unconditional maximum likelihood estimation method (19).
As above, a correction factor was included for any patient who had their pretransplant C-peptide level sent before their last pretransplant hemodialysis session. Preemptive patients or those on peritoneal dialysis (and thus presumed to be in a relative steady state for fasting C-peptide levels) did not have their C-peptide level adjusted.

Timing of C-peptide levels (other than their relation to the last hemodialysis session) were not captured in this study; however, the majority of samples were sent less than 24 hours before transplant. C-peptide levels have been shown to vary diurnally, with morning values around 1.1× higher than values later in the day (20). Therefore, in a sensitivity analysis, we corrected all elevated C-peptide levels (greater than median) by a factor of 0.91 (1/1.1) to account for the unlikely event that all elevated C-peptide levels were taken in the morning and all lower levels taken in the evening. We then re-dichotomized these adjusted C-peptide levels and repeated our primary analysis.

Given the known association between pretransplant obesity and PTDM, we repeated our primary analysis in a cohort restricted to a BMI of 20–35 kg/m².

Given the known association between transient hyperglycemia post transplant and PTDM, we included an elevated early post-transplant glucose ≥11 mmol/L in our multivariable analysis to determine if this modified the association of C-peptide with the outcome of PTDM.

This study followed EQUATOR reporting guidelines and was approved by the Nova Scotia Health Research Ethics Board. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism. For all statistical comparisons, a P value <0.05 was the threshold for statistical significance.

Results
Baseline Characteristics
Over the study period, pretransplant C-peptide data were available on 132 adult nondiabetic patients at the time of kidney transplantation: Mean and median C-peptide values were 3923.5±2358.2 pmol/L and 3251 pmol/L (Q1 2480, Q3 4724), respectively, with a minimum C-peptide value of 410 pmol/L and a maximum value of 16,262 pmol/L (Figure 1). PTDM occurred in 25 (19%) individuals. Baseline characteristics, stratified by C-peptide status, are depicted in Table 1.

Primary Analysis
For the primary analysis, pretransplant C-peptide levels were dichotomized at 3000 pmol/L. Twenty-four (30%) patients in the high and only one (2%) patient in the low C-peptide groups developed PTDM (P<0.001). In univariable analysis, a high C-peptide level (≥3000 pmol/L) was significantly associated with the development of PTDM (odds ratio [OR]=21.1; 95% confidence interval [95% CI], 2.75 to 161.3). This remained significant after adjusting for recipient BMI at transplant (OR=15.0; 95% CI, 1.91 to 118.3 for C-peptide ≥3000 pmol/L). In multivariable analysis, a high C-peptide level remained associated with PTDM at 1 year post transplant (OR=18.9; 95% CI, 2.06 to 174.2; Table 2).

Secondary Analyses
The median HbA1c value at 1 year post transplant was 5.6% (Q1 5.3, Q3 6.35). The 1-year HbA1c level was significantly higher in the high C-peptide group (5.9%; Q1 5.4, Q3 6.6) than in the low C-peptide group (5.5%; Q1 5.3, Q3 5.8; P=0.02). Median peak glucose in the first 2 weeks post transplant was 9.8 mmol/L (Q1 7.9, Q3 12.3). There was no difference by pretransplant C-peptide level (10.2 mmol/L in the low and 10.5 mmol/L in the high groups, respectively; P=0.35). Median nadir magnesium in the first 2 weeks post transplant was 0.64 mmol/L (Q1 0.57, Q3 0.73). There was no difference by pretransplant C-peptide level (0.64 mmol/L in the low and 0.66 mmol/L in the high C-peptide groups; P=0.4).

Sensitivity Analyses
When treating pretransplant C-peptide level as a continuous variable, it remained significantly associated with the outcome of PTDM at 1 year post transplant in univariable analysis (OR=1.51; 95% CI, 1.20 to 1.90 per each 1000 pmol/L increase), after adjusting for BMI (OR=1.35; 95% CI, 1.08 to 1.72 per each 1000 pmol/L increase) and in multivariable analysis (OR=1.50, 95% CI, 1.12 to 2.00 per each 1000 pmol/L increase). In multivariable analysis, pretransplant C-peptide level was the only variable significantly associated with the outcome of interest (Supplemental Table 1).

There were no significant differences in results obtained when exact logistic regression was utilized, nor when we accounted for potential diurnal variation in C-peptide levels by correcting all C-peptide levels ≥3000 pmol/L by a factor of 0.91 (results not shown). Median C-peptide levels did not differ in those on hemodialysis (3247 pmol/L; Q1 2509, Q3 4719), peritoneal dialysis (3414 pmol/L; Q1 2340, Q3 4977), or transplanted preemptively (3212 pmol/L; Q1 2552, Q3 3300; P>0.5 for all comparisons). When we used a correction factor (×0.6) to reflect a 40% reduction in any C-peptide level drawn before the last pretransplant hemodialysis session, our results changed very little. Median C-peptide after adjusting for those with levels sent before
last hemodialysis session was 2770.5 pmol/L (Q1 1931.5, Q3 4091.5). All 25 (100%) patients developing PTDM had a hemodialysis-corrected pretransplant C-peptide level ≥2500 pmol/L.

When restricting recipient BMI at the time of transplant to 20–35 kg/m², an elevated pretransplant C-peptide remained associated with the risk of PTDM in univariable (OR = 15.7; 95% CI, 1.99 to 123.01) and multivariable (OR = 15.7; 95% CI, 1.64 to 150.3) analyses. C-peptide was the only factor independently associated with PTDM in this restricted BMI cohort (Supplemental Table 2). Peak glucose in the first 2 weeks post transplant was dichotomized at 11 mmol/L (median). C-peptide remained associated with the outcome of interest after including early post-transplant hyperglycemia in the regression analysis (which was also independently associated with PTDM; Supplemental Table 3).

### Discussion

In this study, we show that an elevated fasting C-peptide level before kidney transplant is strongly associated with PTDM at 1 year post transplant. We demonstrate a 1-year risk of PTDM of 19% in our cohort, which is in keeping with that demonstrated in the literature. In the United States, approximately 40% of kidney transplant recipients are expected to develop PTDM in the 3 years after transplantation (4). The highest incidence of PTDM occurs in the first 6 months after transplant (12%–21%) (21,22) when immunosuppression doses are highest (23).

Although each of reduced insulin sensitivity, increased insulin resistance, and decreased insulin secretion is observed (24), PTDM has been proposed to reflect β cell dysfunction (i.e., impaired insulin secretion) more than insulin resistance (7). Thus, patients with impaired β cell

### Table 1. Baseline characteristics in patients with and without post-transplant diabetes at 1 year post transplant, stratified by pretransplant fasting C-peptide level

| Patient Characteristic | C-peptide <3000 pmol/L (N=51) | C-peptide ≥3000 pmol/L (N=81) | P Value |
|------------------------|-----------------------------|-----------------------------|--------|
| **Sex**                |                             |                             |        |
| Men                    | 25 (47.1)                   | 57 (70.4)                   | 0.07   |
| Women                  | 27 (52.9)                   | 24 (29.6)                   |        |
| **Age, yr**            | 56.2 (49, 66.1)             | 55.6 (44, 63.7)             | 0.58   |
| **Race**               |                             |                             |        |
| White                  | 50 (98)                     | 75 (93.75)                  | 0.48   |
| Other                  | 1 (2)                       | 5 (6.25)                    |        |
| **Cause of ESKD**      |                             |                             |        |
| Glomerulonephritis     | 17 (34)                     | 34 (44.2)                   |        |
| Hypertension           | 17 (34)                     | 19 (24.7)                   | 0.55   |
| PCKD                   | 1 (2)                       | 3 (3.9)                     |        |
| Other                  | 15 (30)                     | 21 (27.3)                   |        |
| **BMI, kg/m²**         |                             |                             |        |
| <20                    | 21 (41.2)                   | 14 (17.7)                   |        |
| 20–25                  | 3 (5.9)                     | 3 (3.8)                     | 0.01   |
| 25–30                  | 19 (37.4)                   | 32 (40.5)                   |        |
| 30–35                  | 6 (11.8)                    | 16 (20.3)                   |        |
| ≥35                    | 2 (3.9)                     | 14 (17.7)                   |        |
| **Comorbidities**      |                             |                             |        |
| Coronary artery disease| 4 (9.8)                     | 2 (2.5)                     | 0.07   |
| Hypertension           | 47 (92.2)                   | 75 (93.8)                   | 0.73   |
| Peripheral vascular disease | 1 (2)                  | 0 (0)                       | 0.21   |
| **Donor type**         |                             |                             |        |
| Deceased               | 48 (94.1)                   | 75 (93.8)                   | 0.93   |
| Live                   | 3 (5.9)                     | 5 (6.25)                    |        |
| **Dialysis vintage, d**| 801 (357, 1352)             | 899 (529, 1671)             | 0.46   |
| **CIT**                | 9.0 (4.9, 12.4)             | 9.5 (6.5, 12.1)             | 0.66   |
| **Previous kidney transplant** | 7 (13.7)                 | 9 (11.1)                    | 0.65   |
| **HLA mismatch**       | 4 (3.5)                     | 4 (3.5)                     | 0.89   |
| **Peak PRA**           | 0 (0, 35)                   | 0 (0, 0)                    | 0.2    |
| **Donor CMV serostatus** |                             |                             |        |
| Negative               | 33 (64.7)                   | 49 (61.3)                   | 0.69   |
| Positive               | 18 (35.3)                   | 31 (38.7)                   |        |
| **Recipient CMV serostatus** |                     |                             |        |
| Negative               | 32 (62.8)                   | 49 (60.5)                   | 0.8    |
| Positive               | 19 (37.2)                   | 32 (39.5)                   |        |
| **Pretransplant HbA1c** | 5.2 (5, 5.4)                | 5.3 (4.9, 5.5)              | 0.4    |

Baseline characteristics amongst all study patients, stratified by pretransplant fasting C-peptide level. Missing: recipient race (n=1), cause of ESKD (n=5), recipient BMI (n=2), coronary artery disease (n=2), hypertension (n=1), peripheral vascular disease (n=1), dialysis wait time (n=12), cold ischemia time (n=24), and donor CMV serostatus (n=1). PCKD, polycystic kidney disease; BMI, body mass index; PRA, panel reactive antibody; CMV, cytomegalovirus; HbA1c, hemoglobin A1c.
function pretransplant (lower pretransplant C-peptide levels) may be hypothesized to represent a subgroup at higher risk for developing diabetes after transplant (7). However, that is contrary to what we observed. Rather, we showed a nearly 20-fold higher adjusted odds of PTDM 1 year post transplant for patients with high (≥3000 pmol/L) pretransplant fasting C-peptide levels. In nondiabetic patients, higher C-peptide levels are felt to reflect early insulin resistance and potentially an impending metabolic syndrome phenotype (8). Thus, the strong association between high pretransplant C-peptide levels and PTDM may support more of an insulin resistance mechanism than β cell dysfunction as the main pathogenesis driving PTDM.

However, whether pretransplant insulin resistance leads to β cell dysfunction ultimately culminating in PTDM requires further study, including prospectively collected serial C-peptide levels post transplant.

In obese individuals, adipose tissue releases proinflammatory cytokines involved in the development of insulin resistance (25). Obesity is the leading risk factor for the development of type 2 diabetes (26) and one of the leading risk factors for PTDM (10,18). However, we show that pretransplant C-peptide level is independently associated with PTDM, even after accounting for recipient obesity status. Thus, an elevated C-peptide level before transplant is not simply a marker of recipient obesity-mediated insulin resistance and thereby PTDM. Interestingly, pretransplant HbA1c level and recipient age at transplant were not associated with PTDM at 1 year.

The one-step OGTT has been considered the gold standard for assessment of pretransplant glucose metabolic status (27–29) and current Kidney Disease Improving Global Outcomes guidelines for transplant workup suggest performing an OGTT in candidates who are not known to have diabetes (30). However, the OGTT is generally performed at the time of transplant workup and may not reflect true PTDM risk in patients who gain or lose weight on the transplant waitlist, is cumbersome for patients, and is costly (31). Conversely, C-peptide is a one-time blood draw taken at the time of transplant that is highly predictive of PTDM, with emerging analytics reducing the cost of a single test to around US$13 (32,33).

Transient hyperglycemia during the index hospital stay at the time of transplant has been shown to associate with later PTDM (17). The mechanism for this is unknown but may reflect a greater degree of pretransplant insulin resistance, more advanced β cell dysfunction, or greater susceptibility to the diabetogenic side effects of immunosuppressive therapy (17). Similarly, postoperative hypomagnesemia after kidney transplant has also been shown to associate with PTDM (6,18). The mechanism for this is controversial but may involve altered glucose transport, reduced insuline, or defective insulin signaling pathways (6,18). Whether C-peptide plays a role in post-transplant hypomagnesemia and how this relates to the subsequent development of PTDM has not been studied previously. Therefore, we examined the association of pretransplant C-peptide level with peak glucose and nadir magnesium concentration in the 2 weeks post kidney transplant to explore if an elevated C-peptide level may result in PTDM through either a hyperglycemia- or hypomagnesemia-inducing mechanism; however, there was no association with either.

There are important limitations to our study. Given that maintenance immunosuppression at our center consists of tacrolimus, prednison, and mycophenolic acid in nearly all patients, individual effects of either tacrolimus or prednison maintenance therapy could not be determined (34). This may affect the external generalizability of our results. In addition, Nova Scotia is a largely White Canadian province, with the 2022 population census suggesting that 85% of the province is White (35). This further limits generalizability to more racial and ethnically diverse programs. Ideally, in a prospective study, fasting C-peptide levels would be drawn at the same time of day for each patient

### Table 2. Multivariable logistic regression model for factors associated with post-transplant diabetes mellitus in the first year after transplant

| Patient Characteristic | Odds Ratio | 95% Confidence Interval | P Value |
|------------------------|------------|------------------------|---------|
| C-peptide, pmol/L      |            |                        |         |
| <3000                  | Ref.       | —                      | —       |
| ≥3000                  | 18.9       | 2.06 to 174.2          | 0.009*  |
| Sex                    |            |                        |         |
| Men                    | Ref.       | —                      | —       |
| Women                  | 1.18       | 0.24 to 5.74           | 0.63    |
| Age, per yr            | 0.97       | 0.91–1.03              | 0.29    |
| Cause of ESKD          |            |                        |         |
| Glomerulonephritis     | Ref.       | —                      | —       |
| Hypertension           | 0.58       | 0.03 to 9.63           | 0.7     |
| PCKD                   | 0.62       | 0.13 to 3.04           | 0.56    |
| Other                  | 0.57       | 0.13 to 2.54           | 0.46    |
| BMI, kg/m²             |            |                        |         |
| <20                    | 16.1       | 0.46 to 564.7          | 0.13    |
| 20–<25                 | Ref.       | —                      | —       |
| 25–<30                 | 6.83       | 0.62 to 74.8           | 0.12    |
| 30–<35                 | 12.0       | 1.02 to 141.7          | 0.05*   |
| ≥35                    | 17.9       | 1.39 to 230.9          | 0.03*   |
| Hypertension           |            |                        |         |
| No                     | Ref.       | —                      | —       |
| Yes                    | 0.95       | 0.07 to 12.4           | 0.97    |
| Donor type             |            |                        |         |
| Live                   | Ref.       | —                      | —       |
| Deceased               | 0.95       | 0.24 to 3.8            | 0.95    |
| Previous kidney transplant |        |                        |         |
| No                     | Ref.       | —                      | —       |
| Yes                    | 0.16       | 0.008 to 3.4           | 0.24    |
| Peak PRA, per %        | 1.0        | 0.98 to 1.03           | 0.72    |
| Donor CMV serostatus   |            |                        |         |
| Negative               | Ref.       | —                      | —       |
| Positive               | 3.16       | 0.84 to 11.92          | 0.09    |
| Recipient CMV serostatus |        |                        |         |
| Negative               | Ref.       | —                      | —       |
| Positive               | 0.55       | 0.15 to 2.03           | 0.37    |
| Pretransplant HbA1c, per % | 1.16   | 0.24 to 5.55           | 0.24    |

PCKD, polycystic kidney disease; BMI, body mass index; Ref., reference; PRA, panel reactive antibody; CMV, cytomegalovirus; HbA1c, hemoglobin A1c.

*Denotes statistical significance at a P value of <0.05.
(after the last hemodialysis session), given potential circadian variation in C-peptide levels with higher levels (around 9%) observed in the morning in some but not all earlier studies (20,36). Timing of C-peptide levels (other than their relation to the last hemodialysis session) was not captured in this study, although timing would be expected to be distributed at random. In a sensitivity analysis, correcting the C-peptide level by a factor of 0.91 for any patient with an initial C-peptide level ≥3000 pmol/L (to account for the unlikely event that all elevated C-peptide levels were taken in the morning and all lower levels taken in the evening) did not alter our findings. Likewise, C-peptide is in part renally cleared. So, patients with more residual kidney function may have had lower fasting C-peptide levels. We similarly did not have access to residual function, and this would also be an important consideration in a prospective study, although we showed no difference in C-peptide levels for those on hemodialysis and those transplanted preemptively. Therefore, residual kidney function may have played little role. Ideally, we would have examined a glucose and creatinine corrected pretransplant C-peptide level in a sensitivity analysis as suggested by Faradji et al. (37); however, we did not have this information available, and this earlier study was conducted in a small cohort of patients with type 1 diabetes post islet cell transplant with stable kidney function (median creatinine 0.8 mg/dl), and as such, the relevance to our population is unclear. Although C-peptide levels were sent during a fasting state, the duration of fasting before the blood draw was not available in this retrospective analysis. In nondiabetic patients, several studies have demonstrated higher C-peptide levels to be associated with an increased risk of cardiovascular and all-cause mortality, likely as a surrogate for the metabolic syndrome (38,39). At this point, we do not have long-term follow-up data to determine if a higher pretransplant C-peptide level is associated with increased mortality after transplant; however, this is certainly an area for future study. In noninsulin-dependent diabetics in the general population, those with lower C-peptide levels (using varying cut points) have been shown to have worse glycemic control (40,41) and an increased risk of requiring insulin therapy for diabetes management, felt to represent impending superimposed β cell dysfunction (42,43). How C-peptide levels may have changed post transplant and at the time of PTDM diagnosis remains to be seen, and whether a subsequent drop in C-peptide levels in these patients may confer worse glycemic control requires further investigation. Likewise, we did not have information regarding subsequent weight gain post transplant, and ideally this too would be captured in a prospective study.

In this study, we demonstrate that higher C-peptide levels at the time of kidney transplant can reliably predict patients likely to develop PTDM, independent of recipient obesity status. Given the significant risk to patient and graft survival posed by PTDM, identifying populations at increased risk is critical. A C-peptide level ≥3000 pmol/L is associated with a nearly 20-fold increased odds of PTDM after adjustment for other risk factors. Although this finding needs confirmation in a larger (and ideally prospective cohort), this may suggest a role for specific strategies to minimize risk, including aggressive health promotion programs directed at weight loss through lifestyle intervention (10,44), although in our analysis, the risk of C-peptide appears to be at least somewhat independent to that of obesity. Other potential strategies may include tailoring of immunosuppression to minimize/avoid steroids or tacrolimus (11–14,22), or consideration of early basal insulin therapy in at-risk nondiabetic patients post transplant, which has been shown to reduce the incidence of PTDM at 1 year post kidney transplant (34).

Finally, this finding provides clues to the pathogenesis of PTDM and serves as an important target for future research.

Disclosures

L. Gunaratnam reports consultancy for AstraZeneca Canada, Inc., Novartis Canada Inc., and Paladin Labs, Inc.; honoraria from AstraZeneca Canada, Inc., Novartis Canada Inc., and Paladin Labs Inc.; an advisory or leadership role for AstraZeneca Canada, Inc., Bayer, Inc., and Paladin Labs, Inc.; and participation in a speakers’ bureau for AstraZeneca Canada, Inc. K.K. Tennankore reports consultancy for AstraZeneca, Bayer, Otsuka, and Vifor; research funding from Otsuka Canada; honoraria from Astra Zeneca, Baxter, GSK, and Otsuka; an advisory or leadership role for the Canadian Journal of Kidney Health and Disease (associate editor); and participating in a speakers’ bureau for AstraZeneca, Baxter, and Bayer. A.J. Vinson reports consultancy for Paladin Labs, Inc., and research funding from Paladin Labs, Inc. K. West reports consultancy for Envarsus Canada, and honoraria from Envarsus Canada. All remaining authors have nothing to disclose.

Funding

Funding for this study was supported by an investigator driven research fellowship grant from Paladin Labs, Inc.

Acknowledgments

Funders had no involvement in the study design, conduct, or reporting of results.

Author Contributions

L. Gunaratnam, K.K. Tennankore, and A.J. Vinson were responsible for the methodology; L. Gunaratnam, B.A. Kiberd, F.S. Siddiqi, K.K. Tennankore, and K. West reviewed and edited the manuscript; A. Thanamayooran and A.J. Vinson were responsible for data curation; and A.J. Vinson was responsible for conceptualization, formal analysis, funding acquisition, the investigation, and wrote the first draft of the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0003742022/-/DCSupplemental.

Supplemental Table 1. Multivariable logistic regression model for factors associated with post-transplant diabetes mellitus in the first year after transplant (including pretransplant C-peptide as a continuous variable).

Supplemental Table 2. Multivariable logistic regression model for factors associated with post-transplant diabetes mellitus in the first year after transplant, restricting to patients with a body mass index of 20–35 kg/m².

Supplemental Table 3. Multivariable logistic regression model for factors associated with post-transplant diabetes mellitus in the first year after transplant (including hyperglycemia in the first 2 weeks post kidney transplant).
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Received: May 25, 2022 Accepted: June 28, 2022
See related editorial, “Association of Pre-Transplant C-Peptide with Post-Transplant Diabetes: A New Approach to Identifying High-Risk Patients?,” on pages 1660–1661.