Incidence, Risk Factors, and Trends for Postheart Transplantation Diabetes Mellitus

Vidit N. Munshi, MA[a,*], Soroush Saghafian, PhD[b], Curtiss B. Cook, MD[c], D. Eric Steidley, MD[c], Brian Hardaway, MD[c], and Harini A. Chakkera, MD, MPH[c]

This retrospective study analyzed glycemic trends, incidence of post-transplant diabetes mellitus (PTDM) incidence and associated risk factors in a cohort of patients who underwent first-time heart transplantation (HT). Univariate analyses compared patient with and without pretransplant diabetes mellitus (DM). Multivariate regression analyses were conducted to determine association between PTDM and different risk factors. Finally, trends in glucometrics and other outcomes are described across follow-up time points. There were 152 patients who underwent HT between 2010 and 2015, 109 of whom had no pretransplant history of DM. PTDM incidence was 38% by the 1-year follow-up. Pretransplant body mass index (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.01 to 1.23, p = 0.03), insulin use during the final 24 hours of inpatient stay (OR 4.26, 95% CI 1.72 to 10.56, p <0.01), mean inpatient glucose (OR 2.21, 95% CI 1.33 to 3.69, p <0.01), and mean glucose in the final 24 hours before discharge (OR 1.29, 95% CI 1.03 to 1.60, p = 0.03) were associated with increased odds of PTDM at 1 year. In patients on insulin before discharge, blood glucose values were significantly higher compared with those who were not (136 mg/dl vs 114 mg/dl at 1 to 3 months, 112 vs 100 at 4 to 6 months, 109 vs 98 at 8 to 12 months, all p <0.01). This analysis improves understanding of PTDM incidence, glucometric trends, and risk differences by DM status in the HT population. Similar to liver and kidney patients, inpatient glucometrics may be informative of PTDM risk in HT patients. Guidelines for this population should be developed to account for risk heterogeneity and need for differential management. **(Am J Cardiol 2020;125:436−440)**

Post-transplantation diabetes mellitus (PTDM) is a common complication of solid organ transplantation affecting patients without a previous history of DM, leading to increased risk of graft failure, decreased survival, and other co-morbidities.[1,2] Although the risk of PTDM exists with all organ transplants, most of the literature on this disease focuses on kidney and liver transplant recipients, which make up most of all solid organ transplantations.[3,4] PTDM features and the types of feasible management strategies may differ between transplanted organs. The number of HTs has been increasing in recent years and optimizing long-term outcomes in this group is an important goal.[5] To this end, there is limited data on the frequency and risk factors associated with PTDM in the HT population. In this study, we utilize a dataset from a single HT center to assess changes in glycemic control and determine risk factors in development of PTDM.

Methods

This was a retrospective study of a dataset consisting of 152 patients compiled through a de-identified chart review with Institutional Research Board approval. The patients underwent first time heart-only transplant between 2010 and 2015. Information collected on each patient included demographic data and medical history, as well as Hemoglobin A1c (HbA1c), fasting blood glucose (FBG), uric acid, and cholesterols at 1-, 2-, 3-, 4-, 6-, 8-, and 12-months post-transplant. In addition, we obtained pretransplant DM status and medication information, as well as immunosuppressant blood trough levels at 8- and 12-months post-transplant.

The immunosuppression protocol consists of intravenous methylprednisolone 125 mg preoperative and 500 mg intraoperatively, and then gradual glucocorticoid tapering over the first 120 postoperative days. Thymoglobulin is also infused intraoperatively and on postoperative days 1 to 3. Mycophenolate mofetil is initiated immediately after transplantation whereas tacrolimus is initiated after completion of thymoglobulin therapy.

We classified patients with PTDM using the updated 2014 International Consensus Guidelines criteria of a FBG level >126 mg/dl or HbA1c >6.5%.[6] In contrast to kidney and liver patients from the same institution who are followed up at prescheduled intervals,[7−9] heart transplant patients were followed up at different frequent time intervals, making collection of outpatient glucose data at specific time points difficult. Therefore, to compare glucose values over time, we grouped follow-up visits into 3 time

[a]Harvard University PhD Program in Health Policy, Cambridge, Massachusetts; [b]Harvard Kennedy School, Harvard University, Cambridge, Massachusetts; and [c]Mayo Clinic Arizona, Scottsdale, Arizona. Manuscript received August 30, 2019; revised manuscript received and accepted October 30, 2019.

This work was partially supported by the National Science Foundation (NSF) under the Award Number CMMI-1562645. There are no other sources of funding to report.

See page 440 for disclosure information.

*Corresponding author: Tel: (781) 454-7065.

E-mail address: vmunshi@g.harvard.edu (V.N. Munshi).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.10.054

"periods": 1 to 3 months, 4 to 6 months, and 8 to 12 months. If a patient only had a measurement available for one of the follow-ups within a time period, this value represented the entire time period. When variables were collected at multiple follow-ups within a time period, we used the mean. For example, if a patient had a fasting blood glucose value of 100 at 1-month, no value at 2-months, and 200 at 3-months, then the value for the 1 to 3 month interval was recorded as 150. For HbA1c values, when more than 1 value existed within an interval, we took the maximum value in the time period. PTDM patients were defined as those who met at least one of the criteria for hyperglycemia at any of the follow-up periods.

We first report descriptive statistics (means and standard deviations) on demographic information and pretransplant variables of interest for patients with and without pretransplant diabetes. These include age, sex, race, body mass index (BMI), and FBG. Relevant inpatient variables include insulin use, mean glucose over the patient stay, and mean glucose in the 24 hours before discharge.[10–18] Differences in means were tested for statistical significance using standard *t* tests.

We used logistic regression models to describe the strength of association between these risk factors and PTDM incidence at any point over the course of the first year after transplant. Our regression models adjust for age, sex, race, BMI, pretransplant hemoglobin, and year of transplant. We used *t* tests to describe changes in risk factors over the course of the first year of follow up across patients who had pretransplant diabetes and those who did not. Patients with pretransplant diabetes were further separated by medication at time of transplant. Inpatient glucose data represent point-of-care (POC) capillary measurements performed using the Accucheck Inform (Roche Diagnostics), whereas outpatient values (the ones used to establish the diagnosis of PTDM) were blood glucoses.

Results

Table 1 gives descriptive statistics according to presence of pre-transplant DM. Compared with pretransplant patients with DM, those who did not have DM were more likely to be white ($p = 0.04$), significantly younger, with lower BMI, and FBG (all $p < 0.01$). In addition, those who did not have DM had lower mean patient stay glucose while hospitalized and mean glucose in the final 24 hours before discharge ($p < 0.01$). Overall, 49% of those without pretransplant DM were on insulin in the 24 hours before discharge, 38% of whom developed PTDM.

Criteria for diagnosing PTDM included the possibility of outcomes in which patients experienced previously described "relapsing" or "remitting" hyperglycemia.[7] Table 2 shows all possible scenarios for patient trends in hyperglycemia status over time. For example, column 1 represents 65 patients (61.9%) who did not meet PTDM criteria during any of the 3 periods. Column 2 represents 15 patients (14.3%) who met PTDM criteria at the first time period, but not during the second and third periods. Finally, column 8 represents 6 patients (5.7%) who met the definition of PTDM at all 3 follow-ups. In the 105 living patients who were not diagnosed with DM before HT, 80 (76.2%) patients either did not meet the criteria at all or only met the criteria at the earliest time period (1 to 3 months). When considering all the time where patients met diagnostic criteria, 40 (38%) developed PTDM.

Logistic regressions were conducted to test the association of relevant risk factors with PTDM risk. The variables that were significantly associated with PTDM incidence (Table 3) were BMI, insulin use in the final 24 hours of hospital stay, mean POC blood glucose during inpatient

Table 1
Descriptive statistics on patient characteristics and PTDM risk factors for patients with and without pretransplant diabetes

Characteristic	No pre-Tx DM (n = 109)	95% CI	Pre-Tx DM (n = 43)	95% CI	p Value
Age (years)	51 (12.8)	(49, 54)	58 (8.1)	(56, 61)	<0.01
Men	69%	(60, 78)	79%	(66, 92)	0.20
White	69%	(60, 78)	51%	(36, 67)	0.04
Pre-Tx BMI (kg/m^2)	25.9 (4.5)	(25.1, 26.8)	29.1 (4.5)	(27.7, 30.5)	<0.01
Pre-Tx FBG (mg/dl)	108 (36.0)	(101, 115)	140 (39.0)	(128, 153)	<0.01
Pre-Tx HbA1c (%)	5.75 (.5)	(5.64, 5.86)	6.93 (1.8)	(6.36, 7.50)	<0.01
Mean patient hospital stay glucose (mg/dl)	134 (10)	(132, 136)	155 (13)	(151, 159)	<0.01
Mean glucose 24 hours before discharge (mg/dl)	134 (23)	(129, 139)	171 (37)	(160, 182)	<0.01
Insulin use in 24 hours prior to discharge (%)	49%	(39, 58)	95%	(89, 100)	<0.01

Table 2
Hyperglycemia outcomes of heart transplantation patients without pretransplantation diabetes, stratified by status at each time period

Time (months)	Satisfying the criteria for hyperglycemia							
	1	2	3	4	5	6	7	8
1-3	No	Yes	No	No	Yes	Yes	No	Yes
4-6	No	No	Yes	No	Yes	No	Yes	Yes
8-12	No	No	No	Yes	No	Yes	Yes	Yes
# of Patients (%)	**65 (61.9%)**	**15 (14.3%)**	**2 (1.9%)**	**2 (1.9%)**	**10 (9.5%)**	**4 (3.8%)**	**0**	**7 (6.7%)**

Table 3
Logistic regression coefficients for association between pretransplant and inpatient patient characteristics and PTDM risk

Variable	Adjusted odds ratios	95% CI	p Value
Age, per 5 years	1.07	0.86 – 1.28	0.46
BMI, kg/m^2	1.12	1.01 – 1.23	0.03
Race (White)	0.50	0.20 – 1.23	0.13
Male (vs Female)	0.62	0.24 – 1.60	0.32
Pre-Tx hemoglobin	0.87	0.73 – 1.04	0.13
Insulin use during last 24 hours on hospital stay (vs no use)	4.26	1.72 – 10.56	<0.01
Inpatient mean glucose post-transplant, per 10 mg/dl	2.21	1.33 – 3.69	<0.01
Mean glucose 24 hours before hospital discharge, per 10 mg/dl	1.29	1.03 – 1.60	0.03
Transplant year (vs 2010)	0.99	0.77 – 1.28	0.96

Note: Adjusted models control for available pretransplant patient characteristics (age, sex, race, BMI, pretransplant hemoglobin).

hospital stay, and mean POC blood glucose in the final 24 hours before discharge. For every unit increase in BMI, the odds of PTDM increased by 112% (odds ratio [OR] 1.12, 95% confidence interval [CI] 1.01 to 1.23, p = 0.03). Use of insulin during the final 24 hours was associated with increased PTDM odds of 426% (OR 4.26, 95% CI 1.72 to 10.56, p <0.01). Additionally, a 10 mg/dl increase in mean inpatient glucose was associated with an increased PTDM odds of 221% (OR 2.21, 95% CI 1.33 to 3.69, p <0.01). Finally, mean glucose in the final 24 hours before discharge was associated with a 129% increase in PTDM odds (OR 1.29, 95% CI 1.03 to 1.60, p = 0.03).

Figure 1 demonstrates differences in FBG and HbA1c between patients who were on insulin during the final 24 hours of inpatients stay compared with those who were not for each of the 3 time periods. Glucose values were significantly higher in the insulin group at all time-points (136 mg/dl vs 114 mg/dl at 1 to 3 months, 112 vs 100 at 4 to 6 months, 109 vs 98 at 8 to 12 months, all p <0.01). Conversely, there were no statistically significant differences in HbA1c between the 2 groups at any of the time periods.

Over time, mean glucose values in the no insulin group decreased from 114 mg/dl (95% CI 107 to 120 mg/dl) at 1 to 3 months to 98 mg/dl (95% CI 94 to 102 mg/dl) at 8 to 12 months (p <0.01). In patients who were on insulin during the final 24 inpatient hours, glucose dropped on average from 131 mg/dl (95% CI 120 to 142 mg/dl) to 109 mg/dl (95% CI 104 to 115 mg/dl; p <0.01). Changes in HbA1c were insignificant for the both the insulin and no insulin groups.

Figure 2 shows differences in relevant patient variables between the 3 main study groups study: those who had pretransplant diabetes, those who developed PTDM, and those who did not have diabetes before or after transplant. For blood glucose (Panel A), all 3 means (139 mg/dl for No pre-tx DM, 97 mg/dl for no PTDM, 115 mg/dl for PTDM) were statistically significantly different from each other (all p <0.01). HbA1c (Panel B) was only significantly different between the pretransplant diabetes and the no diabetes groups with pretransplant DM patients having a higher HbA1c (6.5 vs 5.7, p <0.01). BMI (Panel C) was significantly higher in the pretransplant diabetes group compared with post-transplant PTDM patients (29.0 vs 26.1, p <0.01). In those without pretransplant diabetes, those who developed PTDM had a significantly higher pretransplant BMI than those who did not (28.1 vs 24.9, p = 0.02). Tacrolimus trough levels (Panel D) at 12 months were not significantly different across any of the 3 patient groups.

Discussion

In this analysis, we introduce a data set collected by a single center in the United States which describes risk and trends in heart transplantation PTDM outcomes. This study may also allow for better comparison across organs as it complements other collected data from the same institution.[7–9,19] One of the noteworthy contributions of this analysis is a new PTDM incidence estimate of 38% which is in

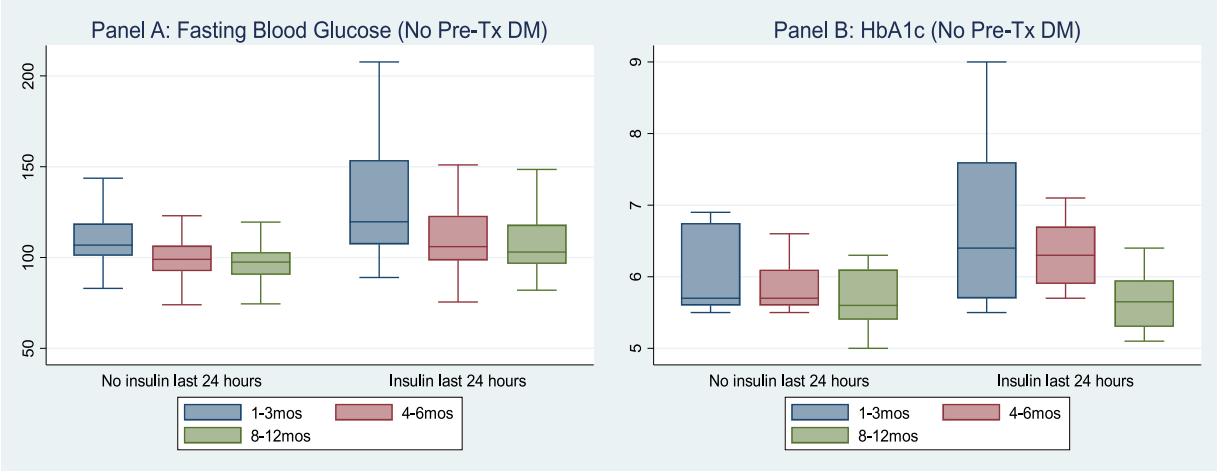

Figure 1. FBG and HbA1c trends across 2-3, 4-6, and 8-12 month follow-ups split by use of insulin in final 24 hours of hospital stay for patients without pretransplant DM.

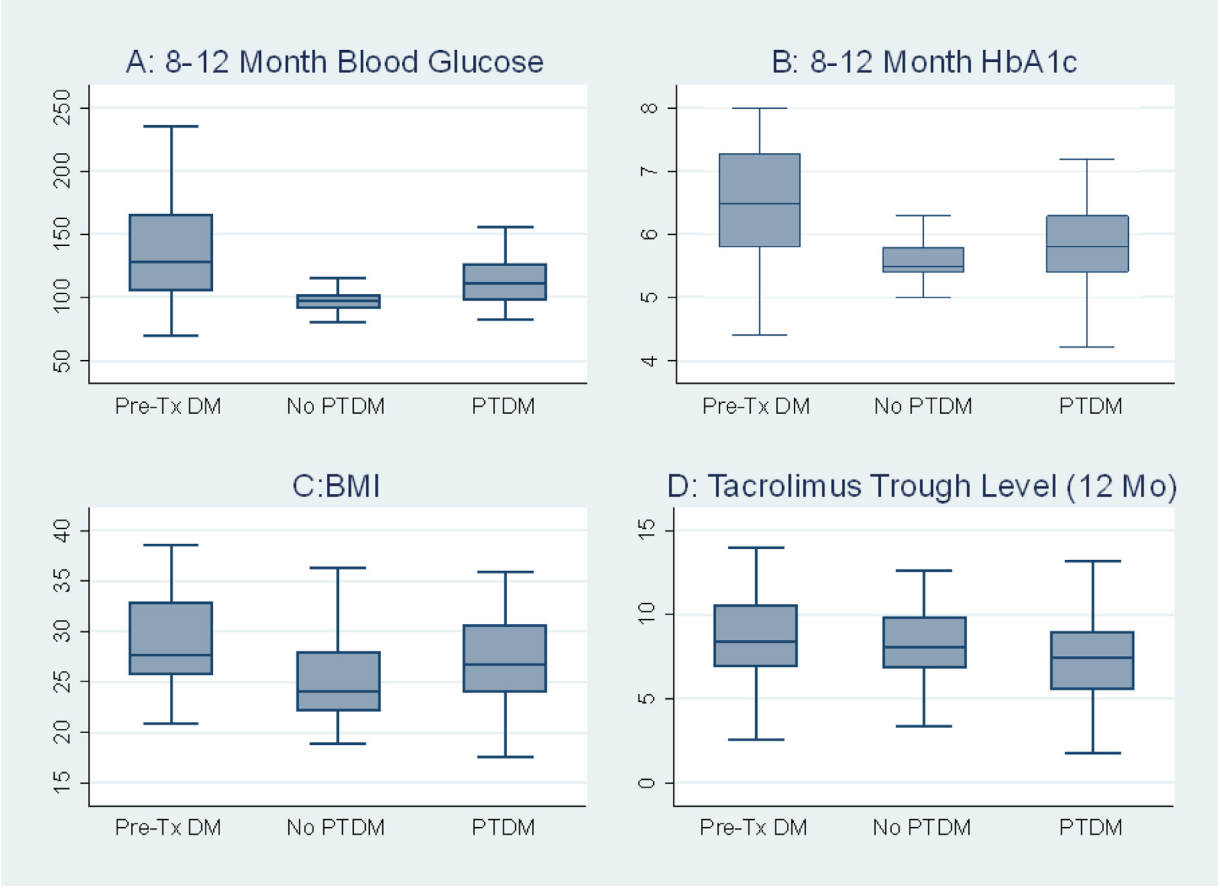

Figure 2. Comparison of tacrolimus blood trough level and glucometrics between 8 and 12 months for patients who developed PTDM, those who did not develop PTDM, and those who had pretransplant DM.

the upper range of the 4% to 40% estimates provided by previously cited publications.[20] Along with upper-range PTDM estimates for kidney and liver from the same institution, this estimate includes revised definitions for PTDM criteria which use blood glucose and HbA1c and illustrates that some of the lower estimates provided by previous literature are likely underestimating PTDM burden.[21] In particular, this higher range estimate does not account for the significant lack of data collection of HbA1c in this population group as only 5 patients had collected HbA1c at all 3 time periods, making blood glucose the primary diagnostic metric. Updated guidelines that reflect this lack of data collection and potentially larger PTDM effect on the heart transplantation patient population may be needed.

One area of interest for PTDM research in heart transplant recipients may be to better understand how to predict those at greater risk for PTDM based on known and observable risk factors. With this information, decision makers can better differentiate management of those at risk for PTDM compared with standard DM and allocate resources accordingly. In this analysis, we confirm results from previous analysis of liver transplant patients that inpatient mean glucose and glucose in the 24 hours before transplant are both significant predictors of PTDM when controlling for pretransplant risk factors.[21] In addition, we identify a risk factor that is previously not discussed in the literature, particularly with respect to heart transplant patients: insulin use in the final 24 hours before hospital discharge after transplant. Insulin in the final 24 hours was associated with a large increase in the risk of hyperglycemia at the 1-year time period. Furthermore, the group of patients on insulin during the final 24 hours had significantly higher glucose values across each of the 3 time periods. These results further indicate that inpatient glycemic control and the therapy needed to manage it might be the earliest indicators of PTDM risk. These observations justify the need to begin diabetes self-management education (e.g., glucose monitoring and insulin administration) before hospital discharge.

We find significant differences in the 3 distinct groups of patients analyzed with respect to 1-year outcomes in blood glucose, HbA1c, and BMI (Figure 2). With respect to BMI, differences in pretransplant values between those who eventually developed PTDM and those who did not may suggest interventions in the pretransplant setting can be effective in mitigating longer-term PTDM risk. Put together, these values indicate that further research is needed to better identify the differences in risks and outcomes between these patient groups with respect to longer-term outcomes.

There are several limitations that are important to consider in this study. First, this is a retrospective study on a smaller (n = 152) sized data set. As a result, some variables

of interest were not collected and available. For example, lack of information on steroid use at each timepoint did not allow for analysis of correlation between steroid use and PTDM. However, lack of a comparator (all patients received steroids for up to 4 months after transplant) makes this variable difficult to evaluate.

In the case of HbA1c, low collection of data in some cases left us with too small of a sample to detect significant differences. In 52 of the 109 patients who did not have pretransplant DM, we did not have HbA1c available at any of the 3 time periods. This introduces the potential for underestimation of PTDM burden as much of the PTDM diagnosis was based on glucose values alone. In contrast, 14.3% of patients were diagnosed with PTDM on the basis of the first 1 to 3 months period. The early part of this time period may represent transient hyperglycemia in the post-transplant period and may not indicate true PTDM. Although glucoses are measured routinely in the post-transplant period, HbA1c's are not. There is no standard for measuring HbA1c in patients without known DM. However, adding HbA1c monitoring as part of the after transplant surveillance could increase the chances of earlier identification of more patients with PTDM. Finally, due to this being a small data set from a single center only covering HTs over a small time period (5 years), the results of this analysis may have limited generalizability to the larger population. Overall, however, this analysis represents one of the first attempts to characterize after cardiac PTDM from a large heart transplant center in the United States and should serve as a motivation for further monitoring, data collection, and analysis in this field.

This analysis improves understanding of PTDM incidence, glucometric trends, and differences in risk by DM status in the HT population.

Disclosures

The authors have no conflicts of interest to report.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.10.054.

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