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VIEWPOINT

Analyzing outcomes following pancreas transplantation: Definition of a failure or failure of a definition

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Pancreas transplantation has an identity crisis and is at a crossroads. Although outcomes continue to improve in each successive era, the number of pancreas transplants performed annually in the United States has been static for several years in spite of increasing numbers of deceased donors. For most practitioners who manage diabetes, pancreas transplantation is considered an extreme measure to control diabetes. With expanded recipient selection (primarily simultaneous pancreas-kidney transplantation) in patients who are older, have a higher BMI, are minorities, or who have a type 2 diabetes phenotype, the controversy regarding type of diabetes detracts from the success of intervention. The absence of a clear and precise definition of pancreas graft failure, particularly one that lacks a measure of glycemic control, inhibits wider application of pancreas transplantation with respect to reporting long-term outcomes, comparing this treatment to alternative therapies, developing listing and allocation policy, and having a better understanding of the patient perspective. It has been suggested that the definition of pancreas graft failure should differ depending on the type of pretransplant diabetes. In this commentary, we discuss current challenges regarding the development of a uniform definition of pancreas graft failure and propose a potential solution to this vexing problem.

KEYWORDS
C-peptide, hemoglobin A1c, insulin, pancreas graft failure, pancreas transplantation

> "If everybody is thinking alike, then somebody isn't thinking." General George Patton

> "If you can't explain it simply, you don't understand it well enough." Albert Einstein

December 2022 will represent the 56th anniversary of the first successful vascularized pancreas transplant performed at the University of Minnesota. It is perplexing that more than half a century later, we still do not have a uniform definition of pancreas graft failure (PGF). What would seem to be straightforward is, on further investigation, unexpectedly complex.

Prior to 2000, the prevailing definition of death-censored PGF was the need for any exogenous insulin therapy on a consistent (usually daily) basis. This definition was uncomplicated and reflected the primary indication for pancreas transplantation, namely insulin-requiring type 1 diabetes with complications. However, with the development of islet transplantation coinciding with an improved

Abbreviations: HbA1c, hemoglobin A1c (glycated hemoglobin); PGF, pancreas graft failure; SPKT, simultaneous pancreas-kidney transplant; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

understanding of glucose homeostasis and the availability of new technology, glycemic control metrics evolved to include outcomes such as C-peptide production, hemoglobin A1c (HbA1c) levels, assays of glycemic excursion (Lability Index), static measures of insulin resistance, dynamic measures of insulin secretion and sensitivity, and continuous glucose monitoring.[1–6] If the need for insulin is the basis for the definition of PGF, does this imply that a pancreas transplant is meant solely to treat the need for insulin? Should the success of pancreas transplantation be judged only upon the avoidance of an alternative treatment for the target disease? Instead, if a pancreas or islet graft improves glycemic control in a measurable way, then perhaps the allograft should be considered functional. Attention to clinical measures of glycemic control reorients the purpose of pancreas or islet transplantation to management of diabetes rather than just obviating the need for insulin.

When the updated United Network for Organ Sharing (UNOS) pancreas and kidney-pancreas allocation system changes went into effect on October 30, 2014, the definition of PGF at that time was the following: A recipient's pancreas is removed; a recipient re-registers for a pancreas retransplant; a recipient registers for an islet transplant after receiving a pancreas transplant; or a recipient dies.[7] These criteria are consistent with the definition of allograft failure for all types of organ transplants. UNOS Tiedi guidance documents on reporting of PGF included further classification into three categories: (1) Functioning: The graft has sufficient function so that the recipient is NOT receiving any insulin or oral medication for blood sugar control; (2) Partial Function: The patient is taking some insulin, but ≤50% of the usual amount taken before transplant or C-peptide is present; and (3) Failed: The graft has totally failed and the patient is completely dependent upon insulin or oral medication for blood sugar control. As these guidance criteria were not formally a component of policy and some were relatively vague and dependent on prior insulin administration, they were seldom utilized in center reporting of PGF. Ultimately, this assigned the definition of actual organ function up to the individual transplant center's discretion. Some programs, to determine when PGF occurred, used other factors such as changes in C-peptide levels, HbA1c levels, or dose and duration of insulin therapy whereas others reported PGF as any resumption of exogenous insulin (or failed to endorse PGF until "complete" resumption of insulin based on pretransplant requirements had occurred). It is important to note that this definition is already a much higher standard for declaring graft failure than is required for any other organ transplanted. For example, if dialysis is never initiated and a patient is never retransplanted or has their kidney graft removed, a patient in advanced renal failure after a kidney transplant (partial function) would still be considered a current "success". Consequently, a system of center-based self-reporting of PGF arose in which variable definitions were used, which was not conducive to comparing outcomes amongst centers for subsequent modelling. For a period, the Scientific Registry of Transplant Recipients (SRTR) actually refrained from reporting pancreas transplant outcomes in program-specific reports because of the heterogeneity of center-specific definitions used to determine PGF.[8,9] Moreover, the lack of a uniform definition of PGF made it difficult to compare pancreas transplant outcomes to alternative therapies for diabetes.

In 2018, the UNOS Pancreas Transplant Committee revisited the definition of PGF and added a threshold amount and minimum period of time for daily insulin requirement.[10] The amount was decided by consensus and the duration was added to avoid reporting brief resumption of insulin in times of stress or if the patient was receiving medications that temporarily increase serum glucose levels such as steroids. In summary, a total insulin use of ≥0.5 units/kg/day for a consecutive 90 days was added to the definition of PGF in an attempt to provide more granularity and consistency. Of note, there was interest in including C-peptide and/or HbA1c levels in the updated definition of PGF, but as these were not previous data points that were routinely collected from transplant centers for pancreas recipients, there were no data to support their inclusion. In fact, a study performed by the UNOS Pancreas Transplantation Committee and other invited investigators using their own institutional data concluded that C-peptide levels do not correlate with reported PGF.[11] However, there was a consensus that the absence of detectable C-peptide does indicate PGF. We concede that we participated in this process and played a role in promoting this rather arbitrary distinction between partial pancreas function versus complete PGF.

However, in the interim it remains unclear whether the current insulin requirement threshold achieves the intended goal. For example, how does this aspect of the definition relate to patients transplanted for type 2 (C-peptide detectable) diabetes mellitus, or whether it is applicable for patients who develop type 2/post-transplant diabetes mellitus following pancreas transplantation in the absence of any apparent pancreas allograft dysfunction (normal C-peptide levels). The latter condition may be seen in patients with excessive weight gain post-transplant or in some patients with chronic pancreas allograft rejection. An additional complicating feature in this circumstance is concomitant kidney dysfunction, either from chronic kidney disease in a renal allograft or native kidney disease progression in recipients of a pancreas transplant alone. For example, in simultaneous pancreas-kidney transplant (SPKT) recipients who develop kidney alone graft failure and subsequently undergo successful kidney retransplantation, 20% become insulin-requiring in the first year following retransplantation.[12] Additionally, in a patient with a failed kidney allograft on dialysis and with a failing pancreas allograft, insulin requirements may be misleadingly low, making it difficult to determine timing of PGF. These situations underscore the relationship between kidney and pancreas allograft function. Moreover, with an upsurge in the multitude of new oral and injectable (non-insulin) agents available to manage hyperglycemia, is a definition of PGF based exclusively on daily insulin use germane to the discussion? Importantly, the need for insulin therapy is a prerequisite for listing patients for SPKT but does this criterion need to be revisited given the current boom in newer non-insulin alternatives to treat diabetes?

At Wake Forest, PGF is identified as the need for any insulin therapy on a daily basis because the requirement for exogenous insulin administration is well-defined and characterizes what is important

from a patient perspective. We concede that this strict definition largely overlooks cases of "partial pancreas function" in which the patient may actually be relatively well protected against large swings in glycemic excursions (especially hypoglycemia) in spite of the administration of low dose daily insulin therapy. In our experience spanning 30+ years in pancreas transplantation, the mean pretransplant insulin dose for recipients was 40 units/day and mean recipient weight was 71 kg (mean daily insulin requirement 0.56 units/kg/day), which suggests that nearly half of patients have mean daily insulin requirements <0.5 units/day PRIOR to transplant. In a review of our cases of PGF in the past 10 years (in the absence of death, pancreatectomy, or retransplantation), nearly half of the cases of PGF did not meet the current UNOS definition based on daily insulin requirements, yet all of these patients were clearly "diabetic". For example, some post-transplant patients may be on daily insulin doses that are actually higher than their pretransplant daily insulin requirements, while others are on insulin doses of <0.5 units/kg/day but may have HbA1c levels in the 8%–9% range. In both of these situations, however, the current UNOS definition of PGF is not met. In patients who gain excessive weight following transplantation, are taking a calcineurin inhibitor and/or steroids, or have normal renal function, should their daily insulin requirements at the time of PGF have any relationship to pretransplant daily insulin usage? Moreover, the current definition of PGF in essence incentivizes providers to use non-insulin alternatives to manage hyperglycemia following pancreas transplantation (to avoid declaring PGF), which actually may be detrimental to patient care while attempting to preserve center-specific outcomes. Proper application of the UNOS definition of PGF assumes, however, that the patient is being appropriately managed. In essence, it is how to define appropriate glycemic management that is so problematic. As an important component of the PGF definition policy change, new additional data fields were added for center reporting to permit the Pancreas Transplant Committee to revisit inclusion of these variables (C-peptide and HbA1c levels, data on insulin usage) in the definition of PGF at a future date.

In 2018, the International Pancreas and Islet Transplantation Association and the European Pancreas and Islet Transplant Association held a workshop in Igls, Austria, in order to develop criteria pursuant to the definition of function versus failure for beta-cell replacement therapy.[6] There was consensus that beta-cell graft function was characterized by both functional and clinical outcomes including a HbA1c level ≤6.5%–7.0%, absence of hypoglycemia, daily insulin requirements <50% of baseline, and presence of detectable C-peptide levels above baseline. However, it was noted that C-peptide levels might not be reliable in uremic patients or in those with evidence of C-peptide production prior to transplant. Additionally, HbA1c levels are likewise subject to variability depending on concomitant medications (such as Dapsone) or severe anemia.[6,13] Conceding that no definition of PGF is all-inclusive, we propose that the definition of PGF reflect the context in which it is used. The current UNOS definition adequately addresses the inconsistencies that arise if individual transplant centers utilize their own definition of function, but is not satisfactory from a research or patient perspective. The "reporting" definition is simple and sensitive for detecting functioning grafts but insensitive to the patient's perception of graft failure secondary to the low clinical threshold. For instance, a quality of life study using the current UNOS PGF definition might miss the beneficial impact of pancreas transplantation. Thus, clinical investigation should employ alternative or at least additional definitions. For example, scientific definitions of PGF should include patients with persistently elevated HbA1c levels >6.5% as well as any daily insulin requirements or the need for any oral hypoglycemic agent and/or injectable medication for ≥3 consecutive months irrespective of C-peptide levels. Although this stricter definition of PGF will capture a higher rate of graft loss, it permits transparency, facilitates granularity, provides consistency, and more closely resembles the clinical indications for performing pancreas transplantation and the benefits sought by the patient. Conversely, one downside of a more stringent definition is the negative labelling effect of PGF and lower reported overall outcomes over time. However, sacrificing a lower rate of PGF for greater clarity and ease of reporting is a laudable goal that should foster more trust and confidence in the process, which may actually result in "better" reporting irrespective of any perceived effect on pancreas transplant volumes.

Pancreas transplantation offers superior glycemic control and prevention of hypoglycemia compared to exogenous insulin administration. The new UNOS reporting definition of PGF is based upon glycemic control rather than avoidance of insulin, but the validity of the definition depends upon appropriate glycemic management. The new fields in UNOS reporting, may, upon future analysis, help to further define glycemic management and should then be incorporated into the reporting definition. In the meantime, investigational studies should use well-described definitions of PGF that include clinical parameters and these definitions should be assessed by the peer review process. Ultimately, a definition of PGF based upon clinical parameters of diabetes management may encourage access to pancreas transplantation.

"To define is to limit." Oscar Wilde

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data available on request from the authors due to privacy/ethical issues.

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