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PANCREAS TRANSPLANTATION (DA AXELROD, SECTION EDITOR)

Pancreas Transplantation for Type 2 Diabetes Mellitus: Who and Why?

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Abstract In the past, type 2 diabetes mellitus (T2DM) was a contraindication for simultaneous pancreas-kidney transplantation (SPKT) even though it was generally accepted to be an effective treatment option for selected patients with type 1 DM (T1DM) and advanced chronic kidney disease. However, because there may be tremendous overlap in the clinical presentations of T1DM versus T2DM, the presence of detectable C-peptide is no longer considered reliable in determining DM "type." Experiences with SPKT in uremic patients with detectable pretransplant C-peptide levels with a type 2 diabetes phenotype (older age of onset of DM and older age at transplant, shorter duration of insulin-requiring DM, higher body weight/BMI, higher proportion of African-Americans) have demonstrated outcomes equivalent to those with T1DM although clearly a more robust selection bias exists for patients with presumed T2DM. The success of SPKT in this setting provides evidence that the pathophysiology of T2DM is heterogeneous and not related exclusively to insulin resistance. The purpose of this review is to summarize evidence that appropriately selected uremic patients with T2DM may benefit from SPKT, with a focus on recipient selection in order to optimize outcomes.

Keywords C-peptide · Obesity · Pancreas transplantation · Portal-enteric drainage · Simultaneous pancreas-kidney ?transplantation · Type 2 diabetes mellitus

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Abbreviations

AA	African-American
BMI	Body mass index
DM	Diabetes mellitus
ESRD	End stage renal disease
IPITA	International Pancreas and Islet Transplant Association
IPTR	International Pancreas Transplant Registry
PAK	Pancreas after kidney
PRA	Panel reactive antibody
PTA	Pancreas transplant alone
PTx	Pancreas transplantation
SPKT	Simultaneous pancreas-kidney transplantation
SRTR	Scientific Registry of Transplant Recipients
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UNOS	United Network for Organ Sharing
US	United States

Introduction

Diabetes mellitus (DM) is a chronic disease of glucose dysmetabolism that has reached pandemic levels worldwide and represents a growing burden both on health-care

expenditures and the quality of life of affected individuals. Of the estimated 29.1 million patients with DM in the USA (9.3 % of the total population), about 21 million are diagnosed, 6 million take insulin, and 1.7 million new cases of DM emerge each year in Americans aged more than 20 years [1]. In the USA, DM is the leading cause of end-stage renal disease (ESRD), accounting for 49,677 new cases (44 %) of kidney failure in 2011 [1]. Patients with DM currently comprise >40 % of the kidney transplant waiting list in the USA. In 2011, a total of 228,924 people of all ages with kidney failure secondary to DM were living either on chronic dialysis or with a kidney transplant [1].

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The vast majority of cases of DM fall into two broad etio-pathogenetic categories, which historically were categorized as juvenile onset type 1 DM (T1DM) or adult onset type 2 DM (T2DM) based on clinical presentation and epidemiology [1, 2]. T2DM accounts for up to 95 % of all cases, is associated with the metabolic syndrome and higher preexisting cardiovascular morbidity, is usually diagnosed in patients whom are older and obese, is characterized by both insulin resistance as well as relative insulin deficiency, is not associated with autoimmunity, and does not usually require exogenous insulin therapy. However, there exists tremendous overlap between the clinical presentations of T1DM and T2DM, which suggests that DM is a heterogeneous disorder in which T1DM and T2DM may be similar disorders of insulin resistance that develop in patients with a genetic predisposition to selective beta-cell failure [3].

Beta-cell replacement strategies, such as islet cell or vascularized pancreas transplantation (PTx), are currently the only known therapies that reliably establish a long-term stable euglycemic state [4–6]. Successful PTx achieves endogenous insulin secretion (C-peptide production) reactive to normal feedback mechanisms, which results in normalization of glycosylated hemoglobin levels without the need for either exogenous insulin administration or close glucose monitoring. PTx is a well-accepted but underutilized therapeutic option mainly for patients with T1DM and ESRD, who undergo either simultaneous pancreas-kidney transplantation (SPKT) or kidney alone transplantation first followed by sequential pancreas after kidney (PAK) transplantation [7, 8••]. PTx can also be performed in the absence of ESRD as a PTx alone (PTA). However, only about 100 PTAs are performed annually in the USA, and this procedure is almost exclusively reserved for patients with T1DM. In the USA, for every 10,000 patients with T1DM, only three will actually receive a PTx or islet transplant in their lifetime, secondary to multiple factors such as the lack of suitable pancreas donors, the burden of chronic toxicity determined by lifelong immunosuppression, and financial and access obstacles to transplantation.

Although SPKT is generally accepted as an effective treatment option for appropriately selected T1DM patients with ESRD, there is considerably less agreement regarding its role in the treatment of patients with insulin-requiring T2DM in the setting of ESRD [9••, 10•]. In the recent past, T2DM was a contraindication for SPKT because its primary pathophysiology was believed to be exclusively insulin resistance, which should in theory render PTx ineffective in the management of this condition [9••, 10•]. However, initial intentional (and unintentional) experiences with SPKT in patients with detectable pretransplant C-peptide levels and in some cases a "type 2 diabetes phenotype" have demonstrated that augmentation of endogenous insulin (C-peptide) production following successful SPKT may result in complete insulin independence, improved glucose counter-regulation, and enhanced quality of life [9••, 10•, 11, 12•, 13, 14•, 15]. The success of SPKT in this setting provides evidence that the pathophysiology of T2DM is heterogeneous and is comprised of elements of both insulin resistance and insulin deficiency secondary to beta-cell failure.

Because there may be tremendous overlap in the clinical presentations of T1DM versus T2DM, the presence of C-peptide by itself is no longer considered reliable in determining "type" of diabetes, particularly in the setting of ESRD [16•, 17]. To add to the confusion, it is well established that the immunosuppressive medications requisite to transplant may "cause" T2DM [18]. Experiences with SPKT in patients with detectable pretransplant C-peptide levels with a T2DM phenotype have demonstrated outcomes equivalent to those with T1DM although clearly a more robust selection bias exists for patients with T2DM [9••, 10•, 11, 12•, 13, 14•, 15]. In the USA, for every 1 million patients with T2DM, only three will actually undergo SPKT. The purpose of this review is to provide evidence that selected patients with T2DM may benefit from SPKT, with a focus on recipient selection in order to optimize outcomes.

Recipient Selection: Who?

Although indications for SPKT may vary among different centers, certain guidelines are followed that have been modified by clinical experience (Table 1). Among these standard guidelines are the presence of insulin-requiring DM (either "type 1 or 2," irrespective of C-peptide production) and the predicted abilities to tolerate the operative procedure and possible associated complications in conjunction with managing, understanding, and affording the requisite long-term posttransplant immunosuppression and close follow-up. Patients and their families must fully comprehend and accept the nature of the acute surgical procedure as well as the chronic long-term medical consequences. Emotional and psychosocial stability and support are paramount to success. Because of older age, obesity or comorbidities, many PTx centers in effect

Table 1 Eligibility guidelines for pancreas transplantation

Exclusion criteria
Age >65–70 years
Non-insulin-requiring DM with absence of glucose hyperlability or progressive diabetic complications
BMI >35 kg/m^2
Insufficient cardiovascular functional reserve (one or more of the following): Coronary angiographic evidence of significant noncorrectable coronary artery disease, ejection fraction below 30–40 %, recent history of myocardial infarction or congestive heart failure, right ventricular end diastolic pressure >45–50 mmHg
Moderate to severe dysfunction in other (nonrenal) organ system (lung, liver, CNS)
Presence of severe peripheral vascular (aortoiliac) disease
Ongoing, untreated substance abuse (drug, alcohol, tobacco)
Ongoing, untreated psychiatric illness or noncompliance
Active, untreated infection (including positive hepatitis B surface antigen serology) or malignancy (other than localized basal cell or squamous cell skin cancer)
Inadequate psychosocial support and financial resources
Poor overall functional and performance status (severe deconditioning or malnutrition, frailty, dementia, wheelchair-bound, need for chronic oxygen therapy)
Any chronic illness that cannot be controlled with medication or any systemic illness that would severely limit life expectancy or compromise recovery
Inability to provide informed consent
Positive crossmatch with a specific donor
Inclusion Criteria
Age below 65 years
Presence of insulin-requiring DM (either "type 1 or 2," irrespective of C-peptide production) with glucose hyperlability, hypoglycemia unawareness, well-defined diabetic complications, or significant physical or psychological complications of insulin therapy
BMI <30 kg/m^2
Ability to understand and tolerate the operative procedure, possible associated complications, and chronic immunosuppression
Emotional and psychosocial stability and support
Financial resources
Specific criteria for SPKT
Creatinine clearance (or estimated GFR) <20 ml/min or dialysis dependent
Specific criteria for PAK transplant
Stable renal allograft function on maintenance immunosuppression without recent episodes or acute rejection or major infection, creatinine clearance or estimated GFR >35–40 ml/min (if patient already on a calcineurin inhibitor) or >50–60 ml/min (if not on a calcineurin inhibitor and plan is to place patient on a calcineurin inhibitor)
Specific criteria for PTA
Creatinine clearance (or estimated GFR) >60–70 ml/min and 24-h protein excretion <1.0 g
Specific criteria for PTx in T2DM
Age <55–60 years
BMI <30–32 kg/m^2
Fasting C-peptide level <10 ng/ml
Total daily insulin dose <1 u/kg/day and <100 u/day
Insulin-requiring for minimum of 3–5 years
Presence of "complicated" diabetes including glucose hyperlability
Absence of smoking, major amputation, severe cardiac or vascular disease
No recent history of dietary and medication compliance
Adequate psychosocial and financial support
Risk factors/relative contraindications
Age <15 or >55–65 years
BMI <18 or >30–35 kg/m^2
Non-insulin-requiring or daily insulin requirements >80 u
Cardiac ejection fraction 30–40 %
Major wall motion abnormalities or moderate to severe valvular disease on echocardiography
Pulmonary artery pressure 40–50 mmHg

Table 1 (continued)

Active smoking
Human immunodeficiency or hepatitis C viral infection
Unilateral or bilateral lower extremity amputations
History of substance abuse, psychiatric illness, or noncompliance/nonadherence
Positive thrombophilia screen or history of hypercoagulable syndrome
Peritoneal dialysis with multiple episodes of peritonitis
Multiple previous laparotomies
Previous intra-abdominal/pelvic irradiation or multiple surgical procedures
Presence of aortoiliac bypass graft
Severe orthostasis or gastroparesis
Presence of an ostomy, feeding tube, or chronic bladder drainage catheter
Symptomatic cerebrovascular or peripheral vascular disease
Limited social support (lives alone, relies on public transportation)
Limited financial resources

exclude the majority of patients with T2DM based on their standardized selection criteria [19]. It is important to note, however, that recipient selection is largely determined by clinical, psychosocial, and financial criteria rather than the "type" of DM. In other words, the recipient evaluation and selection processes are virtually the same regardless of the presumed "type" of DM, which is largely irrelevant from a clinical perspective [12•]. With that being said, however, "specific" selection criteria for SPKT in "type 2" (C-peptide positive) DM are listed in Table 1.

Patient selection is aided by a comprehensive medical evaluation before transplantation (Table 2) performed by a multidisciplinary team that confirms the diagnosis of insulin-requiring DM, determines the patient's ability to withstand the operative procedure and chronic immunosuppression, establishes the absence of any exclusion criteria (Table 1), and documents end-organ complications for future tracking after transplantation [20]. The primary determinants for recipient selection are the presence of glucose hyperlability, progressive diabetic complications, degree of nephropathy (which determines type of transplant), cardiovascular risk, and overall functional and performance status. With increasing experience, previous absolute have become relative contraindications, and relative contraindications have become risk factors for PTx (Table 1). We do not view active smoking as an absolute but rather a relative contraindication to PTx but strongly endorse smoking cessation in all patients. We do not have any experience with urine cotinine levels in this setting. In addition, the presence and severity of peripheral vascular (particularly iliac arterial) disease is assessed by a non-contrast abdominal and pelvic computerized tomographic scan in combination with duplex ultrasonographic examination of the iliac vessels.

In general, if a patient believes that DM is controlling their life more than they are controlling DM, or if the presence of DM is self-perceived to be causing a significant impairment in overall quality of life, then PTx should be considered as a treatment option. In our experience, the above queries are critical to understanding the relationship between the patient and their diabetic condition. Although qualitative and not rigorously scientific, most patients can tell you if/when they lost control of their diabetes management. In this setting, PTx to improve quality of life is not only an endpoint but a "turning point" in their overall health and well-being. In addition to severe metabolic derangements from diabetes, significant physical or psychological complications of insulin therapy are another indication for PTx. Probably, the single most important aspect of recipient selection is the overall assessment of cardiovascular risk, burden, and reserve [21, 22, 23•].

The cardiac status of each candidate must be assessed carefully because significant (and silent) coronary artery disease is not uncommon in this population. The cardiac evaluation consists of a noninvasive functional assessment such as an exercise or a pharmacological stress test in addition to echocardiography [20–22, 23•]. Some centers mandate coronary angiography in all potential SPKT candidates, whereas at other centers, it is reserved for specific indications such as age >45 years, DM for >20–25 years, a positive smoking history, long-standing hypertension, previous major amputation due to peripheral vascular disease, history of cerebrovascular disease, pulmonary hypertension, cardiac arrhythmia, valvular disease, or cases in which the history, physical examination, or noninvasive cardiac studies reveal an abnormality [20–22, 23•]. A history of previous myocardial infarction, angioplasty, stenting, or coronary artery bypass grafting is not considered an absolute contraindication for PTx because excellent outcomes have been reported in patients with previous cardiac interventions or events [24••]. However, sudden cardiac death, in the absence of significant structural heart disease, continues to be a major cause of cardiac mortality following PTx [21, 22, 23•, 24••, 25, 26]. It is important to note, however, that most SPKT candidates have identifiable cardiac and peripheral vascular disease. It is not the presence but rather the severity (or correctability/treatability) of the cardiovascular disease that

Table 2 Recipient evaluation

Standard blood testing
Complete blood count with differential, platelet count; coagulation studies including thrombophilia screen; chemistry profile including serum amylase, lipase, glycosylated hemoglobin, and C-peptide levels; lipid and iron profiles; parathyroid hormone and thyroid stimulating hormone levels; drug screening panel
Other laboratory testing
Urinalysis with culture, 24-h urine for creatinine and protein clearance (or spot urine protein/creatinine ratio with calculated GFR); hemoccult ×3; prostate specific antigen level in males above age 45 years, serum pregnancy test in women of childbearing potential, colonoscopy in all patients above age 50 years (repeat every 5 years if history of polyps, otherwise repeat every 10 years)
Imaging studies
Chest radiograph, abdominal ultrasound, non-contrast abdominal and pelvic computerized tomographic scan, mammography in women above age 40 years
Cardiovascular testing
12-lead electrocardiogram, transthoracic echocardiography, cardiac stress testing, coronary angiography (when indicated), carotid and iliac Doppler arterial and venous studies (when indicated)
Interview and consults
History and physical examination by transplant physician and surgeon
Assessment by diabetes specialist
Social work and financial evaluation
Assessment by transplant coordinator, pharmacist, and dietitian
Cardiology clearance
Dental clearance
Ophthalmology, Psychiatry, Podiatry/Orthopedic, Dermatology, Neurology, Infectious Disease, Pulmonary, Urology or Gastrointestinal Clearance when indicated
Gynecologic consultation with complete pelvic examination and Pap smear for women (in absence of total hysterectomy)
Serologic and immunologic testing
ABO blood type, human leukocyte antigen tissue type, panel reactive antibody levels; viral studies (hepatitis B and C, HIV, cytomegalovirus, varicella-zoster, Epstein-Barr virus), VDRL/FTA
Additional (optional) studies
Completion of quality of life questionnaire, pulmonary function studies and arterial blood gas (when indicated), anti-islet and insulin antibodies, glucose stimulation testing, gastric emptying study, voiding cystourethrogram with post-void residual, urodynamic studies, herpes simplex virus serology, tuberculosis screening, BK virus

determines whether or not the patient is an appropriate candidate for PTx.

In general, age >65 years, heavy smoking, a left ventricular ejection fraction <30–40 %, recent myocardial infarction, severe pulmonary hypertension (pulmonary artery pressure >45–50 mmHg), and obesity (BMI >35 kg/m^2) are usually viewed as contraindications for PTx [4, 5, 10•, 20–22, 23•, 24••, 25–32] (Table 1). Most patients <45 years of age are considered to be acceptable candidates for PTx until proven otherwise, provided that they are not obese and no significant coronary or peripheral vascular disease is present. Patients with DM older than 55 years of age are not candidates for SPKT until proven otherwise and need to undergo an extensive cardiovascular and peripheral vascular evaluation [27–29]. Because obese patients may have a higher rate of surgical complications following PTx, a BMI >35 kg/m^2 is usually considered an absolute contraindication and BMI >30 kg/m^2 a relative contraindication for SPKT unless the individual is either able to lose weight or their body habitus is such that most of their body weight is posterior [30–32]. Limited data are available in SPKT for patients who have previously undergone bariatric surgery.

SPKT Outcomes in T2DM: Why?

International Pancreas Transplant Registry Data

Data on SPKT outcomes in patients with T2DM began appearing in the annual International Pancreas Transplant Registry (IPTR) reports starting in the mid-1990s. In these reports, the annual proportion of SPKT recipients reported as having T2DM initially increased from 2 % prior to 2002 to 8 % from 2002 to 2006 and subsequently remained stable at 7 % from 2007 to 2011 [7, 33, 34•]. In contrast, the proportion of patients designated as having T2DM is 3 % in the PAK and

1 % in the PTA categories. In all PTx categories, however, common characteristics of patients reported as having T2DM compared to T1DM include older age (both at time of onset of DM and also at time of PTx), higher BMI, more frequently male and AA, and shorter duration of DM. According to IPTR data, survival outcomes in SPKT are similar irrespective of DM classification. Because reporting of diabetes "type" to the IPTR is usually based on C-peptide levels, some have questioned the validity of these findings. However, analysis of IPTR data looking at survival outcomes according to age of onset of DM (categorized by decade of life) has revealed similar findings. In most studies to date, pancreas graft survival is defined as freedom from exogenous insulin therapy.

Single Center Studies

At present, there are no randomized studies comparing SPKT in patients with T1DM versus T2DM. However, retrospective cohort studies have demonstrated similar survival and functional outcomes in SPKT recipients with either T1DM or T2DM [9••, 10•, 11, 12•, 13, 14•, 15, 35]. From 1996 to 2004, there were several case reports in the literature of successful SPKT in "unrecognized" non-insulin-dependent DM, adult-onset DM, "lean" T2DM, or "maturity-onset" DM of the young [19, 36–39]. In these reports, a consistent finding was that in appropriately selected patients with T2DM, the clinical course and outcomes following SPKT were remarkably similar to concurrent patients with T1DM undergoing SPKT.

However, the true genesis of the controversial application of SPKT to patients with T2DM can be traced back to a series of landmark publications by Jimmy Light's group at the Washington Hospital Center [11, 12•, 13]. In a recent publication, Light et al., chronicle their 20-year experience with 173 patients who underwent SPKT for either T2DM (n=58) or T1DM (n=115) based on C-peptide levels either <0.8 or ≥0.8 ng/ml, respectively [40••]. Recipient selection was based exclusively on clinical criteria without consideration of pretransplant C-peptide levels. The group characterized as having T2DM was older at the time of DM diagnosis (mean age 24.2 versus 15.4 years) and older at the time of SPKT (mean age 42.8 versus 38.5 years, both p<0.0001). The T2DM group also had fewer years of insulin use (mean 19.2 versus 22.6 years, p=0.01), had a higher BMI pre- and posttransplant (both p<0.0001), and was predominantly AA (68.9 versus 41.7 %, p=0.007) compared to their T1DM counterparts. Each of the above characteristics has been used to describe a T2DM phenotype. Overall patient survival was superior (p=0.019) in the T1DM group, whereas censored graft survival was slightly higher (p=0.064) in the T2DM group. Donor or recipient ethnicity did not influence survival outcomes. In addition, 17 % of patients considered to have T1DM based on clinical criteria actually had pretransplant C-peptide levels >0.8 ng/ml, whereas nearly 40 % of patients considered to have T2DM had C-peptide levels <0.8 ng/ml. Based on this experience, the authors concluded that beta-cell exhaustion did not occur in patients who were not insulinopenic at the time of SPKT; patients with T1DM and T2DM can equally benefit from SPKT even though stratification may be difficult; excellent results were achieved in patients with a T2DM phenotype regardless of ethnicity or pretransplant random C-peptide levels; and the practice of categorizing DM and basing selection for SPKT on C-peptide levels is of limited value and not useful in determining candidacy.

In 2005, Nath et al., analyzed outcomes in 17 PTxs (7 SPKT, 4 PAK, 6 PTA) performed in patients classified as having T2DM without reference to C-peptide levels including three patients who were non-insulin requiring [14•]. At 1-year follow-up, both patient and pancreas graft survival rates were 94 %. At a mean follow-up of 4+years, respective survival rates were 71 and 65 %. This is one of the few studies reporting outcomes in patients with T2DM who were either not on insulin pretransplant or who were undergoing solitary PTx as opposed to SPKT.

We reported out initial experience in 2008 with SPKT in 67 patients with a pretransplant C-peptide level <2.0 ng/ml compared to 7 patients with a C-peptide level ≥2.0 ng/ml. A higher threshold level of C-peptide was used to "define" T2DM versus T1DM because of a report stating that levels above 3.0 ng/ml are an absolute contraindication to PTx coupled with another study suggesting that patients with C-peptide levels above 1.8 ng/ml do not actually need insulin therapy [16•, 41]. We recently updated this experience to analyze 162 SPKTs including 132 in patients with absent or low C-peptide levels (<2.0 ng/ml, C-peptide "negative") and 30 (18.5 %) with C-peptide levels ≥2.0 ng/ml pretransplant (C-peptide "positive" group, mean C-peptide level 5.7 ng/ml, range 2.1–12.4) [42]. Clinical management and immunosuppression were similar between groups because the C-peptide status of individual patients was not known prospectively. C-peptide positive patients had a higher proportion that were age ≥50 years (40 versus 23 %, p=0.06) at the time of SPKT, had a later age of onset (mean age 34 versus 16 years, p=0.0001) and shorter duration of pretransplant DM (mean 17 versus 25 years, p=0.01), and had a greater proportion of AAs (AA, 47 versus 17 %, p=0.001) compared to C-peptide negative patients. Pancreas graft loss was defined as death with function, allograft pancreatectomy, pancreas retransplantation, or the need for daily exogenous insulin therapy irrespective of C-peptide levels. With a mean follow-up of 5.5 years, patient survival (85 versus 87 %), kidney graft survival (72 versus 77 %), and pancreas graft survival (66 versus 57 %, all p=NS) rates were comparable in C-peptide negative and positive patients, respectively. Death-censored kidney (both 85 %) and pancreas (77 % C-peptide negative versus 61 % C-peptide positive) graft survival rates were similar. Survival outcomes

in C-peptide negative (n=25) versus C-peptide positive (n=14) AA patients were likewise similar.

Analysis of patterns and timing of graft failure demonstrated that the incidence of pancreas graft loss secondary to "chronic rejection" occurring 1–4 years following SPKT was higher in C-peptide positive patients and was associated with posttransplant weight gain and the continued presence of detectable C-peptide levels. However, the diagnosis of chronic pancreas rejection was not based on either histopathology (presence of scarring and fibrosis) or imaging abnormalities (demonstrating atrophy or reduced perfusion) but was presumptive to explain worsening glucose control and the need for exogenous insulin therapy over time in the absence of thrombosis, pancreatitis, or evidence for acute rejection. Consequently, one might speculate that this trend toward eventual resumption of scheduled insulin therapy may actually represent "patient failure" or "monitoring failure" rather than true pancreas graft failure. In addition, one must also consider the cumulative "diabetogenic" effects of immunosuppression over time. In other words, the presence of pretransplant C-peptide positivity (or a T2DM phenotype) may be indicative of less endocrine reserve, a greater propensity to insulin resistance and a lower threshold to resume exogenous insulin in the setting of continued C-peptide production by an otherwise "functioning" pancreas allograft. Greater emphasis on post-SPKT dietary modification and weight control, C-peptide and glycohemoglobin level monitoring, and timely adjustments in immunosuppression may help modify or even prevent some of these "late failures." What is lacking from this binary view of pancreas graft success versus failure based on the need for (any) scheduled exogenous insulin therapy are cases in which patients continue to exhibit the absence of either hypoglycemia or severe hyperglycemia on low dose or once daily insulin therapy, which in essence would be identified as a "success" in islet transplantation.

In our experience, patients with C-peptide levels ≥2.0 ng/ml at the time of SPKT appear to have a T2DM phenotype (older, overweight, more frequently AA, later age of onset and shorter duration of DM) compared to insulinopenic patients undergoing SKPT. However, short-term survival and functional outcomes were comparable between groups. Consequently, pretransplant C-peptide levels, provided that they are <10 ng/ml, are not used exclusively to determine candidacy for SPKT at our center but remain a useful adjunct in the context of the individual patient's overall clinical assessment and suitability. Based on this experience as well as review of the literature, we have listed in Table 1 specific selection criteria for consideration for SPKT in patients with T2DM.

In 2010, the group at Mayo Clinic Scottsdale reported SPKT outcomes in 10 patients with T2DM compared to 70 with T1DM [35]. Variables used to characterize T2DM in a composite fashion included absence of anti-GAD65 antibody, no history of ketoacidosis, history of using oral antidiabetic agents for a period of time prior to starting insulin, and detectable C-peptide levels. Patients with a BMI >30 kg/m^2 or daily insulin requirement >1 u/kg/day were excluded from consideration for SPKT. Using a Cox regression survival analysis, similar outcomes were reported in the two groups with a median follow-up of 16 months. Of note, 15 % of patients with T1DM had detectable C-peptide levels. Conversely, a number of patients with T2DM had very low C-peptide levels. Using a C-peptide level of < or ≥0.8 ng/ml as a threshold for diagnosis would have misclassified 30 % of patients with T2DM and 8 % of patients with T1DM.

Registry Studies

In 2011, Sampaio and colleagues, using the United Network for Organ Sharing (UNOS) database, analyzed 6756 primary SPKTs performed between 2000 and 2007; 6141 patients were identified as having T1DM and 582 (8.6 %) as having T2DM [43•]. Compared to recipients with T1DM, recipients with T2DM were older at diabetes onset and time of transplant; were more often male, obese, and either AA or Hispanic; had fewer years of DM prior to SPKT; had longer pretransplant duration of dialysis; were more commonly sensitized (defined as a panel reactive antibody [PRA] level >20 %), less frequently had private health insurance; but had similar mean pretransplant daily insulin doses. Rates of delayed kidney graft function (7.8 % T1DM versus 11.7 % T2DM, p<0.001) and kidney primary nonfunction (0.47 % T1DM versus 1.03 % T2DM, p=0.03) were significantly higher in recipients with T2DM. Five-year overall and death-censored kidney graft survival rates were significantly inferior in patients with T2DM, whereas patient and pancreas graft survival rates were not statistically different. However, after adjustment for other donor, recipient, and transplant characteristics, survival outcomes in SPKT recipients with T2DM were comparable to those with T1DM with a median follow-up of 3.7 years. In this study, the major covariates influencing survival outcomes (independent of type of DM) were older donor and recipient age as well as recipient duration of dialysis, cardiovascular disease, AA ethnicity, and obesity. In an accompanying editorial, Kaufman and Sutherland [44] underscored the importance of the candidate selection process and pointed out that recipient age >45 years and comorbidities such as coronary and peripheral vascular disease were significant risk factors for death following SPKT regardless of whether patients had T1DM or T2DM. Moreover, they highlighted the study findings that insulin-requiring patients with T2DM who were younger than 50 years and had a BMI <30 kg/m^2 would more than likely become insulin independent and predictably do well following SPKT, which mitigated the concern that the insulin resistance thought to be associated with T2DM would result in inferior pancreas graft survival rates because of beta-cell exhaustion.

In 2012, Wiseman and Gralla, using the Scientific Registry of Transplant Recipients (SRTR) database, compared outcomes in selected patients with T2DM (age 18–59 years, BMI 18–30 kg/m^2) undergoing either SPKT (n=424), living donor kidney transplantation alone (n=1987), or deceased donor kidney transplantation alone (n=4005) from 2000 to 2008 [45•]. Patient and kidney graft survival rates were highest following living donor kidney transplantation, intermediate following SPKT and lower following deceased donor kidney transplantation. Based on these findings, the authors concluded that carefully selected patients with T2DM experience good patient and graft survival rates following SPKT, which supports cautious application of SPKT in this population when living donation is not an option. In an accompanying editorial, Cohen and Ratner [46] emphasized that kidney quality exerted a dominant influence on outcomes in this study, which conservatively supports broader application of SPKT in T2DM within the constraints of the new UNOS pancreas allocation policy.

Recent Studies

In 2013, Margreiter et al. reported their 9-year single center retrospective experience with SPKT in 21 patients with T2DM compared to 195 patients with T1DM and 32 patients with T2DM receiving a deceased donor kidney transplant alone [47]. Survival outcomes were highest in patients with T1DM undergoing SPKT, intermediate in patients with T2DM undergoing SPKT, and lowest in patients with T2DM following kidney transplantation alone. However, after performing a multivariate analysis adjusting for multiple donor, recipient and immunologic risk factors, differences between the two SPKT groups were no longer apparent. The authors concluded that appropriately selected patients with T2DM who are younger than age 55 and have an acceptable coronary risk profile should not be excluded from SPKT as a matter of principle.

At the International Pancreas and Islet Transplant Association (IPITA) meeting in 2013, Patel, Bry, and colleagues from the California Pacific Medical Center reported an 11-year experience with SPKT in 55 patients with T2DM (defined as a random C-peptide level >2.0 ng/ml) compared to 164 concurrent patients with T1DM [48]. Five-year pancreas graft survival rates were 86 % in patients with T1DM compared to 78 % in patients with T2DM; no differences in outcomes were noted in patients with a BMI either < or >30 kg/m^2 [49].

Conclusions

Differentiation between T1DM and T2DM can be difficult because both conditions may overlap clinically and represent the heterogeneity of gluco-metabolic disorders. Initial experiences with SPKT in patients with T2DM and ESRD suggested that augmentation of endogenous insulin production by PTx in patients with C-peptide positive, insulin-requiring diabetes resulted in insulin independence, improved glucose counter-regulation, and enhanced quality of life. The literature to date comprises a number of single center retrospective cohort studies as well as registry data that report comparable outcomes in SPKT irrespective of "type" of DM. However, given the limitations of interpreting C-peptide levels in the setting of ESRD coupled with the heterogeneous nature of DM, rigorous diagnostic criteria to distinguish between T2DM and T1DM are lacking. Be that as it may, a T2DM recipient phenotype has emerged from these experiences that include later onset and shorter duration of insulin-requiring DM, presence of measureable C-peptide pretransplant, older age at the time of SPKT, higher body weight/BMI, and an increased proportion of AA recipients. Standard selection criteria for SPKT in T2DM include patients <55–60 years of age with a BMI <30–32 kg/m^2, insulin-requiring for a minimum of 3–5 years with a total daily insulin requirement <1 u/kg/day or <100 u/day, a fasting C-peptide level <10 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiopulmonary function, and presence of "complicated" diabetes. In November 2011, UNOS approved new eligibility and allocation criteria for PTx candidacy, which are scheduled to be implemented in the last quarter of 2014 [50•]. Eligibility criteria for SPKT are patients who have insulin-requiring DM and a C-peptide level <2.0 ng/ml; or patients who are insulin-requiring, have a C-peptide level ≥2.0 ng/ml, and have a BMI <28 kg/m^2. However, the BMI cutoff may be adjusted upward every 6 months (not to exceed 30 kg/m^2) based upon the proportion of candidates who are listed for SPKT in this category. For SPKT patients meeting the above criteria, they will receive allocation priority ahead of patients on the kidney alone waiting list when a donor is identified as a potential kidney-pancreas donor.

Compliance with Ethics Guidelines

Conflict of Interest Robert J. Stratta, Alan C. Farney, Giuseppe Orlando, and Jeffrey Rogers declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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