TOPIC HIGHLIGHT

Maurizio Salvadori, Professor, *Series Editor*

Pancreas transplantation in type Ⅱ diabetes mellitus

Phillip Weems, Matthew Cooper

Phillip Weems, Matthew Cooper, MedStar Georgetown Transplant Institute, Washington, DC 20007, United States
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Correspondence to: **Phillip Weems, MD,** MedStar Georgetown Transplant Institute, 3800 Reservoir Road, NW 2 Main, Washington, DC 20007,
United States. weems.s.phillip@gunet.georgetown.edu
Telephone: +1-202-4440032 **Fax:** +1-202-4440899
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Abstract

Although the diagnosis of type 2 diabetes mellitus was once considered a contraindication to simultaneous pancreas-kidney transplantation, a growing body of evidence has revealed that similar graft and patient survival can be achieved when compared to type 1 diabetes mellitus recipients. A cautious strategy regarding candidate selection may limit appropriate candidates from additional benefits in terms of quality of life and potential amelioration of secondary side effects of the disease process. Although our current understanding of the disease has changed, uniform listing characteristics to better define and study this population have limited available data and must be established.

Key words: Pancreas transplantation; Type 2 diabetes mellitus; Simultaneous pancreas-kidney transplantation

Core tip: Comparable outcomes have been achieved in simultaneous-pancreas kidney transplant among both type 1 diabetes mellitus and type 2 diabetes mellitus (DM2) recipients. Our current understanding of the pathogenesis of DM2 is in evolution and denial of simultaneous pancreas- kidney transplantation to appropriately screened DM2 recipients may limit access to a potential life-saving measure with beneficial quality of life improvements. Cautious utilization of DM2 listing criteria should be employed among all pancreas transplant centers in order to ensure optimum patient and graft survivals are achieved.

INTRODUCTION

In October 1920, Dr. Frederick Banting approached Professor John Macleod with an idea that would result in one of the most significant discoveries of twentieth century medicine. Dr. Banting correctly theorized the presence of an "antidiabetic secretion" isolated from a surgically ligated pancreas. His proposed method for isolation and extraction was reluctantly rewarded with skepticism, an inadequate work space, ten canines to form an animal model, and the assistance of a young medical student, Charles Best. Banting and Best named the initial product of their extraction technique "isletin" and would use this substance to prove the endocrine function of the pancreas. Their impressive results were furthered with the addition of a talented biochemist, Bertram Collip, who was tasked with the purification of the insulin extract for testing in human subjects. In January 1922, a 14-year-old diabetic boy, Leonard Thompson, was chosen to be the first human to receive the team's purified insulin[1]. This landmark experiment led to the reversal of the young man's near-death condition and the effort was quickly expanded to other volunteer test subjects with equally positive results. The brilliant results of this team were rewarded with the Nobel Prize in Physiology and

Medicine in 1923[2].

The end of the twentieth century was greeted with the emergence of a new worldwide pandemic. It has been estimated that more than 340 million people are afflicted with diabetes worldwide, with 90% of cases manifesting as type 2 diabetes mellitus (DM2)[3,4]. In the United States alone, diabetes mellitus is the leading cause of end-stage renal disease (ESRD), accounting for 48215 new cases (44%) of renal failure in 2006; an incidence increasing at twice the rate of all other causes of ESRD[5]. The current United States renal transplant waiting list is compromised of > 40% of patients suffering from ESRD complications secondary to diabetes mellitus (DM).

With the discovery of insulin, diabetes was transformed from a rapidly fatal disease to a chronic condition with the emergence of noteworthy secondary conditions related to the primary disease process. Diabetes has been shown to vastly increase the risk of heart disease and stroke and is among the leading causes of chronic renal disease[6]. Diabetic retinopathy, a result of long-term accumulated damage to the small blood vessels of the retina, has been estimated to contribute to one percent of cases of blindness worldwide[7]. Diabetic neuropathy increases the risk of foot ulceration and, when found in conjunction with peripheral vascular disease, may lead to infectious limb complications and accelerated limb loss[6]. Since its proposal in the mid-twentieth century, the goals of pancreas transplantation have remained universal: to establish insulin independence and prevent/ameliorate the damaging secondary complications of the disease process.

PHENOTYPICAL ANALYSIS AND GENETICS OF DIABETES MELLITUS

Diabetes mellitus as a global disorder is characterized by hyperglycemia resulting from either an inadequate production or a decreased sensitivity to circulating insulin. Clinically, diabetes is broadly categorized as either type 1 (DM1) or DM2, depending on the genetic preponderance, age of onset, body habitus, inciting origin, and associated symptoms[8]. Traditionally, the DM2 phenotype is that of an older age and a larger body habitus with a lack of underlying autoimmunity prior to disease onset. In contrast, DM1 patients tend to present with an abrupt onset at an early age, possess a lean body habitus, and require immediate insulin therapy to reverse the consequences of the disease (Table 1).

As our knowledge regarding the pathophysiology of diabetes has further expanded, the distinction between these two seemingly separate disease processes has become decidedly less clear. The accelerator hypothesis of DM proposes a unique pathogenetic origin whereby excess body mass contributes to hyperglycemia resulting in increased insulin production to meet physiologic demands, the acceleration of β-cell apoptosis, and the induction of β-cell "immunogens" in a subset genetically predisposed to islet autoimmunity[9]. The accelerator hypothesis proposes an overlay rather than an overlap exists between the clinical manifestations of diabetes types with excess body mass central to the rising incidence of the disease worldwide[10].

Although the exact etiology of DM2 remains elusive, a series of common genetic variants, most of which (CDKAL1, CDKN2A, CDKN2, MTNR1B, TCF7L2, KCNJ11B) are associated with either reduced islet cell mass or reduced β-cell function, have been identified[11,12]. Recent studies have shown a similar frequency of DM2 risk genotypes for the transcription factor TCF7L2 in latent autoimmune (DM1) diabetic adults when compared to DM2[12]. The genomic identity of a similar pathologic predisposition further suggests that DM1 and DM2 are representative of the same disorder of insulin resistance, set against different phenotypic backgrounds.

EFFICACY OF PANCREAS TRANSPLANTATION IN DM2

Since the first reported successful pancreas transplant in 1966[13], more than 35000 pancreas transplantations have been reported to the International Pancreas Transplant Registry (IPTR). Of those, more than 24000 were reported from United States centers[14]. Traditionally, pancreas transplantation has been reserved for medically and surgically suitable candidates with DM1 suffering with ESRD (simultaneous kidney and pancreas, SPK), DM1 patients that have previously received a functioning renal graft (pancreas after kidney transplantation, PAK), or patients with brittle diabetes and hypoglycemic unawareness (pancreas transplant alone, PTA).

Although the diagnosis of DM2 was once considered a contraindication to pancreas transplantation, a growing body of evidence has revealed that favorable results can be achieved in selected candidates. Reluctance among some physician groups has favored denial to DM2 candidates secondary to a poorly understood mechanism by which transplanted pancreata may overcome the underlying pathophysiology of insulin resistance. In addition, elevated cardiovascular risks, an enlarged body habitus, an associated older age, and advanced secondary diabetic complications have been suggested as listing deterrents. This cautious judiciary strategy may account for the limited number of DM2 pancreas transplant recipients and small yet encouraging results reported for SPK transplants in DM2[15].

Light has reported a large retrospective series of SPK recipients with 20-year follow-up stratified according to detectable (> 0.8 ng/mL) *vs* undetectable (< 0.8 ng/mL) C-peptide values[16]. The patients with detectable C-peptide values were found to be older in age at the time of clinical diagnosis [24.2 years *vs* 15.4 years ($P < 0001$)], age of transplant [42.8 years *vs* 38.5 years ($P < 0001$)], and had a shorter duration of insulin dependence [19.1 years *vs* 23.1 years ($P < 0.012$)]. Study findings revealed increased graft survival with similar rates of glycemic control in detectable C-peptide patients when compared to non-detectable patients ($P = 0.064$). This finding was contrasted by increased

Table 1 Epidemiologic features differentiating type 1 from type 2 diabetes mellitus

Characteristic	Type 1 DM	Type 2 DM
Age (yr, at diagnosis)	< 25	> 25
Onset	Abrupt	Gradual
Body Habitus	Lean (weight < 105% of IBW)	Overweight/Obese (weight > 115% of IBW)
HLA-association	Yes	No
C-peptide	Undetectable	Detectable
Ketoacidosis	Yes	No
Immediate need for insulin	Yes	No

DM: Diabetes mellitus; IBW: Ideal body weight; HLA: Human leukocyte antigen.

patient survival discovered in the non-detectable C-peptide group ($P = 0.019$), hypothesized secondary to a younger age and fewer long-term secondary side effects associated within the undetectable C-peptide group. Light's findings caution the use of C-peptide to determine candidacy for pancreas transplantation and adds further controversy to the observed clinical overlap of the two disease phenotypes. In fact, of the study population, 17% of patients who were considered to have DM1 based upon standard clinical criteria (Table 1) were found to have elevated c-peptide values (≥ 0.8 ng/mL) while nearly 40% of patients considered having DM2 (where c-peptide should have been positive) had undetectable values[16].

Margreiter *et al*[17] conducted a single-center retrospective review analyzing twenty-one DM2 SPK recipients with comparisons to historical DM1 SPK and DM2 kidney transplant alone (KTA) controls. Actuarial pancreas graft survival for SPK recipients at 1- and 5-years post-transplant were calculated to be 92.6% and 80.7% respectively for the DM1 SPK group *vs* 81% and 75.9% respectively for the DM2 SPK group ($P = 0.19$). Kidney allograft survival at 5 years post-transplant was found to be 83.6% for DM1 SPK recipients, 80.4% for DM2 SPK recipients, and 52.7% for DM2 KTA recipients ($P < 0.001$). A multivariate analysis adjusting for potential confounders (donor/recipient age, presence of diabetic secondary complications, body mass index (BMI), wait list time, cold ischemic time, delayed graft function, and coronary risk factors) revealed no findings of statistical significance[17].

Several noteworthy registry-based studies have been conducted in order to further analyze clinical outcomes of SPK recipients among DM2 recipients. Sampaio *et al*[18] utilized the United Network for Organ Sharing (UNOS) database to compare outcomes of SPK transplants based upon recipient diabetes type. Of the 6756 SPK recipients transplanted between 2000 and 2007, 586 (8.6%) were reported as having type 2 diabetes. Rates of delayed graft function (11.7% *vs* 7.8%, $P < 0.001$) and kidney primary non-function (0.47% *vs* 1.03%, $P < 0.03$) were significantly more frequent in DM2 patients. Pancreas transplant complications were similar between groups and not statistically significant. Initial findings revealed inferior

five-year overall and death-censored kidney graft survival in type 2 diabetics. However, after adjustment for recipient (age, race, body weight, dialysis time, and cardiovascular comorbidities), donor, and transplant immune characteristics, DM2 was not associated with increased risk of death or kidney or pancreas allograft failure when compared to DM1.

Wiseman utilized Scientific Registry of Transplant Recipients (SRTR) data to conduct a review of DM2 pancreas transplant recipients while utilizing a historical control population of selected DM2 transplant recipients (18-59 years of age, BMI from 18-30 kg/m^2) having received either a live donor kidney alone (LDKA) *vs* deceased donor kidney alone (DDKA)[19]. On adjusted analysis, patient and kidney graft survival rates were superior for LDKA *vs* SPK and DDKA. After 1-year post-transplant, patient and graft survival began to favor SPK when compared to DDKA (82.0% *vs* 75.5%; $P = 0.04$); a finding on multivariable analysis related to younger recipient and donor ages within this cohort. Surprisingly, 40% (269 out of 424 patients) of the SPK cohort were aged 50-59 years of age, and a significant percentage of these were older than age 55 years. Unadjusted pancreas allograft survival rates were 83.7% and 71% at 1- and 5-years, respectively, whereas death-censored pancreas graft survival rates were 87.7% at 1-year and 83.6% at 5-years[20]. These numbers are markedly similar to reported pancreas allograft survival rates within DM1 recipients and further reiterate the premise that excellent outcomes of SPK transplantation can be achieved regardless of recipient diabetes type.

CURRENT CONTROVERSIES IN PANCREAS TRANSPLANTATION AMONG TYPE 2 DIABETICS

In a review of > 35000 pancreas transplants reported to the International Pancreas Transplant Registry (IPTR), Gruessner *et al*[14] revealed an upward trend in the rate of pancreas transplantation performed upon DM2 candidates. Since 1994, diabetic type has been consistently reported within the registry with an overall rate of DM2 recipients increasing from 2% in 1995 to 7% in 2010 ($P < 0.0001$)[14]. Despite this upward trend, the rate of DM2 may in fact be lower (or higher) secondary to the absence of a unified and defined criteria by which transplant centers select DM2 candidates.

Although many defined criteria (age at diagnosis, BMI, family history, HLA association, detectable C-peptide) have been proposed to differentiate DM1 from DM2, no reliable and objective test(s) exist. In fact, as noted prior, several patients are found to categorically overlap. Fasting or stimulated C-peptide levels have long been used as a primary differentiating criterion to define DM1 *vs* DM2 transplant candidates[20-22]. As C-peptide is primarily metabolized in the kidney, levels in patients with ESRD can be disproportionately high and not representative of

Table 2 Proposed simultaneous pancreas-kidney type 2 diabetic selection criteria

Age < 55 yr
BMI < 30 kg/m^2
Insulin dependence
Total insulin requirements < 1 U/kg of IBW/d
Presence of renal failure (dialysis dependent or pre-dialysis advanced
diabetic nephropathy with GFR ≤ 20 mL/min per 1.73 m^2
Fasting c-peptide < 10 ng/mL
Low cardiac and vascular disease risk
History of medical and dietary compliance

IBW: Ideal body weight; GFR: Glomerular filtration rate.

the actual functioning β-cell mass. Wang *et al*[22] furthered this controversy by demonstrating that C-peptide levels, using ultrasensitive methods, may be detected in 10% of DM1 patients up to 30-years after disease onset. In addition, Singh confirmed that pre-transplant C-peptide levels had no influence on death-censored SPK survival rates for up to 3-years post-transplant. In this study, the selection criteria utilized to define their DM2 group included minimum insulin requirements of more than 5-years duration with daily requirements less than 1 U/kg per day, C-peptide levels ≥ 1.8 ng/mL, BMI ≤ 32 kg/m^2, and absence of advanced cardiovascular disease[23].

In order to properly evaluate and define selected DM2 candidates for SPK transplantation, universal listing criteria should be adopted. The definition of DM2 has been left to the discretion of the individual reporting centers and often does not account for variations in diabetes phenotype. Until recently, neither the UNOS database nor the SRTR required data regarding patient medication use, C-peptide values, or any other feature which may further confirm categorization of diabetes type. Others have proposed listing criteria to define the DM2 SPK populations. These have often been selected according to younger age, a relatively lean body habitus, and a limited advanced diabetic cardiovascular disease[16,23]. We propose the adoption of a defined list of selection criteria to better define potential DM2 recipients that may benefit from SPK transplantation and allow for closer population-based longitudinal studies (Table 2).

Contemporary management of DM2 patients has been profoundly influenced by the results of the United Kingdom Prospective Diabetes Study (UKPDS)[24-27]. The authors demonstrated a continuous relationship between euglycemia and microvascular complications, with a 35% reduction in risk for each 1% decrement in HbA1c. In most patients with DM2, a multimodal management scheme is employed to address the issue of euglycemia as well the long-term secondary influences on the disease. Central to this approach are dietary and lifestyle modifications, management of dyslipidemia and hypertension, and pharmacologic therapy with a goal of improved glycemic control.

Current available pharmacologic treatments are vast and include medications in the following drug classes:

biguanides, sulfonylureas, meglitinide derivates, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidy-l peptidase Ⅳ (DPP-4), selective sodium-glucose transporter-2 (SGLT-2) inhibitors, amylinomimetics, and insulin. With demonstrated treatment failure from any of the aforementioned combination of medical and/or lifestyle modifications, pancreas transplantation may provide the positive effects of normoglycemia in insulin requiring DM2 patients with end-stage renal disease.

In DM2 patients, peripheral insulin resistance, which is associated with relative insulin deficiency and insulin secretory defects, plays a central role[19]. It was once hypothesized that β-cells within the transplant would be subjected to overstimulation leading to "islet exhaustion" in a damaging cascade resulting in allograft failure. This has been disproved in a large, often cited longitudinal case series by Chakkera *et al*[21] and Light *et al*[28,29]. In fact, insulin secretion and sensitivity have been shown to improve long term after SPK in DM2 recipients[30].

Although a greater survival advantage at 5 years post-transplant has been reported for LDKA *vs* both SPK and DDKA in DM2 recipients[19], the quality of life benefits of euglycemia or the possible effects that euglycemia might have on the secondary complications of DM cannot be underestimated[31-33]. These added benefits have been shown to result in improved mental and physical health, disease perception, mobility, vitality, and patient satisfaction[31,32]. Whether the euglycemic effects of the added pancreas ultimately may lead to a survival advantage when compared to LDKA cannot be ruled out, as large retrospective analyses of DM1 SPK recipients have shown the added benefits of the additional pancreas over a kidney transplant alone become more evident over time[34,35].

Importantly, however, expansion of this transplantable cohort may decrease the number of donor pancreata available, further affecting a larger pool of DM1 SPK, PAK, and PTA recipients; a population whose survival benefits have been better defined[19,36]. In addition, the current UNOS algorithm awards priority to SPK recipients over all other forms of DDKA transplants within a given region. Coupled with judicious donor selection criteria at most centers and a relatively short simultaneous kidney-pancreas compared to deceased donor kidney waitlist, listing selected DM2 candidates for SPK may improve an individual's chance to obtain a quality organ transplant with less waiting time. In order to address this potential, UNOS policy has employed a 6-mo review process with proposed reduction in BMI eligibility criteria 2 kg/m^2 if more than 10% of the SPK waiting less is composed with DM2 candidates[19]. Cautious utilization of DM2 listing criteria should be employed among all pancreas transplant centers in order to ensure optimum patient and graft survivals are achieved. As the long-term outcomes of pancreas transplantation in DM2 candidates is not entirely known, SPK transplantation in this cohort should be limited to specialized and well experienced transplant centers to ensure the possibility of continued positive outcomes.

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