Pancreas Transplantation in C-Peptide Positive Patients: Does "Type" of Diabetes Really Matter?

Robert J Stratta, MD, FACS, Jeffrey Rogers, MD, FACS, Alan C Farney, MD, PhD, Giuseppe Orlando, MD, PhD, Hany El-Hennawy, MD, Michael D Gautreaux, PhD, Amber Reeves-Daniel, DO, Amudha Palanisamy, MD, Samy S Iskandar, MBBCh, PhD, Jason K Bodner, MMS, PA-C

BACKGROUND: In the past, type 2 (C-peptide positive) diabetes mellitus (DM) was a contraindication for simultaneous pancreas-kidney transplantation (SPKT).

STUDY DESIGN: We retrospectively analyzed outcomes in SPKT recipients according to pretransplantation C-peptide levels $\geq$2.0 ng/mL or $<$ 2.0 ng/mL.

RESULTS: From November 2001 to March 2013, we performed 162 SPKTs including 30 (18.5%) in patients with C-peptide levels $\geq$2.0 ng/mL pretransplantation (C-peptide positive group, range 2.1 to 12.4 ng/mL) and 132 in patients with absent or low C-peptide levels ($<$2.0 ng/mL, C-peptide "negative"). C-peptide positive patients were older at SPKT, had a later age of onset and shorter duration of pretransplantation DM, and more were African-American (all $p < 0.05$) compared with C-peptide negative patients. With a mean follow-up of 5.6 years, patient (80% vs 82.6%), kidney graft (63.3% vs 68.9%), and pancreas graft survivals (50% vs 62.1%, all p = NS) rates were comparable in C-peptide positive and negative patients, respectively. At latest follow-up, there were no differences in acute rejection episodes, surgical complications, major infections, readmissions, hemoglobin A1c levels, serum creatinine, and estimated glomerular filtration rate levels between the 2 groups. C-peptide levels were higher (mean 5.0 vs 2.6 ng/mL, $p < 0.05$) and post-transplant weight gain ($\geq$5 kg) was more common (57% vs 33%, $p = 0.004$) in the C-peptide positive group. Survival outcomes in C-peptide positive (n = 14) vs C-peptide negative (n = 22) African-American patients were similar, as were outcomes in C-peptide positive patients with a body mass index $<$ or $\geq$ 28 kg/m^2.

CONCLUSIONS: Patients with higher pretransplantion C-peptide levels appear to have a type 2 DM phenotype compared to insulinopenic patients undergoing SPKT. However, survival and functional outcomes were similar, suggesting that pretransplantation C-peptide levels should not be used exclusively to determine candidacy for SPKT. (J Am Coll Surg 2015;220:716–727. © 2015 by the American College of Surgeons)

Diabetes mellitus (DM) is a chronic metabolic disease of glucose dysmetabolism characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The vast majority of cases of DM fall into 2 broad etio-pathogenetic categories, which historically were classified as either type 1 DM (T1DM) or type 2 DM (T2DM), according to the presumed mechanisms of disease as well as epidemiologic features and clinical manifestations.[1,2] Of the estimated 29.1 million patients with DM in the US, (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 older than 20 years.[1] In the US, DM is the leading cause

Disclosure Information: Nothing to disclose.

Presented at the Southern Surgical Association 126th Annual Meeting, Palm Beach, FL, November 30–December 3, 2014.

Received December 14, 2014; Accepted December 15, 2014.

From the Departments of General Surgery (Section of Transplantation [Stratta, Rogers, Farney, Orlando, El-Hennawy, Gautreaux, Bodner]), Pathology (Gautreaux, Iskandar), and Internal Medicine (Section of Nephrology [Reeves-Daniel, Palanisamy]), Wake Forest School of Medicine, Winston-Salem, NC.

Correspondence address: Robert J Stratta, MD, FACS, Department of General Surgery, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157. email: rstratta@wakehealth.edu

http://dx.doi.org/10.1016/j.jamcollsurg.2014.12.020
ISSN 1072-7515/14

Abbreviations and Acronyms

BMI = body mass index
DM = diabetes mellitus
DWFG = death with a functioning graft
ESRD = end-stage renal disease
IPTR = International Pancreas Transplant Registry
PTx = pancreas transplantation
SPKT = simultaneous pancreas-kidney transplantation
T1DM = type 1 diabetes mellitus
T2DM = type 2 diabetes mellitus

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 US. In 2011, 228,924 people of all ages with kidney failure secondary to DM were living either on chronic dialysis or with a kidney transplant.[1]

Type 2 DM accounts for up to 95% of all cases of DM, is associated with the metabolic syndrome and higher preexisting cardiovascular morbidity, is usually diagnosed in patients who are older and obese, is characterized by both insulin resistance and relative insulin deficiency, is not associated with autoimmunity, and does not usually require immediate exogenous insulin therapy. However, patients with T1DM may develop the disease later in life and not show any signs of autoimmune disease; patients with T2DM may present signs of autoimmunity and develop the disease at a younger age. Therefore, the classic distinction between these 2 "types" of DM has been questioned and has become less clear with the realization that DM is a group of heterogeneous conditions 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] Type 1 DM may be differentiated from T2DM by the timing and severity of onset, determined in part by the impact of environmental and behavioral variables on a specific genetic milieu.

Beta cell replacement strategies, such as islet cell or vascularized pancreas transplantation (PTx), were initially developed as treatments for T1DM by re-establishing endogenous insulin secretion responsive to normal feedback controls and have evolved to methods of autoregulating total pancreatic endocrine replacement that reliably achieve a euglycemic state and normal glucose homeostasis without the need for either exogenous insulin therapy or close glucose monitoring.[4-6] As of December 2012, more than 42,000 PTxs performed worldwide were reported to the International Pancreas Transplant Registry (IPTR) and Scientific Registry of Transplant Recipients.[7,8] Pancreas transplantation in patients with DM is divided into 3 major categories; those performed simultaneously with a kidney transplant (SPKT), usually from a deceased donor; those performed after a successful kidney transplant in which the kidney source was either a living or deceased donor; and PTx alone in the complete absence of a kidney transplant. Most PTxs in the US (75%) are performed as SPKTs; approximately 16% are performed as pancreas after kidney transplants and 9% as pancreas transplants alone, respectively.[7,8] Simultaneous pancreas-kidney and pancreas after kidney transplants are well accepted but underused therapeutic options mainly for patients with T1DM and ESRD; only about 100 pancreas transplants alone are performed annually in the US, and this procedure is almost exclusively reserved for patients with T1DM. In the US, for every 10,000 patients with T1DM, only 3 will actually receive a PTx or an islet transplant in their lifetime.

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 (if any) in the treatment of patients with insulin-requiring T2DM in the setting of ESRD.[9,10] In the recent past, T2DM was considered a contraindication for SPKT because the primary pathophysiology of T2DM was believed to be exclusively insulin resistance, which should, in theory, render PTx ineffectual in the management of this condition.[9,10] However, initial intentional (and unintentional) experiences with SPKT in patients with detectable pretransplantation C-peptide levels and in some cases, a "type 2 diabetes phenotype," have demonstrated that augmentation of endogenous insulin (C-peptide) production after successful SPKT may result in complete insulin independence, improved glucose counter-regulation, and enhanced quality of life.[9-15] The success of SPKT in this setting provides evidence that the pathophysiology of T2DM is heterogeneous and comprises 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 vs 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 transplantation may "cause" T2DM.[18] Preliminary experiences with SPKT in patients with detectable pretransplantation 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.[9-15] In the US, for every 1 million patients with T2DM, only 3 will actually undergo SPKT. The purpose of this study was to review retrospectively our experience in adult recipients of SPKTs stratified according to higher or lower/undetectable pretransplantation C-peptide levels.