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Original research

Impact of duration of diabetes on outcome following pancreas transplantation

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HIGHLIGHTS

- Longstanding T1DM does not seem to negatively impact recipient outcomes following all types of pancreas transplantation.
- Duration of diabetes exposure significantly correlates with the need for kidney transplantation.
- The majority of pancreas recipients with longer standing diabetes (21–30 and >30 years) were also undergoing kidney transplantation as SPK or PAK, likely because renal failure is a late complication of diabetes.
- PTA recipients, on the other hand, tended to make up a much larger portion of the group with the shortest duration of diabetes.

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ABSTRACT

Introduction: The impact of duration of T1DM on outcomes following simultaneous pancreas and kidney transplantation (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA) is currently unknown.

Materials and methods: A total of 451 pancreas transplants performed at a single institution between January 2003 and April 2013 (SPK n = 238, PAK, n = 97, and PTA, n = 116) were divided into three groups based on cumulative years of T1DM (0–20 years, 21–30 years, and >30 years). Early (7-day) and late (90-day) pancreas allograft loss, patient and pancreas allograft survivals were analyzed.

Results: While, PAK was more common in recipients with >30 years of T1DM (29%, $p < 0.0047$), PTA was more common in recipients with 0–20 years of T1DM (41%, $p < 0.0011$). In all transplant types, recipients age was significantly higher the longer the duration of diabetes. Although longer duration of T1DM correlated with a higher rate of major amputations in PAK recipients ($p < 0.0032$), no difference was observed in SPK or PTA. While early pancreas graft loss was 2–4% in SPK and PAK with shorter or longer T1DM (p = n.s.), it reached to 10% in PTA with T1DM > 30 years ($p < 0.0097$). Longer duration of T1DM affected late pancreas graft loss in PAK patients (8%, $p < 0.0349$). Patient and death-censored graft survival rates were similar in all types of pancreas transplantation extracted by accumulation of years of T1DM prior to transplant.

Conclusions: Longstanding T1DM does not seem to negatively impact recipient outcomes following all types of pancreas transplantation.

Abbreviations: CAD, coronary artery disease; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; n.s., not significant; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; rATG, rabbit antithymocyte globulin; SPK, simultaneous pancreas and kidney transplantation; T1DM, type 1 diabetes mellitus; UNOS, United Network for Organ Sharing.

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1. Introduction

Recent analyses of national U.S. data from 1980 to 2012 suggest a doubling of the incidence and prevalence of diabetes during 1990–2008, and a plateauing between 2008 and 2012 [1]. An estimated 10–15% of the US population is affected by diabetes and 8–10% of these have type 1 diabetes mellitus (T1DM) [2]. T1DM is associated with severe late complications, including end-stage renal disease (ESRD), requiring renal replacement therapy or kidney transplantation [3]. Diabetes is also an independent major risk factor for cardiovascular and cerebrovascular disease, which is dependent on the years of exposure. Studies have shown that during the first 20 years of T1DM most of the excess mortality is attributed to renal failure, however after this period, it is considered to result largely from cardiovascular events [3–5]. International studies have revealed different mortality rates depending on the duration of diabetes exposure. The Finnish study demonstrated a cumulative mortality of 6.8% at 20 years and 15% at 30 years after diabetes diagnosis with a cumulative incidence of ESRD of 2.2.and 7.8%, respectively [6]. The impact of duration of diabetes on mortality has been reported by several groups, with rates varying between 6.8 and 13% after 20 years, and 15–29% after 30 years [3,6–9].

Pancreas transplantation is most commonly performed in the context of renal transplantation for end stage diabetic nephropathy (simultaneous pancreas and kidney transplantation (SPK) or pancreas after kidney (PAK) transplantation), or as an isolated transplant for poor glycemic control, particularly hypoglycemia unawareness (pancreas transplantation alone (PTA)), and is the only definitive long-term therapy which restores the euglycemic state and prevents and reverses secondary complications of diabetes [2,10]. The impact of recipient age, which can correlate with the duration of T1DM exposure, has been investigated in pancreas transplantation [11–13]. Schenker et al. and Ablorsu et al. have demonstrated that it is possible to achieve similar graft and patient survival rates in pancreas transplant recipients >50 years old compared to younger recipients [11,13]. Our group has recently reported on the impact of age on outcomes after pancreas transplantation. In that study, we also demonstrated that older recipients (50–59 years old, n = 85 and >60 years old, n = 18) have similar patient and graft survival rates compared to younger recipients [14]. Interestingly, in that study, the worst pancreas allograft survival was observed in the youngest recipients (<30 years of age).

Although some studies have reported single center experiences of pancreas transplantation in the diabetic population in large cohorts [15,16] no studies to date have systemically examined the impact of duration of T1DM on outcomes following pancreas transplantation. The current study was designed to determine the impact of the exact duration of diabetes exposure on different types of pancreas transplant recipients.

2. Materials and methods

2.1. Data collection and inclusion criteria

The medical records for all deceased donor pancreas transplants performed at Indiana University between January 2003 and April 2013 were reviewed (n = 451). Retrospective review of data from the transplant center database was approved by the Institutional Review Board of Indiana University School of Medicine. To obtain the data presented in the present manuscript, the comprehensive transplant recipient registry at our center, individual written and electronic medical records, and the original donor medical history were carefully reviewed. Inclusion criteria for the data analysis included all patients undergoing pancreas transplantation (SPK, PAK, or PTA). Pancreas retransplantations, even if performed early after the first transplant, were included in the data analysis. Measurements of recipient pre-transplant HbA1c and cardiac ejection fraction, history of hypertension, smoking, and major amputation were included. Although it was limited, non-heart beating donors were also used and included in data analysis together with recipient demographics and risk factors to stratify the different risk levels in different types of pancreas transplantation. Table 1 and supplementary digital content (SDC) Tables 1s, 2s, and 3s show demographic data for all pancreas transplantation, SPK, PAK, and PTA by accumulated years of T1DM prior to transplant, respectively.

Recipient listing for the transplant was according to standard procedures and protocols as established by the United Network for Organ Sharing (UNOS). All recipients were confirmed to be c-peptide negative prior to transplant. Regardless of type of pancreas transplantation (SPK, PAK, or PTA), the work-up for pancreas transplantation was similar in all recipients. All patients were required by the listing committee to have a negative cardiac stress test prior to pancreas transplantation. Criteria for cardiac catheterization included any patient with known history of coronary artery disease (CAD), multiple risk factors, or a positive finding on a cardiac stress test, as explained before [17].

2.2. Pancreas procurement, preparation and transplantation

Local pancreas allografts were typically procured using an en bloc technique following aortic flush with preservation solution and topical cooling with saline flush and ice packing, as previously described [18]. All pancreas allografts were prepared, as previously described [19]. We have previously shown that there was no difference in outcomes for local and import pancreas allografts in our experience [20]. Therefore, the data analyzed included those recipients of imported pancreas allografts as well.

The recipient operation was performed through a midline incision, as previously described [21,22]. Briefly, the pancreas allograft was positioned with the tail toward the pelvis and the head and duodenum oriented superiorly to facilitate enteric exocrine drainage. All pancreas allografts, regardless of SPK, PAK or PTA, were drained enterically using a stapled technique [23]. Systemic venous drainage was performed to the vena cava or to the right common iliac vein. Arterial perfusion of the allograft was routinely established from the right common iliac artery, although on rare occasions where this vessel was found to be diseased or had been the site for arterial anastomosis for a prior transplant, the inflow would be established either from the aorta or the left common iliac artery. All SPK transplants were performed with ipsilateral placement of both the kidney and the pancreas to the right iliac vessels, as previously described [24]. Pulsatile perfusion was used routinely for the renal allograft portion of the SPK, as described [25].

2.3. Immunosuppressive therapy

The induction immunosuppressive regimen consisted of five doses of rabbit antithymocyte globulin (rATG) (1 mg/kg/dose). A single dose of rituximab (150 mg/m^2) induction was also included in cases of PTA. The maintenance immunosuppressive regimen consisted of tacrolimus (through level of 8–10 ng/mL), and sirolimus (through level of 3–6 ng/mL) [26]. Steroids were only used as a premedication for rATG induction and were discontinued in all recipients, including PAK recipients receiving long-term steroids for a remote renal transplant [27]. Mycophenolate mofetil (MMF) (500 mg po b.i.d) was used as a part of the maintenance immunosuppressive regimen together with tacrolimus and sirolimus in cases of PTA or as a substitute for sirolimus in cases of drug