eScientific Library

ISSN: 2767-6560

Volume 4 Issue 2
www.escientificlibrary.com

ES Journal of Case Reports

Pancreas Transplantation Alone for Brittle Diabetes Mellitus

Review Article

DOI: 10.59152/ESJCR/1044

Rainer WG Gruessner[1,*], Angelika C Gruessner[2]

[1]*Professor of Surgery, State University of New York, USA*

[2]*Professor of Medicine, State University of New York, USA*

Received: December 04 2023; **Accepted:** December 09, 2023; **Published:** December 12, 2023

***Corresponding author:** Rainer WG Gruessner, MD, FACS, Professor of Surgery, State University of New York, USA.

Abstract

Only about 8% of all pancreas transplants for insulin-dependent diabetes mellitus are performed in the Pancreas Transplant Alone (PTA) category. PTAs are primarily performed in diabetic, non-uremic patients with unstable glucose control, hypoglycemia unawareness, and an increased risk of diabetes-related mortality, and who have failed all of the more traditional approaches to glycemic control. Tremendous, yet not widely noticed, progress in PTA outcome has been made over the past two decades. PTA is a very safe procedure with 1-and 5-year patient survival rates of 98.3% and 90.5% according to International Pancreas Transplant Registry (IPTR) data. Since the introduction of tacrolimus and mycophenolate mofetil maintenance therapy in the 1990s and the use of depleting antibody induction therapy, PTA graft survival rates at 1-and 5-years posttransplant are 87.2% and 65.0%. To avoid the need for a future kidney after pancreas (KAP) transplant due to impaired pretransplant native kidney function and the posttransplant use of calcineurin inhibitors, the estimated Glomerular Filtration Rate (eGFR) of PTA candidates should be well within the normal range and preferably > 80 mL/min/1.73m^2. PTAs with stable, long-term function have been shown to have a positive impact on secondary complications of diabetes mellitus. Considering the significantly improved outcome results, PTA should become the pancreas transplant option of choice before the manifestation of devastating secondary complications (kidney failure, cardio-cerebrovascular events, and blindness) that require simultaneous pancreas and kidney (SPK) transplants in qualified candidates, but with higher morbidity and mortality risks. It is important for diabetologists, endocrinologists, and other health professionals involved in the care of diabetic patients to learn about these positive PTA outcome results. Despite improvements in intensive insulin therapy, insulin-delivering devices, bioartificial pancreas, and islet transplantation, a successful PTA is the only treatment option for patients with brittle diabetes that consistently restores normal glucose homeostasis long-term without exposing recipients to the risks of severe hypoglycemia and prevents, halts, or reverses the development or progression of secondary diabetes complications.

Keywords

Pancreas Transplant Alone, Brittle Diabetes, Hypoglycemia Unawareness, Survival Benefit, Pancreas Transplantation for Insulin-Dependent Diabetes Mellitus.

Introduction

Diabetes mellitus is a massive, global problem. The only treatment that reliably cures this pandemic disease long-term is a successful pancreas transplant [1]. Unfortunately, most pancreas transplants are performed after rather than before the manifestation of end-stage renal disease. Hence, diabetic patients with uremia undergoing a simultaneous pancreas and kidney transplant (SPK) and, to a smaller degree, post-uremic patients undergoing a pancreas after a previous kidney transplant (PAK) have benefitted the most from a successful pancreas transplant. However, a "pre-emptive" pancreas transplant alone (PTA)-ie, before the development of ESRD-would benefit diabetic

patients even more as it can prevent, halt or even reverse the development or progression of secondary diabetic complications that so severely impact the quality of life of diabetic patients [2,3]. Hence, it is not surprising that posttransplant life expectancy and patient survival rates are higher for PTA than for SPK and PAK recipients. But, only about 10% of all pancreas transplants are performed in the PTA category [1-4].

Most patients are referred for pancreas transplantation by their nephrologists due to the fact that they will be obligated to immunosuppression by their kidney transplant; the only added risk of a simultaneous or subsequent pancreas transplant is that of surgery which is low. Nephrologists are keenly aware of the survival benefits of a successful kidney transplant over dialysis and have also witnessed the added benefits of a pancreas transplant in terms of metabolic stabilization through normoglycemia and kidney graft protection from recurrence of diabetic disease.

Endocrinologists, on the other hand, are usually not exposed to immunosuppressed patients and may view immunosuppression in general as undesirable as chemotherapy. Hence, pancreas transplant surgeons have to actively reach out to, and collaborate with, endocrinologists and diabetologists to make them aware of the tremendous improvements in terms of patient and graft survival as well as surgical techniques that have been achieved over the past two decades with pancreas transplantats alone. Most of these successes have unfortunately gone unnoticed by the public but, surprisingly, also by health care providers. This is not about persuading or convincing endocrinologists and diabetologists about pancreas transplantation being the general solution to their diabetic patients: it is about assuring that pancreas transplantation can be a solution primarily to a small fraction of diabetic patients who despite everybody's best efforts are brittle diabetics with hypoglycemia unawareness–probably a fraction of no more than 2-5% of all patients with type 1 diabetes, and more commonly young and female patients. These are patients in whom even the most advanced and sophisticated conservative treatment options including the bioartificial pancreas and refined insulin pumps have failed.

While SPK and PAK transplants are considered "no-brainers" for qualified patients, PTA transplants are not. If education of the overall low risks that are associated with immunosuppressive therapy and the surgical procedure turns into common knowledge, PTA may gain widespread acceptance as a preventive and curative treatment for selected diabetic patients. In large part, the future of pancreas transplantation rests on the change from performing pancreas transplants early (PTA) and not late (SPK, PAK). From a societal perspective, this change from SPK to PTA would not only benefit our health system both medically and financially and improve survival of diabetic patients but also allow more non-diabetic patients to receive a life-saving kidney transplant.

To make the case for PTA, the following paragraphs are a description of the diabetic plague in the United States and the ultimately failed attempts to significantly improve the quality of life and the survival of diabetic patients through intensive insulin therapy.

The Diabetes Scourge in the United States

According to the CDC's National Diabetes Statistics Report, 2020, 34.2 million people of all ages—or 10.5% of the US population—had diabetes in 2018 [5]. An estimated 88 million adults aged 18 years or older had prediabetes in 2018 accounting for 34.5% of all US adults.

Prevalence and Incidence: The prevalence estimates of diabetes increased from 9.5% in 1999–2002 to 12.0% in 2013–2016. Prevalence of diagnosed diabetes was highest among American Indians/Alaska Natives (14.7%), people of Hispanic origin (12.5%), and non-Hispanic blacks (11.7%), followed by non-Hispanic Asians (9.2%) and non-Hispanic whites (7.5%). In 2018, it was estimated that 1.5 million new cases of diabetes—or 6.9 per 1,000 persons—were diagnosed.

210,000 children and adolescents younger than age 20 years—or 25 per 10,000 US youths—had diagnosed diabetes. This includes 187,000 with type 1 diabetes. Data from the 'SEARCH for Diabetes in Youth' Study indicated that during 2014–2015, the estimated annual number of newly diagnosed cases in the United States included 18,291 children and adolescents younger than age 20 years with type 1 diabetes. Among US children and adolescents aged less than 20 years, the overall incidence of type 1 diabetes significantly increased for the period 2002–2015 (during 2002–2010, Hispanic children and youth had the largest significant increases in incidence of type 1 diabetes; during 2011–2015, non-Hispanic Asian and Pacific Islander children and youth).

***Emergency Department Visits and Hospitalizations*:** In 2016, a total of 16 million emergency department (ED) visits were reported with diabetes including 224,000 visits for hyperglycemic crisis (9.7 per 1,000 adults with diabetes) and 235,000 for hypoglycemia (10.2 per 1,000 adults with diabetes). In 2016, a total of 7.8 million hospital discharges were reported with diabetes (339.0 per 1,000 adults with diabetes) including: 1.7 million for major cardiovascular diseases (75.3 per 1,000 adults with diabetes), of which 438,000 were for ischemic heart disease (18.9 per 1,000 adults with diabetes) and 313,000 for stroke (13.6 per 1,000 adults with diabetes); 130,000 for a lower-extremity amputation (5.6 per 1,000 adults with diabetes); 209,000 for hyperglycemic crisis (9.1 per 1,000 adults with diabetes); 57,000 for hypoglycemia (2.5 per 1,000 adults with diabetes).

Kidney Disease: Among US adults aged 18 years or older with diagnosed diabetes, crude estimates for 2013–2016 were that 37.0% had chronic kidney disease (stages 1–4), of which over half (52.5%) had moderate to severe chronic kidney disease (stage 3 or 4); 24.9% with moderate to severe chronic kidney disease (stage 3 or 4) were aware of their kidney disease. In 2017, crude incidence of end-stage kidney disease with diabetes as the primary cause was 180.3 per 1 million population (58,372 new cases).

Deaths: In 2017, diabetes was the seventh leading cause of death in the United States. There were 270,702 death certificates with diabetes listed as the underlying or contributing cause of death (crude rate, 83.1 per 100,000 persons).

Costs: The total direct and indirect estimated costs of diagnosed diabetes in the United States in 2017 was $327 billion. Total direct estimated costs of diagnosed diabetes increased from $188 billion in 2012 to $237 billion in 2017; total indirect costs, from $73 billion to $90 billion [5].

The Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study

The DCCT was designed in the 1980s to improve metabolic control and reduce complications associated with diabetes. It demonstrated, in patients with T1DM, that intensive insulin therapy reduces the rate of early-stage secondary complications of diabetes at the expense of causing (life-threatening) iatrogenic hypoglycemia. [6, 7].

At the end of the DCCT, the long-term observational EDIC follow-up study commenced. It demonstrated that the metabolic memory phenomenon during EDIC contributed to a substantially lower burden of advanced complications over time [8,9]. Despite the convergence of HbA1c levels between the two groups during EDIC-due to the adoption of intensive therapy by the original DCCT conventional-treatment group and the return of all participants to their own healthcare providers for diabetes management-, the development and progression of complications continued to be substantially less in the original intensive-treatment group vs the conventional-treatment group ('metabolic memory') [8,9].

However, rates of severe hypoglycemia have equilibrated over time between the two DCCT/EDIC treatment groups in association with advancing duration of diabetes and similar HbA1c levels. Severe hypoglycemia persists and remains a challenge for patients with type 1 diabetes across their life span [10]. This conclusion alone of arguably the best designed study on intensive insulin therapy and with > 30 years of follow up justifies the indication for PTA transplantation.

Indication

A PTA is primarily indicated for diabetic (and non-uremic) patients with obvious metabolic control problems despite "optimized" intensive insulin therapy. This includes, for example, patients with unpredictable, sharp changes in blood glucose levels without an obvious cause; frequent episodes of hypo-and hyperglycemia; greater likelihood and frequency of experiencing ketoacidosis and/or severe hypoglycemia [11]. Poor metabolic control is frequently noted under the following conditions:

***Brittle diabetes*:** Brittle diabetes is defined as insulin-dependent diabetes mellitus associated with glycemic instability of any type, leads to life disruption with recurrent and/or prolonged hospitalizations. It affects about 1-5 per 1000 diabetic patients, but its true prevalence is unknown. For a number of reasons (eg, increasing prevalence of older adults with type 1 diabetes and insulin/food insecurity) brittle diabetes promises to increase in the future [12].

Hypoglycemia unawareness: Hypoglycemia unawareness is defined at the onset of neuroglycopenia before the appearance of autonomic warning symptoms [13]. It is a major limitation to achieving tight metabolic control and reduced quality of life. Hypoglycemia unawareness occurs in approximately 40% of people with type 1 diabetes mellitus (T1DM) and with less frequency in T2DM [13]. As with "brittle" diabetes, the reasons for hypoglycemia unawareness are multifactorial.

Notably, hypoglycemia unawareness carries a substantial mortality risk, and there is an increasing number of series reporting hypoglycemic mortality rates ranging from 4% to 10% [13,14]. Cryer stated that "it is sobering to think that as many as 1 in 25—or even 1 in 10—patients with type 1 diabetes will die of (autonomic or iatrogenic) hypoglycemia. Obviously, life-threatening episodes of hypoglycemia need not be frequent to be devastating" [15]. This further validates the need for PTA for diabetic patients who manifest or continue to demonstrate hypoglycemia unawareness under intensive insulin therapy.

The 2004 American Diabetes Association (ADA) position statement suggests that indications for PTA (and absence of kidney failure) are "frequent, acute and severe metabolic complications (hypoglycemia, hyperglycemia, and ketoacidosis) requiring medical attention" as well as "clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and consistent failure of insulin-based management to prevent acute complications" [16]. The 2014 ADA position statement expanded: "Consider PTA in adults with T1DM, unstable glucose control, hypoglycemia unawareness, and an increased risk of diabetes-related mortality, who have attempted all of the more traditional approaches to

glycemic control and have remained unsuccessful, yet are judged responsible enough to manage the anti-rejection medication regimen, risks, and follow-up required with an organ transplant" [17].

Despite this encouraging support for PTA by the ADA, many PTA candidates are self-rather than endocrinologist-referred despite the fact that 1-5% of insulin-dependent patients fulfill the ADA criteria. Social media have played a major role in self referrals and women have been more proactive than men (who more frequently receive SPK transplants).

Hence, PTA is primarily indicated in non-uremic patients with poor metabolic control despite "optimized" intensive insulin therapy, patients who experience hypoglycemia unawareness and/or suffer from progressive chronic complications of diabetes.

Fitting this description, Sa et al. reported 2 cases of successful PTA in diabetic patients with resistance to insulin administered subcutaneously or intramuscularly, a rare syndrome (DRIASM) that is usually treated with continuous intravenous insulin infusion. The 16-and 18-year-old female patients were diagnosed with T1DM as young children and had labile glycemic control with recurrent episodes of diabetic ketoacidosis which resulted in prolonged periods of hospitalization [18].

PTA is also considered for less common indications such as cystic fibrosis [19-21] and in patients after total pancreatectomy (most frequently performed for chronic pancreatitis, but also for benign pancreatic tumors) with both endocrine and exocrine insufficiency. [22-25] PTA in insulin-dependent T2DM patients is much less common, but increasingly performed in Asian countries such as China where T2DM is much more prevalent than T1DM.

PTA Waiting List Mortality

Given the fact that hypoglycemia unawareness carries a substantial mortality risk, ranging from 4% to 10% [13,14], it is not surprising that waiting list mortality for PTA is significant. This is in contrast to frequent statements that pancreas transplantation unlike, for example, liver and heart transplantation, is not a life-saving procedure. While a pancreas transplant may not be an immediately life-saving procedure it most certainly is over time. According to IPTR/UNOS data, waiting list mortality for PTA is 5% at 1 year, 10% at 2.5 years, 15% at 4 years and almost 20% at 5 years [26] (Figure 1); most deaths are due to hypoglycemia unawares and autonomic insufficiency. These mortality rates are significant–even more so since PTA candidates are non-uremic and without any advanced secondary diabetic complications. In light of these mortality rates it is obvious that a PTA is not only a life-enhancing but also a life-saving procedure [26].

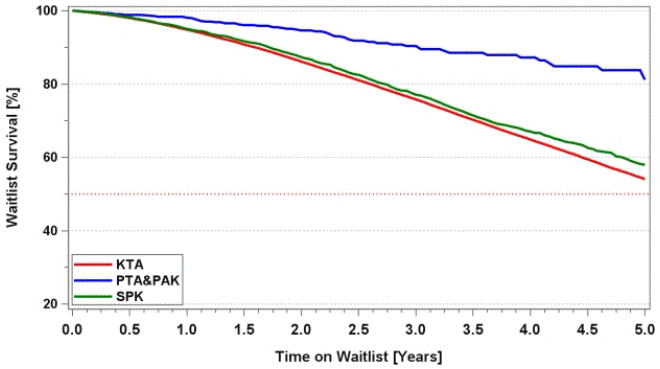

Figure 1: Patient survival while waiting for a transplant for primary DD transplants in diabetic patients 1/1/2000 -12/31/2020.

In general, the median waiting time for a PTA is much shorter (4.4 months) than for an SPK. The waiting time is higher for PTA retransplants, pancreas after islet (PAI) transplants [27], and highly sensitized PTA candidates.

Native Kidney Function

Our understanding of appropriate pretransplant native kidney function in PTA candidates has evolved over time. In the azathioprine and cyclosporine eras, PTA transplants were performed in diabetic patients with relatively low estimated Glomerular Filtration Rates (eGFR < 50 mL/min/1.73 m^2). This resulted in a high number of Kidney after Pancreas (KAP) transplants (see below) since the average decrease in creatinine clearance primarily due to calcineurin-inhibitor administration was reported to be 29–38% at 1 year posttransplant in single-center studies [28-30].

Since 2006, the median eGFR has been > 90 mL/min/1.73m^2 and the 1st quartile > 70 mL/min/1.73 m^2 pretransplant in PTA recipients; thus, over 75% of all PTAs in the Unites States were performed in patients with an eGFR > 70 mL/min/1.73 m^2 (Figure 2) [31,32]. Consequently, the number of KAP transplants has significantly decreased over time.

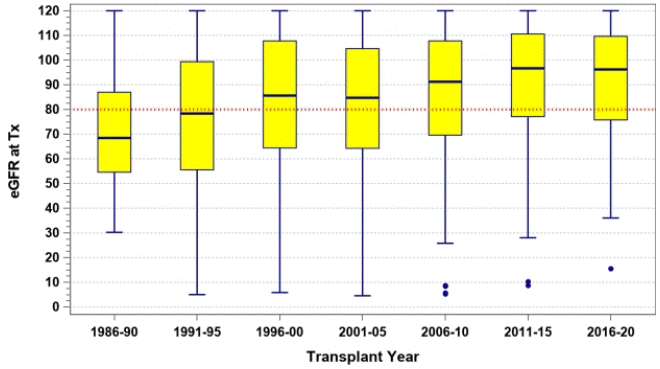

Figure 2: PTA median eGFR at time of transplantation between 1/1/1986 and 12/31/2020 (it has been > 90 mL/min/1.73m² and the 1st quartile > 70 mL/min/1.73 m² pretransplant since 2006).

Several other studies have confirmed that kidney function before PTA is a strong independent predictor of ESRD [33-40]. Scalea et al. reported that in their series of 131 PTAs, 17 (13%) recipients had an eGFR < 50 mL/min/1.73m^2 pretransplant, whereas 64 (49%) recipients did so post-PTA and 24 (18%) had an eGFR < 30 mL/min. Mean eGFR pretransplant was 88.9 vs. 55.6 mL/min/1.73m^2 posttransplant (P<0.0001) with mean follow-up of 3.68 years. All but 16 (12%) patients showed a decrease in eGFR. Mean decrement was 32.1 mg/min/1.73m^2. They also noted that 13 recipients subsequently required a kidney transplant at a mean of 4.36 years posttransplant [34]. Smail et al. found that the actuarial incidence of ESRD at 1, 3 and 5 years was 0, 28.6 and 61.9% in patients with pretransplant eGFR < 60 ml/min/1.73m^2, and 0, 8.2 and 12.5% in patients with pretransplant eGFR > 60 ml/min/1.73m^2, respectively (P=0.006) [35]. Kim et al. reported that patients with eGFR <60 and 60 to 89.9 mL/min/1.73m^2 were 7.74 and 3.25 times more likely to develop ESRD than patients with eGFR ≥ 90 mL/min/1.73m^2 [36]. Le Dinh et al. noted that kidney function deteriorated significantly after PTA: although the baseline eGFR was 89.3 ± 27.9 (range, 58-145), eGFR decreased to 75.7 ± 26.2, 71 ± 20.6, 66.5 ± 14.8, and 62.1 ± 11.2 at 6 months, 1, 3, and 5 years representing-15.2%,-20.5%,-15.8%, and-22.6% percentage decreases respectively (p < 0.05); conversely, serum creatinine levels progressively increased. However, none of their patients needed dialysis or kidney transplantation [37].

In contrast, Boggi et al. found that proteinuria (24-hour) improved significantly after PTA. Renal function declined only in recipients with pretransplant glomerular filtration rate (GFR) > 90 mL/min/m^2, possibly because of correction of hyperfiltration following normalization of glucose metabolism [38]. Chatzizacharias et al. noted that in PTA recipients with pre-transplant eGFR < 70 mL/min/1.73m^2 high tacrolimus levels (> 12 mg/dL) at six months post-transplant was the only independent risk factor identifying a substantial decline in native renal function. The presence of severe pre-transplant proteinuria (urine Pr/Cr ≥ 100 mg/mmol) marginally failed to reach significance (p = 0.056). Of note, low eGFR levels alone (≤ 45 and ≤ 40 mL/min/1.73m^2) at the time of transplant did not correlate with substantial decline in renal function. The data suggested that PTA is a justifiable therapy even for patients with borderline renal function, provided that they do not suffer from severe proteinuria and appropriate monitoring and tailoring of immunosuppression is ensured [39]. In that regard, Kandula et al. suggested that maintenance therapy with tacrolimus and sirolimus may not lead to worsening proteinuria and kidney function when compared with regimens using tacrolimus and mycophenolate mofetil (see below) [40].

The beneficial (long-term) effect of PTA on native kidney function is well documented. Mauer and Fioretto et al. examined the renal structure in several studies by obtaining biopsies of the native kidneys before and 5 and 10 years after PTA in non-uremic patients. All patients had a history of long-term T1DM and mild to advanced diabetic nephropathy lesions at the time of transplantation. Despite prolonged normoglycemia, diabetic glomerular lesions were not significantly changed at 5 years after PTA. In contrast, glomerular lesions were markedly improved after 10 years: in most patients the glomerular structure was normal at 10-year follow-up despite the continued administration of calcineurin inhibitors. Similar findings were observed for tubular and interstitial lesions. These studies in PTA recipients demonstrate that the lesions of diabetic nephropathy are reversible after successful transplantation in PTA recipients [41,42].

Cardiovascular Risk

The cardiovascular risk is significantly lower for PTA vs SPK and PAK transplant candidates [43]. Candidates for PTA have normal or near normal renal function thereby avoiding the increased risk of coronary artery disease (CAD) contributed by renal failure [44]. In addition, PTA candidates are younger than SPK and PAK candidates. However, as the age of PTA eligible candidates increases, the risk of having a cardiovascular event while on the waiting list also increases. Hence, selected patients may become moderate or, albeit rarely, high-risk candidates [45], specifically candidates with a history of hypertension, hyperlipidemia and rising BMI [43]. Only in this subgroup, invasive cardiovascular testing (ie, coronary angiography) is usually indicated. In general, the decision how aggressive the cardiac work-up for PTA candidates should be, must be left to the consulting cardiologist as part of the candidates cardiac and/or pulmonary evaluation.

Posttransplant, the risk for cardiovascular complications in PTA recipients is significantly lower compared to SPK and PAK recipients as also shown in IPTR analyses [46,47].

Advantageous long-term effects of PTA on cardiovascular function are slowly emerging. Occhipinti et al. reported an amelioration of cardiac morphology and function in type 1 diabetic patients with sustained PTA success [46]. Boggi et al. noted improvements in several cardiovascular risk factors and left ventricular ejection fraction [38,48].

Outcome

The following analysis is based on all 2,734 PTAs performed in the United States between 12/17/1966 and 12/31/2020 and reported to UNOS/IPTR. In the United States, the number of PTAs peaked during the years 2004/05 and declined afterwards (Figure 3). In total, 90% were primary and 10% were PTA retransplants.

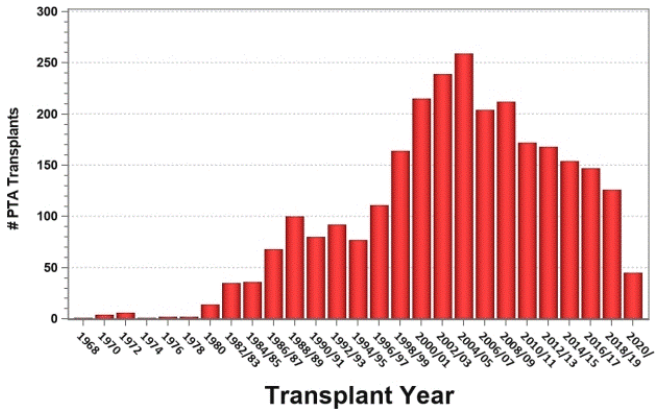

Figure 3: Number of PTAs by Transplant Year: 2,734 PTA transplants were performed in the United States between 12/17/1966 and 12/31/2020 and reported to UNOS/IPTR.

The number of centers that performed at least 1 PTA per year increased initially from 22 centers in 1988/89 to 52 centers in 2008/09. Since then, the number of centers has been declining again: in 2018/19, 39 centers performed at least 1 PTA per year. In 2016-20, less than one-third of all pancreas transplant centers performed at least 1 PTA per year.

***PTA Characteristics*:** Significantly more female patients received a PTA over time: 60% of all PTA recipients from 2016 to 2020 were female. This is in contrast to the SPK and PAK categories where the majority of recipients were male (60%)

There has been a significant continuous increase in recipient median age over time, from 30 years (range, 17–52) in 1966-85 to 44 years (range,12–68) in 2016-20. Likewise, the median duration of diabetes increased from 24 years (range, 2–41) in 1991-95 to 27 years (range, 1–58) in 2016-20.

The rate of sensitized PTA recipients increased significantly over time: 22% of recipients are now sensitized. This is mainly due to the higher number of female recipients who are twice as likely to be sensitized compared to male recipients.

Donor characteristics also changed significantly over time. In 1986-90, 39% of all primary PTA donors were > 30 years of age; this rate decreased to 20% in 2016-20. Of particular interest was the initially high rate of living donors; in 1966-85, 26% of PTAs were from living pancreas donors; since 2005, living donors have not been used in the PTA category due to improvements in the U.S. allocation policies.

Over time, the most common cause of death in deceased donors was trauma which now accounts for 75% of all donor deaths. Pancreas preservation time decreased significantly over time to < 12 hrs in 39% for PTAs performed between 2016 and 2020.

Considerable attention was paid to HLA matching in the early years: five or six HLA mismatches accounted for only 12% of all PTAs in 1991-95, but for 57% in 2016-20.

The management of the pancreatic duct also changed significantly over time. In 1966-85, enteric drainage was used in 59% of transplants. This rate decreased to 7% in 1991-95 when bladder drainage became the preferred technique. In the late 1990s, enteric drainage was again more frequently used and, in 2016-20, accounted for 95% of all PTAs (Figure 4).

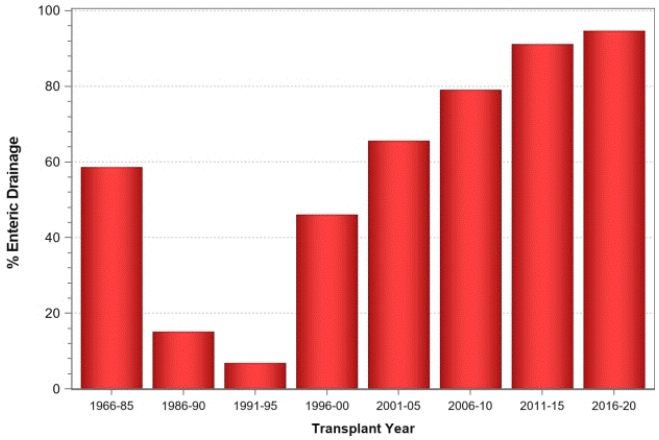

Figure 4: Evolution of Enteric Drainage 12/17/1966 and 12/31/2020.

The changes in duct management technique went along with changes and improvements in immunosuppressive regimens. The use of depleting antibody induction therapy increased over the years continuously and, in 2016-20, accounted for 91% of all PTAs. Nondepleting antibody therapy peaked in 1996-20 with 13% of all PTAs, but declined afterwards (Figure 5). Figure 6 shows the change from cyclosporine/azathioprine (CsA /AZA) based protocols in 1986-95 to tacrolimus/mycophenolate mofetil (TAC/MMF) based protocols; TAC/MMF protocols accounted for 85% of PTA maintenance therapy in 2016-

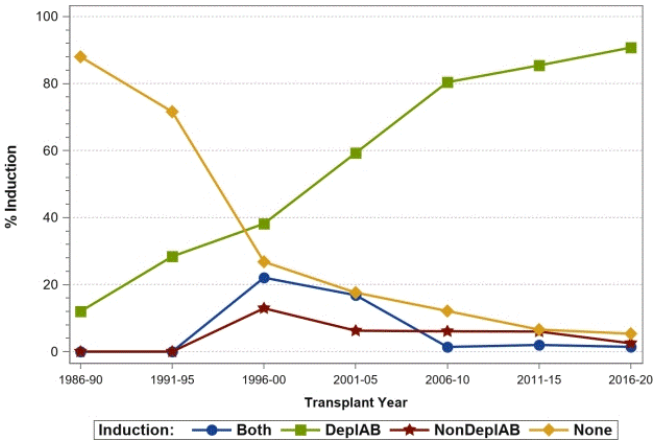

Figure 5: Induction therapy in PTA between 1/1/1986 and 12/31/2020. (Depl – depleting).

20. Sirolimus based protocols showed promise in 2003-10, but declined afterwards (Figure 6). Early steroid avoidance reached its peak with 57% of all PTAs in 2006-10, but declined afterwards and accounted for 32% in 2016-20 (Figure 7).

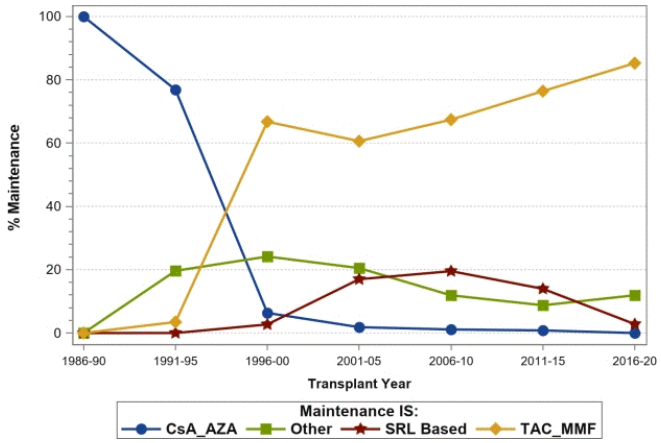

Figure 6: Maintenance therapy in PTA between 1/1/1986 and 12/31/2020. (CsA–cyclosporine A, AZA–azathioprine, SRL–sirolimus, TAC–tacrolimus, MMF–mycophenolate mofetil).

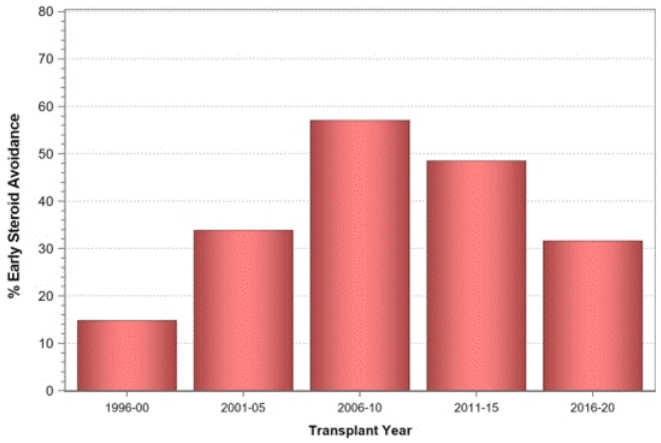

Figure 7: Early steroid avoidance in PTA between 1/1/1996 and 12/31/2020.

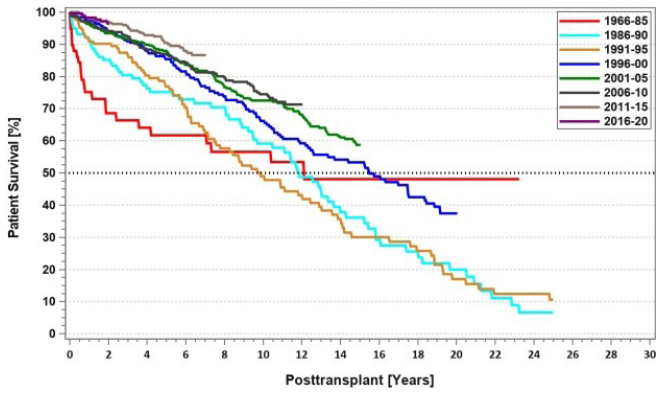

Figure 8: PTA patient survival between 12/17/1966 and 12/31/2020.

***Patient Survival*:** PTA patient survival rates have constantly increased over time (Figure 8). Since 1996, PTA patient survival rates at 1 year have been 97% or higher. Also, since 1996, patient survival rates at 5 years were over 85%, and since 2001 over 73% at 10 years. Over time, the most common cause of early and late deaths in primary PTA recipients was a cardio-or cerebrovascular event.

Despite its invasive surgical nature, PTA is a safe procedure. As stated, the risk of death during the first year posttransplant is now < 2%. Importantly, it is less than the risk of death on the waiting list while waiting for a PTA [26,49]. According to an analysis of the large population-based Allegheny County Type 1 Diabetes Registry (for patients diagnosed with T1DM from 1965 to 1979), the overall mortality rate is 812 deaths/100,000 person-years and for PTA recipients, only 320 deaths/100,000 [50].

***Graft Survival*:** As stated above, the improvement in PTA graft survival rates over time has been very impressive (Figure 9). Graft survival rates at 1 year in primary PTA recipients improved from 19% in 1966-85 to 87% in 2016-20. Between 1966 and 2010, graft survival rates at 5 years improved from 12.3% to 65% and reached 40% at 10 years in 2006-10. Those improvements were primarily due to two developments: 1) a significant reduction in the 3-month technical complication rate, from 31% in 1966-85 to 7% in 2016-20 (Figure 10), and 2) a significant reduction in the 1-year immunologic graft loss rate, from 63% in 1966-85 to 5% in 2016-20 (Figure 11).

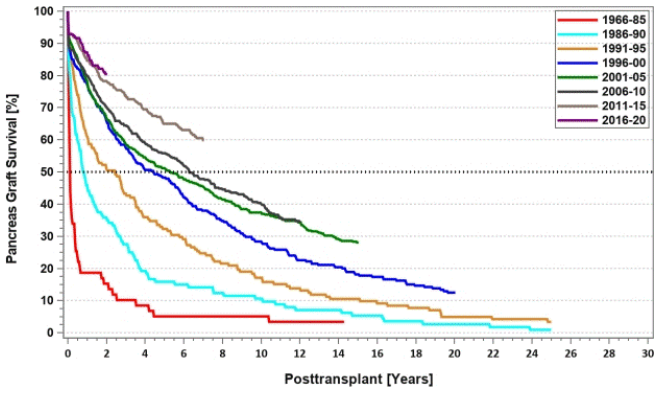

Figure 9: PTA graft survival 12/17/1966 and 12/31/2020.

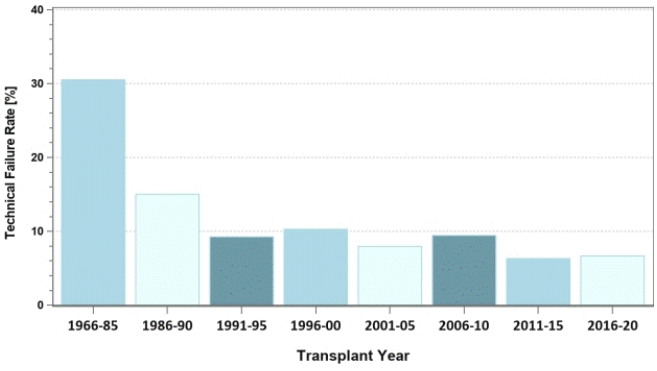

Figure 10: PTA Technical Failure rate 12/17/1966 and 12/31/2020.

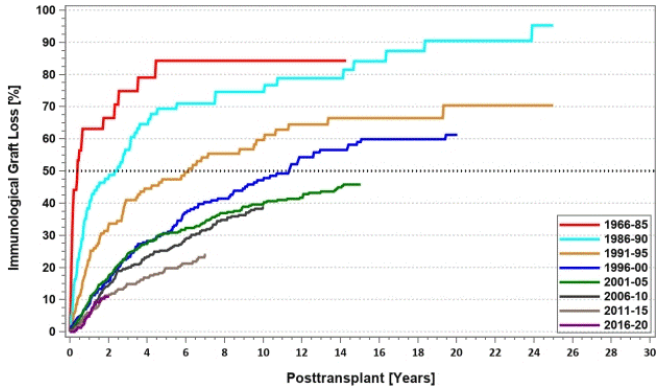

Figure 11: PTA Immunological Graft Loss 12/17/1966 and 12/31/2020.

The introduction of tacrolimus and MMF in combination with enteric drainage of the pancreas duct during 1991-95 had the highest, positive impact on PTA outcome [2,51-57]. Stratta et al. concluded that with depleting antibody induction and tacrolimus-based maintenance therapy, similar medium-term outcomes can be achieved in solitary pancreas and SPK transplants in the new millennium [58].

Because a PTA is considered a highly "immunogenic" transplant, effective induction and maintenance protocols are essential for good outcomes. In 2016-20, PTA graft function was highest in recipients on anti–T-cell induction therapy with depleting antibodies and tacrolimus in combination with MMF. In 2016-20, the 1-year PTA graft survival rate reached 97.9% in these recipients. Maintenance regimens based on Sirolimus or other protocols were only very rarely used, mostly when there were drug side effects or contraindications for using tacrolimus and/or MMF.

An IPTR sub-analysis of 2016-20 transplants compared outcome in PTA versus SPK recipients on depleting antibody induction therapy and TAC/MMF based maintenance immunosuppressive therapy. No short-term difference was found between the 2 recipient categories (p> 0.66), indicating that PTA results were no longer trailing those of SPK results. The overall improved results in both categories were due to decreased rates of early acute rejection episodes and of immunologic graft losses.

Causes of pancreas graft failure in 2016-20 differed by time posttransplant: within the first 3 months, technical failure was most common (>70%); from 3 to 12 months posttransplant, acute rejection; and after 12 months, chronic and acute rejection as well as death with a functioning graft.

The most common cause of early technical failure in PTA recipients in 2016-20 was graft thrombosis (6.4%), followed by infection (0.4%) and leakage (also 0.4%). Because the demand for a PTA has traditionally not been as high as for an SPK transplant, PTA donors were younger, had fewer (if any) comorbidities, and underwent an even more stringent selection process. The most important risk factors for early technical PTA failure were: pancreas graft preservation time >12 h (P = 0.05), donor age > 30, BMI > 30 kg/m2 (P = 0.02), and transplant at a low-volume transplant center (<10 PTA recipients in 5 years). Of note, some transplants may have been incorrectly classified as an early technical failure (thus resulting in an overestimate) because of severe early rejection and associated thrombosis.

Major risk factors for immunologic graft loss included early acute rejection episodes (P = 0.02), African American race (P = 0.04), recipient age <30 years (P < 0.001), and female sex (P = 0.05). The use of TAC/MMF or SRL significantly lowered the risk of immunologic graft loss. However, the risk was not affected by any of the following: type of drainage (bladder vs. enteric), late acute rejection episodes, steroid avoidance, HLA matching, panel-reactive antibody (PRA) >20%, and transplant center volume.

The higher rate of pancreas rejection in the PTA (v. SPK and PAK) category has been confirmed in clinical and large animal studies [2, 59-62].

Immunosuppressive strategies have been the topic of several single-center PTA series.

Sutherland et al., in an effort to decrease the higher rejection rate in PTA (vs. SPK) recipients, gave tacrolimus and MMF pretransplant while the patients were waiting. The average wait time (and thus duration of immunosuppression) was 6.5 months. Graft survival under pretransplant immunosuppression was significantly higher compared with historical controls [60]. Vrakas et al. showed that the use of depleting antibodies as induction immunosuppression (along with cold ischemia time <12 hours) had a positive effect on pancreas allograft survival [63]. Fridell et al. compared rabbit antithymocyte globulin induction therapy without and with rituximab in 166 PTA recipients. There was no significant difference in 7-or 90-day graft loss, 1-year patient or graft survival, or in the rate of rejection or infection. Of note, maintenance therapy consisted of tacrolimus, sirolimus and MMF. The authors concluded that rabbit antithymocyte globulin induction and steroid withdrawal followed by a three-drug immunosuppression regimen is an excellent strategy for PTA recipients [61]. The combined use of sirolimus and tacrolimus was initially found to show favorable results in younger PTA recipients (<42 years of age), but the combination of tacrolimus and MMF has become the most common form of maintenance therapy [64].

***Retransplants*:** In the early years of pancreas transplantation retransplants were more frequently performed. In 1986-90, 31% of all PTA were retransplants.

The PTA retransplant rate decreased afterwards to a constant rate of about 10% per year. Of note, in 2011-20, the pancreas graft function rate in retransplant recipients was not as favorable as in primary PTA recipients. The graft survival rates at 1 and 3 years for retransplants were 81.8% and 64.2% compared to 85.7% and 74.8% for primary transplants, respectively.

The cause of primary graft failure had no significant impact on PTA retransplant outcomes, but the timing of the retransplant did have an impact. PTA recipients who underwent a PTA retransplant within 2–12 months after a primary technical graft failure had a significantly higher graft survival rate (79% at 1 year after retransplantation).

Kidney after Pancreas (KAP) transplantation

The median pretransplant eGFR of primary PTA recipients increased significantly over time. It has been > 80 mL/min/1.73 m^2 since 1998. In 2016-20, almost 75% of all PTA had an eGFR over 80 mL/min/1.73 m^2. This impacted the rate of subsequent kidney transplants. The rate of KAP transplants decreased when compared to previous analyses [65] (Figure 12). The 1-, 5-, and 10 year KAP rates for the time of 1996-2000 were 2.6%, 15.6% and 39.3%; for the time period of 2016-20, the 1-, and 5-year KAP rates have decreased to 0.2% and 3%.

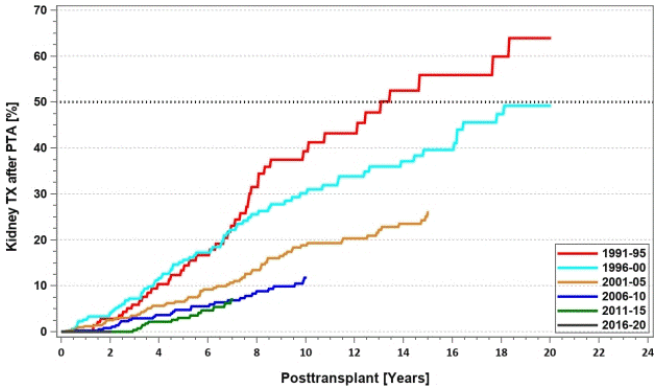

Figure 12: Kidney after Pancreas (KAP) transplantation rate 12/17/1966 and 12/31/2020.

The possible development of ESRD after PTA must be avoided under all circumstances as it is associated with an increased mortality. Singh et al., using the Scientific Registry of Transplant Recipients (SRTR) database, studied all adult PTA recipients from January 1, 1990, to September 1, 2008. Of 1,597 PTA recipients, 207 (13%) developed ESRD after PTA. Those with ESRD had a threefold increase in mortality versus those without [66].

Boggi et al., in a single-center study of 71 PTA recipients reported actual patient and pancreas survival rates at 5 years of 98.6% and 73.2%, respectively. In respect to native kidney function, they showed that proteinuria (24 hours) decreased significantly after transplantation. Only one patient developed end-stage renal disease. In the 51 patients with sustained pancreas graft function, kidney function (serum creatinine and glomerular filtration rate) decreased over time with a slower decline in recipients with pretransplant glomerular filtration rate less than 90 mL/min [67].

PTA vs. Islet Transplant Alone (ITA)

Regarding outcomes and quality of life, PTA and ITA have been compared and special emphasis is frequently placed on the fact that ITA is less invasive. [3,68] Even if funding for ITA were to be provided in the United States, both types of transplants are not mutually exclusive but, rather, complementary.

The results of islet transplants have undoubtedly improved over the past decade especially in patients with a low BMI and low insulin requirements. However, overall islet graft function (specifically, long-term function) still trails overall pancreas graft function. In addition, only one donor organ is required for a successful PTA; in contrast, several (and up to four) donor pancreases-with the risk of considerable sensitization to allo-antigens-have been used for a single islet recipient. But despite multiple infusions, Maffi et al. reported a higher rate of insulin independence in PTA recipients (75%) than in ITA recipients (59%) [68].

It is noteworthy that the primary end-point for National Institutes of Health (NIH)-sponsored phase 3, prospective, islet transplant trials is not insulin independence; instead, the primary end-point is reduction in the incidence and severity of hypoglycemic events which usually goes along with a reduction in exogenous insulin requirements, and an amelioration of HbA1c levels [69,70]. Also, the use of the term "insulin-independence" after islet transplantation has been criticized due to the use of "relaxed glycemic targets for that definition" [71]. A similar, possibly even less favorable impact of ITA (vs. PTA) on native kidney function due to the more aggressive immunosuppressive regimen used in ITA recipients has been reported by different investigators [68,69]: ITA recipients in the NIH-sponsored Phase 3 trial saw a decline in GFR from 102 mL/min/1.73m^2 pretransplant (baseline) to 82 mL/min/1.73m^2 at 2 years posttransplant [69,71].

Ultimately, the choice is the patient's: to undergo a minimally invasive procedure with a significantly lower chance of becoming insulin independent or an invasive procedure with a significantly higher chance of staying insulin-independent long-term.

PTA Survival Benefit and Quality of Life

Rana et al. showed that during a 25-year period (September 1, 1987, through December 31, 2012) solitary pancreas transplants saved 14,903 life-years [4].

Scalea et al. assessed the quality of life for 32 PTA recipients with (n=18) or without (n=14) graft function. Self-reported health scores were better (2.1 vs 3.0) for those with functioning pancreata vs those with a non-functional pancreas (p = 0.036). Significant hypoglycemia was reported in 2 of 18 with a functional transplant vs 9 of 14 patients with a failed transplant (p = 0.003). Daily frustration with blood sugar affecting quality of life was significantly higher for patients with non-functional pancreas grafts (p < 0.001) [72].

In addition, most PTA recipients believe that managing immunosuppression is easier and more satisfactory than repeated daily glucose measurements and insulin injections (and, even more important, than the constant worry about pronounced hypoglycemia). [2,38,73-76].

The Future of PTA

As stated in the introduction, "pre-emptive" PTA transplantation – i.e., before the development of ESRD- would benefit insulin-dependent, non-uremic patients the most as it can prevent, halt or even reverse the development or progression of secondary diabetic complications. PTA transplantation at an early stage in the manifestation of the disease not only makes sense from a preventive medicine point of view, but also for social considerations. A change of pancreas transplantation from uremic (SPK) to non-uremic (PTA) diabetic patients would allow more non-diabetic patients to receive a life-saving kidney transplant.

This strategy implies that PTAs would be performed in young(er) patients. Even with much progress, the rejection rate of all pancreas transplant recipients is still the highest in the 15-29 years of age group and in the PTA category (Figure 13) but the differences between the age groups are vanishing (p=0.21). Unfortunately, over the past decades, little progress has been made in detecting pancreas rejection early due to the lack of efficient rejection markers. In contrast to SPK recipients, serum creatinine monitoring of a simultaneously transplanted kidney – which usually rejects first – is not available for PTA recipients and current serum markers for pancreas rejection have mostly proven to be late and unreliable. The pancreas transplant community must make the same efforts as have been made in kidney transplantation to develop strategies for immune monitoring that will allow to detect pancreas rejection early and non-invasively. The development of novel markers such as (deceased donor) cell free DNA is a new approach to detect rejection episodes very early and improve graft survival due to prompt intervention [77]. If these efforts are successful, PTA will become the treatment of choice for patients with brittle diabetes (hypoglycemia unawareness) and before the development or progression of secondary complications. [78].

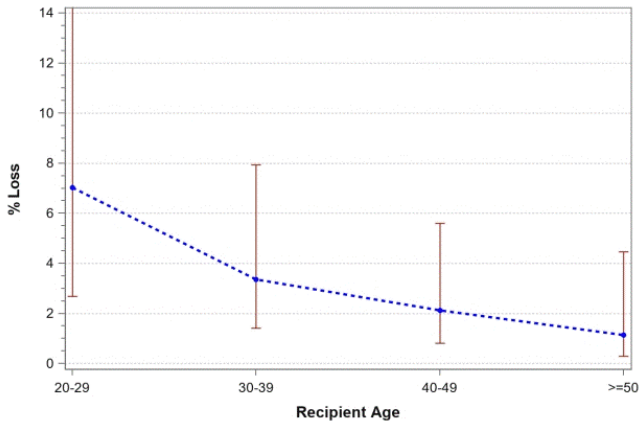

Figure 13: 2-year PTA Immunological Graft Loss by recipient age for primary deceased donor PTAs performed between 1/1/2011 and 12/31/2020.

References

1. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nat Rev Endocrinol. 2013; 9(9): 555-562.
2. Gruessner RW, Sutherland DE, Kandaswamy R, Gruessner AC. Over 500 solitary pancreas transplants in nonuremic patients with brittle diabetes mellitus. Transplantation. 2008; 85(1): 42-47.
3. Gruessner RWG, Gruessner AC. Pancreas transplant alone: a procedure coming of age. Diabetes Care. 2013; 36(8): 2440-2447.
4. Rana A, Gruessner A, Agopian VG, Khalpey Z, et al. Survival benefit of solid-organ transplant in the United States. JAMA Surg. 2015; 150(3): 252-259.
5. https://www.diabetesresearch.org/file/national-diabetes-statistics-report-2020.pdf. Accessed February 19, 2020.
6. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993; 329(14): 977-986.
7. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group; Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med. 2000; 342(6): 381-389.
8. Nathan DM, DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014; 37(1): 9-16.
9. Nathan DM. Realising the long-term promise of insulin therapy: the DCCT/EDIC study. Diabetologia. 2021; 64(5): 1049-1058.
10. Gubitosi-Klug RA, Braffett BH, White NH, Sherwin RS, Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk of Severe Hypoglycemia in Type 1 Diabetes Over 30 Years of Follow-up in the DCCT/EDIC Study. Diabetes Care. 2017; 40(8): 1010-1016.
11. https://www.diabetes.co.uk/brittle-diabetes.html. Accessed February 19, 2020.
12. Hirsch IB, Gaudiani LM. A new look at brittle diabetes. J Diabetes Complications. 2021; 35(1): 107646.
13. Martín-Timón I, del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World J Diabetes. 2015; 6(7): 912-926.

14. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, et al. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care. 2012; 35(9): 1897-1900.

15. Cryer PE. Severe Hypoglycemia Predicts Mortality in Diabetes. Diabetes Care. 2012; 35(9): 1814-1816.

16. Robertson P, Davis C, Larsen J, Stratta R, Sutherland DE; American Diabetes Association. Pancreas transplantation in type 1 diabetes. Diabetes Care. 2004; 27(Suppl 1): S105.

17. Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 Diabetes Sourcebook Authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014; 37(7): 2034-2054.

18. Sa JR, Alvarenga MA, Rangel EB, Melaragno CS, Gonzalez AM, Linhares MM, et al. Extreme subcutaneous, intramuscular and inhaled insulin resistance treated by pancreas transplantation alone. Am J Transplant. 2010; 10(1): 184-188.

19. Fridell JA, Vianna R, Kwo PY, Howenstine M, Sannuti A, Molleston JP, Pescovitz MD, et al. Simultaneous liver and pancreas transplantation in patients with cystic fibrosis. Transplant Proc. 2005; 37(8): 3567-3569.

20. Fridell JA, Wozniak TC, Powelson JA, Reynolds JM. Simultaneous bilateral lung and pancreas transplantation in recipient with cystic fibrosis. Transplant Proc. 2008; 40(2): 494-497.

21. Bandsma RHJ, Bozic MA, Fridell JA, Crull MH, Molleston J, Avitzur Y, et al. Simultaneous liver-pancreas transplantation for cystic fibrosis-related liver disease: a multicenter experience. J Cyst Fibros. 2014; 13(4): 471-477.

22. Gruessner RW, Manivel C, Dunn DL, Sutherland DE. Pancreaticoduodenal transplantation with enteric drainage following native total pancreatectomy for chronic pancreatitis: a case report. Pancreas. 1991; 6(4): 479-488.

23. Gruessner RW, Sutherland DE, Dunn DL, Najarian JS, Jie T, Hering BJ, et al. Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. J Am Coll Surg. 2004; 198(4): 559-567.

24. Gruessner RW, Sutherland DE, Drangstveit MB, Kandaswamy R, Gruessner AC. Pancreas allotransplants in patients with a previous total pancreatectomy for chronic pancreatitis. J Am Coll Surg. 2008; 206(3): 458-465.

25. Mehrabi A, Golriz M, Adili-Aghdam F, Hafezi M, Ashrafi M, Morath C, et al. Expanding the indications of pancreas transplantation alone. Pancreas. 2014; 43(8): 1190-1193.

26. Gruessner RW, Sutherland DE, Gruessner AC. Mortality assessment for pancreas transplants. Am J Transplant. 2004; 4(12): 2018-2026.

27. Gruessner RW, Gruessner AC. Pancreas After Islet Transplantation: A First Report of the International Pancreas Transplant Registry. Am J Transplant. 2016; 16(2): 688-693.

28. Genzini T, Marchini GS, Chang AJ, Antunes I, Hayashi A, Abensur H, et al. Influence of pancreas transplantation alone on native renal function. Transplant Proc. 2006; 38(6): 1939-1940.

29. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 2006; 355(13): 1318-1330.

30. Shin S, Jung CH, Choi JY, Kwon HW, Jung JH, Kim YH, et al. Long-term effects of pancreas transplant alone on nephropathy in type 1 diabetic patients with optimal renal function. PLoS One. 2018; 13(1): e0191421.

31. Gruessner AC. IPTR analysis. Personal communication. June 28, 2020.

32. Niederhaus SV. Pancreas transplant alone. Curr Opin Organ Transplant. 2015; 20(1): 115-120.

33. Wang YL, Stevens RB, Fioretto P, Lokeh A, Kunjummen D, Gruessner A, et al. Correlation of preoperative renal function and identification of risk factors for eventual native renal failure in cyclosporine-treated nonuremic diabetic recipient of pancreas transplants alone. Transplant Proc. 1993; 25(1 Pt 2): 1291-1292.

34. Scalea JR, Butler CC, Munivenkatappa RB, Nogueira JM, Campos L, Haririan A, et al. Pancreas transplant alone as an independent risk factor for the development of renal failure: a retrospective study. Transplantation. 2008; 86(12): 1789-1794.

35. Smail N, Paraskevas S, Tan X, Metrakos P, Cantarovich M. Renal function in recipients of pancreas transplant alone. Curr Opin Organ Transplant. 2012; 17(1): 73-79.

36. Kim SJ, Smail N, Paraskevas S, Schiff J, Cantarovich M. Kidney function before pancreas transplant alone predicts subsequent risk of end-stage renal disease. Transplantation. 2014; 97(6): 675-680.

37. Le Dinh H, Deroover A, Coimbra C, Weekers L, Léonet J, Meurisse M, et al. Evolution of native kidney function after pancreas transplantation alone. Transplant Proc. 2012; 44(9): 2829-2833.

38. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, et al. Results of pancreas transplantation alone with special attention to native kidney function and proteinuria in type 1 diabetes patients. Rev Diabet Stud. 2011; 8(2): 259-267.

39. Chatzizacharias NA, Vaidya A, Sinha S, Sharples E, Smith R, Jones G, et al. Risk analysis for deterioration of renal function after pancreas alone transplant. Clin Transplant. 2012; 26(3): 387-392.

40. Kandula P, Fridell J, Taber TE, Sharfuddin A, Yaqub MS, Phillips CL, et al. Impact of tacrolimus-sirolimus maintenance immunosuppression on proteinuria and kidney function in pancreas transplant alone recipients. Transplantation. 2012; 94(9): 940-946.

41. Fioretto P, Mauer SM, Bilous RW, Goetz FC, Sutherland DE, Steffes MW. Effects of pancreas transplantation on glomerular structure in insulin-dependent diabetic patients with their own kidneys. Lancet. 1993; 342(8881): 1193-1196.

42. Fioretto P, Mauer M. Reversal of diabetic nephropathy: lessons from pancreas transplantation. J Nephrol. 2012; 25(1): 13-18.

43. Mangus RS, Powelson J, Kinsella SB, Farar DT, Creal CA, Fridell JA. Pretransplant coronary artery disease associated with worse clinical outcomes in pancreas transplantation. Clin Transplant. 2013; 27(4): E442-E447.

44. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. NEJM. 2004; 351(13): 1296-1305.

45. Gruessner AC, Gruessner RWG. Pancreas transplantation for the patients with type 1 and type 2 diabetes mellitus in the United States: A registry report. Gastroenterol Clin N Am. 2018; 47(2): 417-441.

46. Kim J, Schulman-Marcus J, Watkins AC, Feldman DN, Swaminathan R, Lee JB, et al. In-hospital cardiovascular complications after pancreas transplantation in the United States from 2003-2012. Am j Cardiol. 2017; 120(4): 682-687.

47. Occhipinti M, Rondinini L, Mariotti R, Vistoli F, Baronti W, Barsotti M, et al. Amelioration of cardiac morphology and function in type 1 diabetic patients with sustained success of pancreas transplant alone. Diabetes Care. 2014; 37(8): e171-e172.

Citation: Gruessner RWG and Gruessner AC. Pancreas Transplantation Alone for Brittle Diabetes Mellitus. ES J Case Rep. 2023; 4(2): 1044.

48. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, et al. Long-term (5 years) efficacy and safety of pancreas transplantation alone in type 1 diabetic patients. Transplantation. 2012; 93(8): 842-846.

49. Dean PG, Kudva YC, Stegall MD. Longterm benefits of pancreas transplantation. Curr Opin Organ Transplant. 2008; 13(1): 85-90.

50. Secrest AM, Becker DJ, Kelsey SF, LaPorte RE, Orchard TJ. All-cause mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes: the Allegheny County type 1 diabetes registry. Diabetes Care. 2010; 33(12): 2573-2579.

51. Gruessner RW, Burke GW, Stratta R, Sollinger H, Benedetti E, Marsh C, et al. A multicenter analysis of the first experience with FK506 for induction and rescue therapy after pancreas transplantation. Transplantation. 1996; 61(2): 261-273.

52. Gruessner RW, Sutherland DE, Drangstveit MB, Troppmann C, Gruessner AC. Use of FK 506 in pancreas transplantation. Transpl Int. 1996; 9(Suppl 1): S251-S257.

53. Gruessner RW. Tacrolimus in pancreas transplantation: a multicenter analysis. Tacrolimus Pancreas Transplant Study Group. Clin Transplant. 1997; 11(4): 299-312.

54. Gruessner RW, Sutherland DE, Drangstveit MB, West M, Gruessner AC. Mycophenolate mofetil and tacrolimus for induction and maintenance therapy after pancreas transplantation. Transplant Proc. 1998; 30(2): 518-520.

55. Gruessner RW, Bartlett ST, Burke GW, Stock PG. Suggested guidelines for the use of tacrolimus in pancreas/kidney transplantation. Clin Transplant. 1998; 12(3): 260-262.

56. Odorico JS, Pirsch JD, Knechtle SJ, D'Alessandro AM, Sollinger HW. A study comparing mycophenolate mofetil to azathioprine in simultaneous pancreas-kidney transplantation. Transplantation. 1998; 66(12): 1751-1759.

57. Gruessner RW, Sutherland DE, Drangstveit MB, Wrenshall L, Humar A, Gruessner AC. Mycophenolate mofetil in pancreas transplantation. Transplantation. 1998; 66(3): 318-323.

58. Stratta RJ, Farney AC, Orlando G, Farooq U, Al-Shraideh Y, Rogers J. Similar results with solitary pancreas transplantation compared with simultaneous pancreas-kidney transplantation in the new millennium. Transplant Proc. 2014; 46(6): 1924-1927.

59. Gruessner RW, Dunn DL, Tzardis PJ, Tomadze G, Adamec M, Moudry-Munns K, et al. An immunological comparison of pancreas transplants alone in nonuremic patients versus simultaneous pancreas/kidney transplants in uremic diabetic patients. Transplant Proc. 1990; 22(4): 1581.

60. Sutherland DE, Gruessner RG, Humar A, Kandaswamy R, Najarian JS, Dunn DL, et al. Pretransplant immunosuppression for pancreas transplants alone in nonuremic diabetic recipients. Transplant Proc. 2001; 33(1-2): 1656-1658.

61. Fridell JA, Mangus RS, Chen JM, Taber TE, Cabrales AE, Sharfuddin AA, et al. Steroid-free three-drug maintenance regimen for pancreas transplant alone: Comparison of induction with rabbit antithymocyte globulin +/- rituximab. Am J Transplant. 2018; 18(12): 3000-3006.

62. Gruessner RW, Nakhleh R, Tzardis P, Platt JL, Schechner R, Gruessner A, et al. Rejection in single versus combined pancreas and kidney transplantation in pigs. Transplantation. 1993; 56(5): 1053-1062.

63. Vrakas G, Arantes RM, Gerlach U, Reddy S, Friend P, Vaidya A. Solitary pancreas transplantation: a review of the UK experience over a period of 10 yr. Clin Transplant. 2015; 29(12): 1195-1202.

64. Porubsky M, Gruessner AC, Rana A, Jie T, Gruessner RW. Excellent outcomes can be achieved in young pancreas transplant alone recipients by addition of sirolimus to maintenance immunosuppression regimen. Transplant Proc. 2014; 46(6): 1932-1935.

65. Nata N, Huang E, Kamgar M, Leeaphorn N, Mehrnia A, Kalantar-Zadeh K, et al. Kidney failure requiring kidney transplantation after pancreas transplant alone. Clin Transpl. 2013: 45-52.

66. Singh SK, Kim SJ, Smail N, Schiff J, Paraskevas S, Cantarovich M. Outcomes of Recipients with Pancreas Transplant Alone Who Develop End-Stage Renal Disease. Am J Transplant. 2016; 16(2): 535-540.

67. Boggi U, Vistoli F, Amorese G, Giannarelli R, Coppelli A, Mariotti R, et al. Long-term (5 years) efficacy and safety of pancreas transplantation alone in type 1 diabetic patients. Transplantation. 2012; 93(8): 842-846.

68. Maffi P, Secchi A. Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice? Curr Diab Rep. 2019; 19(5): 26.

69. Hering BJ, Clarke WR, Bridges ND, Eggerman TL, Alejandro R, Bellin MD, et al.; Clinical Islet Transplantation Consortium. Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia. Diabetes Care. 2016; 39(7): 1230-1240.

70. Markmann JF, Rickels MR, Eggerman TL, Bridges ND, Lafontant DE, Qidwai J, et al.; Clinical Islet Transplantation Consortium. Phase 3 Trial of Human Islet-after-Kidney Transplantation in Type 1 Diabetes. Am J Transplant. 2021; 21(4): 1477-1492.

71. Harlan DM. Islet Transplantation for Hypoglycemia Unawareness/ Severe Hypoglycemia: Caveat Emptor. Diabetes Care. 2016; 39(7): 1072-1074.

72. Scalea JR, Pettinato L, Fiscella B, Bartosic A, Piedmonte A, Paran J, et al. Successful pancreas transplantation alone is associated with excellent self-identified health score and glucose control: A retrospective study from a high-volume center in the United States. Clin Transplant. 2018; 32(2): 10.

73. Giannarelli R, Coppelli A, Sartini MS, Del Chiaro M, Vistoli F, Rizzo G, et al. Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients. Diabetologia. 2006; 49(12): 2977-2982.

74. Coppelli A, Giannarelli R, Mariotti R, Rondinini L, Fossati N, Vistoli F, et al. Pancreas transplant alone determines early improvement of cardiovascular risk factors and cardiac function in type 1 diabetic patients. Transplantation. 2003; 76(6): 974-976.

75. Mazur MJ, Rea DJ, Griffin MD, Larson TS, Prieto M, Gloor JM, et al. Decline in native renal function early after bladder-drained pancreas transplantation alone. Transplantation 2004; 77(6): 844-849.

76. Lee TC, Barshes NR, Agee EE, O'Mahoney CA, Brunicardi FC, Goss JA. The effect of whole organ pancreas transplantation and PIT on diabetic complications. Curr Diab Rep. 2006; 6(4): 323-327.

77. Riad S, Sarumi H, Kandaswamy R. Donor Derived Cell-Free DNA (dd-cfDNA) in Pancreas Transplant Recipients. Am J Transplant. 2021; 21(suppl 3).

78. Gruessner RWG, Gruessner AC. (2023). Pancreas Transplantation Alone. In: Transplantation of the Pancreas. 2nd Edition. Editors: Gruessner RWG, Gruessner AC. Cham: Springer International Publishing. Chapter 24. pp. 291-306.

Citation: Gruessner RWG and Gruessner AC. Pancreas Transplantation Alone for Brittle Diabetes Mellitus. ES J Case Rep. 2023; 4(2): 1044.