“The Recent Decline of Pancreas Transplantation: Causes and Conclusions,” Independent Research Project, Presented by Rhea Sharma

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The Recent Decline of Pancreas Transplantation: Causes and Conclusions

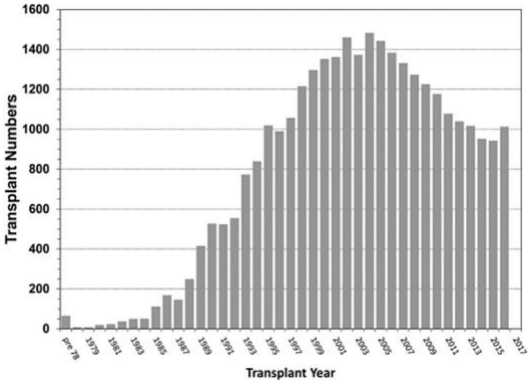
Abstract:

Data reported to the International Pancreas Transplant Registry (IPTR) and the United Network for Organ Sharing (UNOS) indicate that since 2004, transplant procedures have steadily declined, plateauing at approximately 1,000 reported transplants in 2016. The purpose of this research study is to analyze the current rate of pancreas transplantation and examine reasons behind its diminishing numbers. The research was conducted through a literature review, using PubMed and Medline searches and analyses of IPTR and UNOS data and literature. Results indicate that the declining rate is multifactorial: 1) lack of a primary referral source, 2) lack of endorsement for Pancreas After Kidney (PAK) and Pancreas Transplant Alone (PTA) transplants, 3) developments in other areas of treatment (insulin pumps, diabetes management, artificial organs, islet cell transplantation), and 4) donor considerations (low organ utilization, high organ quality selectivity, less recovery teams). Surgical outcomes—including patient survival, graft function, technical failure, immunologic graft failure—have greatly improved over the last 30 years. Outcomes in Type II recipients are improving: patient survival rates at 1 year improved from 91.4% (1995-2001) to 97.6% (2009-2015); pancreas graft survival rates at 1 year improved from 80.2% (1995-2001) to 89.0% (2009-2015). Our findings suggest that restrictive UNOS guidelines should be expanded to include more Type II recipients. Using the new paradigm regarding T2DM recipients, centers should more specifically personalize transplant recipient decisions. Therefore, efforts should be made to minimize the decline in solitary pancreas transplantation for eligible patients by expanding donor criteria, increasing donor pancreas utilization rates, and expanding endorsement/referral systems for PTA and PAK.

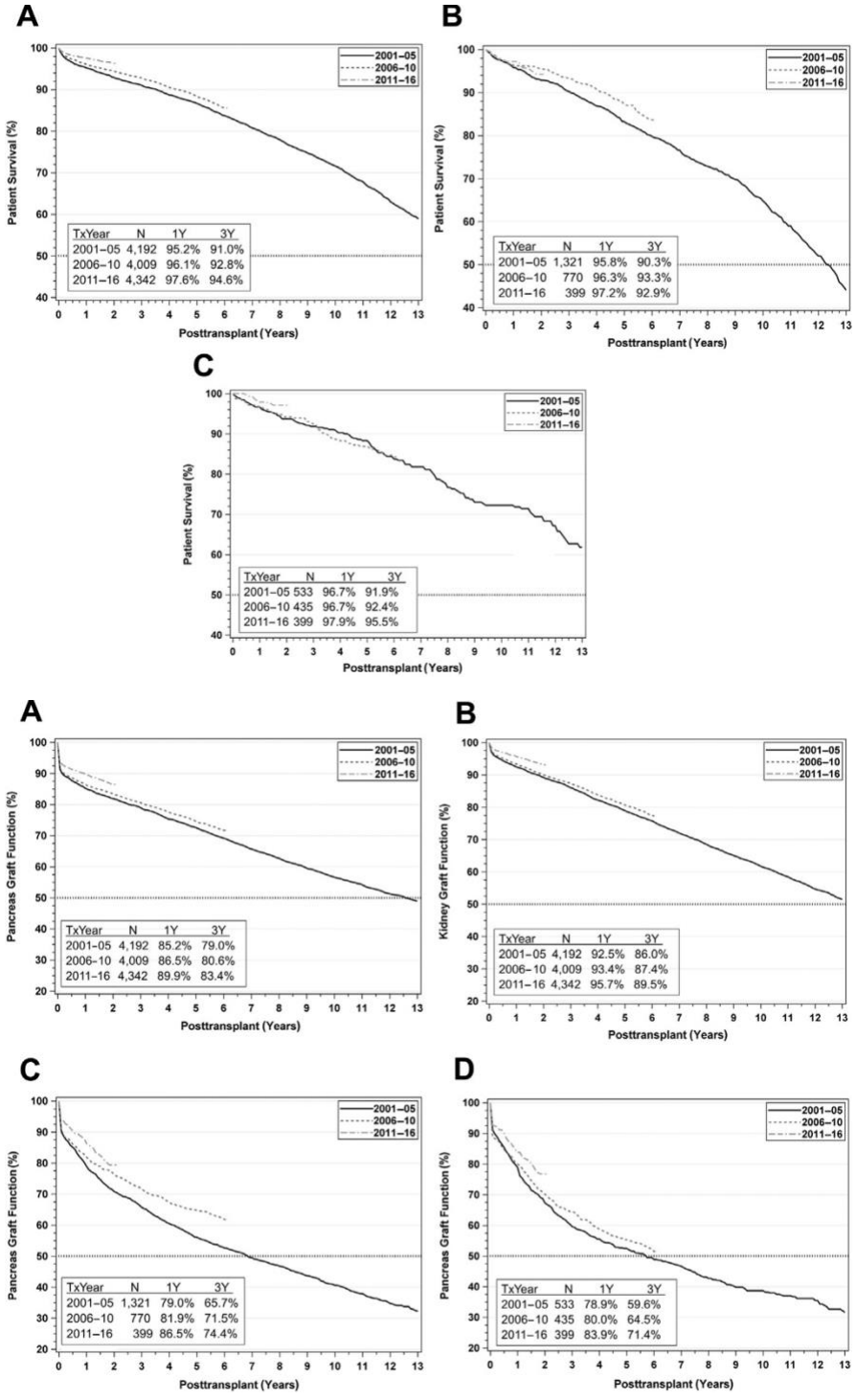
(1) Literature review on PTx and Decline in Numbers

Introduction/Overview:

Pancreas transplants currently serve as a treatment option for patients with diabetes. The criteria for pancreas transplant is described by the American Diabetes Association as 1: patients with ESRD who either plan or have had a kidney transplant and 2: patients with history of frequent, sever, acute metabolic complications yet without abundant renal disease/dysfunction [1]. There are three main types of pancreas transplant, including simultaneous pancreas and kidney transplant (SPK) usually from a deceased donor, a pancreas transplant following a kidney transplant from a living donor (PAK), and a pancreas transplant alone (PTA), with the latter two being referred to as solitary pancreas transplants. Using data reported to IPTR and UNOS from 1966 to 2016, it is clear that transplant numbers have continually increased until 2004. Since then, pancreas transplant numbers have steadily declined, evening out at around only 1000 reported transplants in 2016. [5, 7]



Inherency of the Issue:



This decline is troubling as it correlates with positive statistics on improving patient survival and graft function rates. The rate at which pancreas transplants are being performed is decreasing, despite such promising results. For SPK, patient survival at 1-year improved from 95.2% in 2001-2005 to 97.6% in 2011-2016. For PAK, patient survival at 1-year improved from 95.8% in 2001-2005 to 97.2% in 2011-2016. For PTA, patient survival at 1-year improved from 96.7% in 2001-2005 to 97.9% in 2011-2016.

Graft function rates have similar promising results. For SPK, pancreas graft function at 1-year increased from 85.2% in 2001-2005 to 89.9% in 2011-2016. For PAK, pancreas graft function at 1-year increased from 79.0% in 2001-2005 to 86.5% in 2011-2016. For PTA, pancreas graft function increased from 78.9% in 2001-2005 to 83.9% in 2011-2016 [5, 7]. Regarding PAK transplants, kidney graft function also benefits from the addition of the pancreas transplant. PAK recipients who receive a pancreas transplant within 2 months and 1 year after the kidney transplant show significantly improved long-term kidney function [4].

Possible Contributing Factors: (Stratta 2016 – A Decade of Decline and Stratta 2016 – An Alarming Crisis in Confidence)

Lack of a Primary Referral Source

Most diabetologists, endocrinologists, and family medicine practioners are not referring patients and potential candidates to pancreas transplant. Most pancreas transplant referrals are from nephrologists, and patients with diabetes and renal disease are referred to a kidney transplant center. This contributes to the low amount of ideal and necessary pancreas transplants that must be performed. Other treatment options like diabetes management, artificial organs, insulin pumps, or islet cell transplant seem to be more popular areas of interest [2, 3].

Lack of endorsement of PTA by ADA

Islet cell transplantation is a more recent and popular choice for patients to consider, in direct competition with PTA and is considered to be more favorable on account of being less invasive [2, 3]. Although, islet cell transplantation still has not garnered the same outcomes reliability as PTA transplant. Nevertheless, such up and coming diabetes management options seem to overshadow enthusiasm for PTA [5, 6].

PAK and PTA are not as favorable

Studies based on UNOS database conclude that patients with solitary pancreas transplants have a higher mortality risk than those staying on the waiting list and receiving treatment/therapy, which drives patients away from solitary pancreas transplant. Typically, SPK transplant would be preferred, or patients would remain on conventional medical therapy. A study from the University of Minnesota concluded based on outcomes in patients with PAK transplant that renal function improved significantly, while metabolic issues declined. It is the decline in PAK transplant which renders the seeming decline in pancreas transplant, although it is glaringly evident that pancreas transplant is extremely favorable in improving renal function after a kidney transplant [2, 3].

Donor Considerations

Donor pancreas utilization is currently extremely low, as only 13% of donors actually provide a pancreas which is transplanted. Some of this 13% is sent to islet cell recovery, where islet cell transplantation is not guaranteed.

Despite numbers, quality of donor pancreas also contributes to low utilization, particularly with the development of the pancreas donor risk index, PDRI. The PDRI takes into account risk factors such as donor age, BMI, and cold ischemia time to estimate the graft survival rate, post-transplant. However, the reliability of such calculations is not yet validated.

Additionally, recovery teams seem to be declining in experience regarding donor management and anatomy preservation, resulting in discard of the pancreas.

Another factor is that the number of pancreas transplant surgeons is significantly lower than the number of kidney and liver surgeons, contributing to the low utilization of donor pancreas [2, 3].

Conclusions:

Although evidence proves that pancreas transplant remains of great benefit for specific populations who can benefit from this type of diabetes management, the rate at which it is being performed is declining due to a multitude of factors. A greater emphasis should be placed on expanding donor criteria, increasing donor pancreas utilization rates (through expanding recipient selection regarding older ages and non-type 1 diabetics), and expanding endorsement and referral systems towards solitary pancreas transplant.

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(2) Surgical Outcomes

Introduction/Overview:

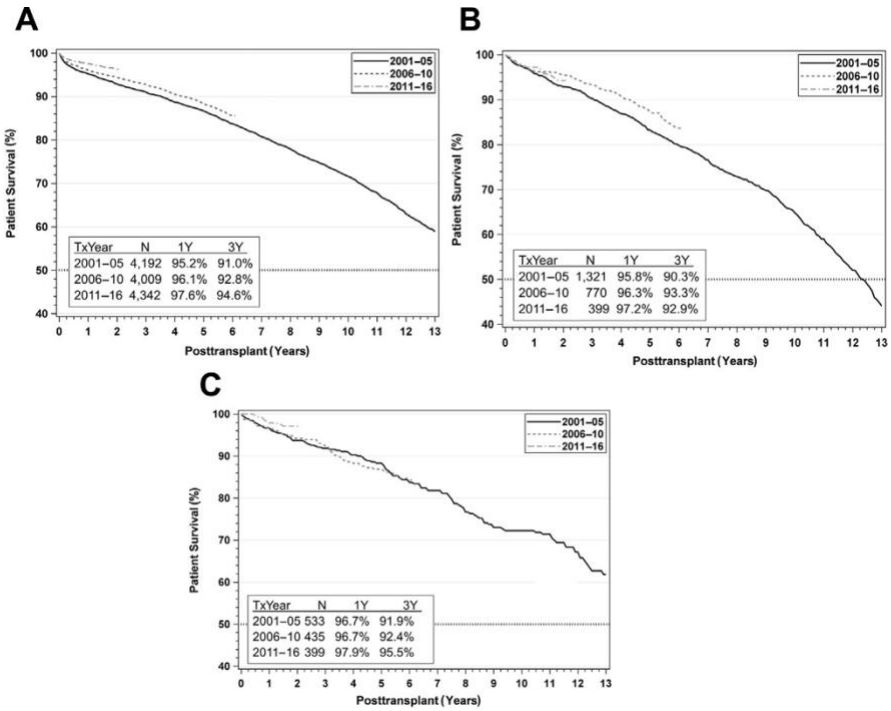
Diabetes mellitus continues to be an ever-increasing and ongoing issue in the US, consuming approximately 30.3 million people in the US. Diabetes is currently the seventh leading cause of death in the US, also being responsible for terminal end stage renal disease. [2]. Although other options, such as diabetes management and insulin pumps, the only proven method to restore long-term normoglycemic control is a pancreas transplant. Recent analyses of data provided through the International Pancreas Transplant Registry (IPTR) and the United Network for Organ Sharing (UNOS) indicate that long-term surgical outcomes are positive and continually improving over the last 30 years. [4]

Patient Survival:

Between 1984 and 2009, 5-year patient survival has increased significantly. For SPK, total 5-year patient survival has increased from 63% in 1984/1985 to almost 90% in 2008/2009. For PAK, total 5-year survival increased from 73% in 1984/1985 to 87% in 2008/2009. PTA holds the highest 5-year patient survival rate, reaching 90% in 2008/2009.

10-year patient survival rates show similar trends over time. For the SPK category, there was a steady improvement in the 10-year patient survival, increasing from 46.7% in 1984/1985 to 76.1% in 2004/2005. However, there was an initial decline in 10-year patient survival rates within the solitary transplant categories, PAK and PTA. This peculiar decline was present from 1984/1985 to 1994/1995, and from 1995 to 2004/2005, rates increased. Reasons for this interesting decline currently remain unknown. Notably, all categories indicate a 10-year patient survival rate above 70% in 2004/2005.

[4]



[2]

Trends from recent years show a similar increase in the rates of patient survival. For SPK, patient survival at 1-year improved from 95.2% in 2001-2005 to 97.6% in 2011-2016. For PAK, patient survival at 1-year improved from 95.8% in 2001-2005 to 97.2% in 2011-2016. For PTA, patient survival at 1-year improved from 96.7% in 2001-2005 to 97.9% in 2011-2016. [2]

Typically, posttransplant cardiocerebrovascular events and infections were reasons for patient death in the first 3 months. Reasons for patient death in the next 9 months changed to infections and unknown causes. Primary reasons for patient death in the next 5 years changed to back cardiocerebrovascular events. [2]

Graft Function:

From 1984/1985 to 2008/2009, there was a continuous increase in 5-year graft function rates in all 3 categories (SPK, PAK, PTA). *Graft function rates of both kidney and pancreas were the highest in SPK.* For SPK, 5-year pancreas graft function reached 73% in 2008/2009 and 5-year kidney graft function reached 81% in 2008/2009. For PAK, 5-year pancreas graft function reached 64% in 2008/2009. For PTA, 5-year pancreas graft function reached 53% in 2008/2009. [4]

Notably, for the 2004/2005 group, 40% of PAK and PTA pancreas grafts and over 56% of SPK pancreas grafts were functioning at 10-year post transplant. [4]

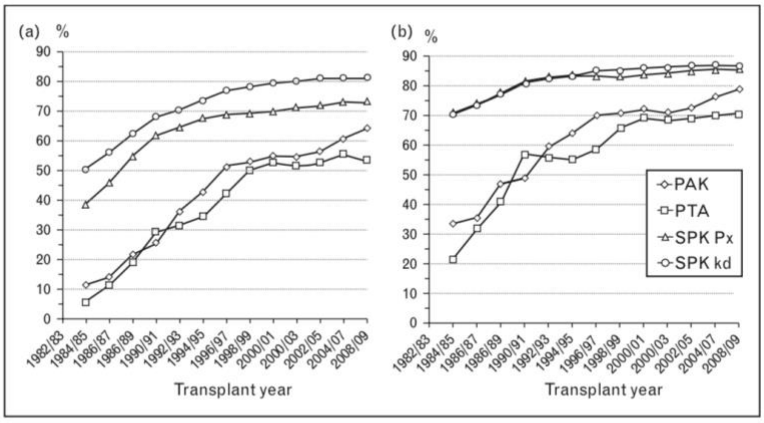


FIGURE 3. Rates of 5-year pancreas and pancreas/kidney graft function after primary deceased donor pancreas transplant performed between 1 January 1984 and 31 December 2009. (a) All recipients included. (b) Recipients with graft function for at least 1 year.

[4]

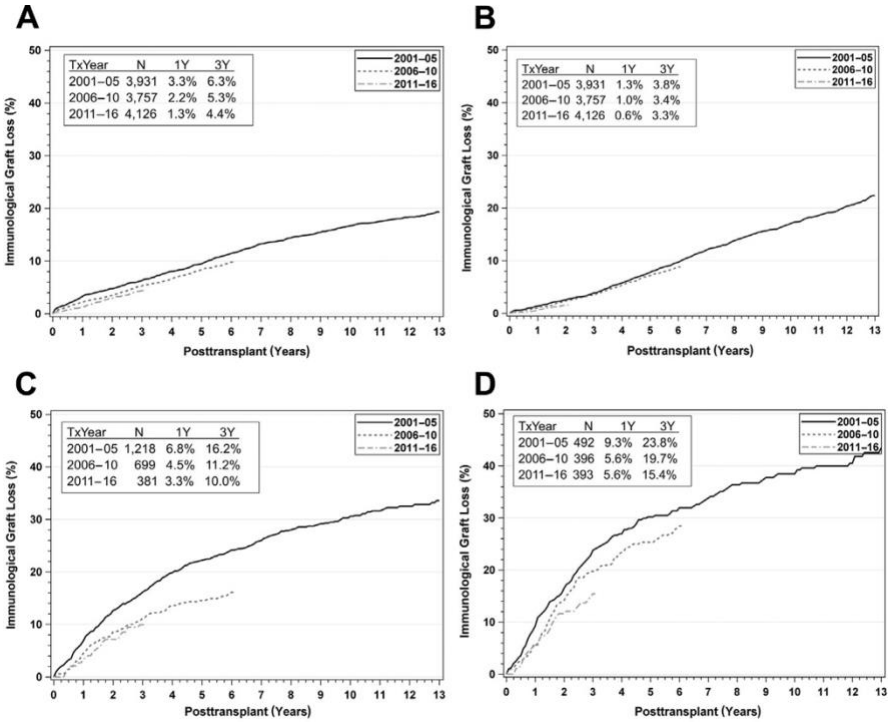
The progression of recent years has also shown an increase in the rate of graft function at 1-year. For SPK, pancreas graft function at 1-year increased from 85.2% in 2001-2005 to 89.9% in 2011-2016. For PAK, pancreas graft function at 1-year increased from 79.0% in 2001-2005 to 86.5% in 2011-2016. For PTA, pancreas graft function increased from 78.9% in 2001-2005 to 83.9% in 2011-2016. For all types of transplant, the main risk factor seems to be donor age. Specifically for SPK, risk factors also include African American race, high BMI, and longer preservation time. [2]

Regarding PAK transplants, kidney graft function also benefits from the addition of the pancreas transplant. PAK recipients who receive a pancreas transplant within 2 months and 1 year after the kidney transplant show significantly improved long-term kidney function [1].

Technical Failures:

In the periods of 2001-2005 to 2011-2016, technical failure of the pancreas graft remained a large issue for all the categories of transplant. Pancreas graft thrombosis was identified as the major cause of technical failures [2]. Other risk factors for SPK were donor age older than 30 years, an obese recipient, and a recipient on dialysis. For PAK, other risk factors were donor age older than 30 years and low center volume. For PTA, another risk factor for technical failure was the increasing duration of transplant [2]. Something noteworthy is that immunologic losses could have been falsely reported as technical losses, as maintenance immunosuppression was noted as a risk factor [2].

Immunologic Graft Loss:



Immunologic graft loss by transplant year for (A) SPK pancreas, (B) SPK kidney, (C) PAK, (D) PTA.

[2]

Immunologic graft loss for SPK improved for pancreas but not for kidney. Immunologic graft loss at 3 years for SPK pancreas improved from 6.3% in 2001-2005 to 4.4% in 2011-2016, however for kidney, the improvement was only seen from 3.8% to 3.3%. African Americans and recipients with an older donor had a higher risk of immunologic graft loss. Although, HLA mismatching volume at the center did not

affect immunologic graft loss. PAK shows the most dramatic improvement, with immunologic graft loss at 3 years improving from 16.2% from 2001-2005 to 10.0% in 2011-2016. HLA mismatch seemed to increase the risk in recipients. PTA holds the most issues with immunologic graft loss at 3 years, but still improved from 23.8% in 2001-2005 to 15.4% in 2011-2016. Male recipients held a lower risk for graft loss [2].

Conclusion:

The analyzed time periods prove that surgical pancreas transplantation techniques and outcomes are improving. Such a trend promises future improvements in long-term patient survival rates and graft function rates. Paradoxically, the number of pancreas transplants being performed is declining. Recipient and donor selection needs to be prioritized and personalized in order to ensure that patients that can benefit from a transplant receive a transplant [3]. These analyses of the IPTR and surgical outcomes illustrate that successful transplants improve quality of life and life expectancy of patients, bmenefitting glycemic control and secondary diabetic complications [4].

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(3) How the approval of PTX in Type II Patients Has Changed the Paradigm

Introduction/Overview:

Diabetes mellitus is a spreading epidemic, with over 220 million people affected worldwide [3]. In the US, diabetes is the leading cause of ESRD, as 44% of kidney failure cases are caused by diabetes [3]. In the US, there are approximately 30.3 million people living with diabetes, with Type 2 Diabetes making up 90% of this population [2]. Pancreas transplants are a promising treatment in restoring glycemic control, with significant results in Type 1 patients [4]. However, Type 2 diabetics make up less than 10% of pancreas transplant patients. Although, studies show that Type 2 patients carefully selected (detectable C peptide, minimal comorbidities, carefully selected BMI and insulin requirement criteria) can greatly benefit from transplants in the same way as Type 1 diabetics [2, 5]. The recent approval of pancreas transplants in Type 2 patients is beginning to shift the paradigm on selecting appropriate patients. [2].

Classification of diabetes mellitus / Selection of T2DM patients:

There are two types of diabetes mellitus, Type 1 (T1DM) and Type 2 (T2DM), in which the development occurs on a range, and may overlap [2, 3]. Typically, people with T2DM are associated with the metabolic syndrome and higher preexisting cardiovascular morbidity. T1DM people do not produce insulin and typically show signs of autoimmunity – they are also diagnosed at younger ages. Both types can overlap as T1DM patients can not show autoimmunity and develop symptoms later in life, and T2DM patients could show signs of autoimmunity and develop symptoms at younger ages. Hence, it is more difficult to distinguish the two types. There are no clinical or lab tests that can reliably, validly, and consistently differentiate between the two types. [3]

The ADA and WHO have somewhat broad guidelines as to classifying T2DM based on the conditions: “onset after 40 years of age, and on of the following: weight at diagnosis and/or maximum weight more than 115% of ideal body weight, OR no consistent insulin therapy during first 2 years after diabetes diagnosis, onset from 30-39 years, no history of diabetic ketoacidosis”. Such criteria is imperfect, and family history, islet and insulin autoantibodies, and insulin requirements are factors to be noted. [2]

The UNOS has also proposed guidelines that further distort the T2DM framework. UNOS’s 2014 guidelines restrict SPK for T2DM patients with insulin-dependence, a C-peptide at least 2ng/ml and maximum allowable BMI that can fluctuate based on percentage of high C-peptide recipients on the waiting list. This ‘fluctuating’ range creates confusion about who can be listed [4]. Because the kidney is a major site of C-peptide excretion, levels can be falsely elevated in patients with kidney disease, and aren’t representative of beta cell function, hence not a significant indicator of diabetes. It becomes harder to fit patients into either Type 1 or 2, as Type 2 is a vast spectrum. The current UNOS guidelines seem to limit how many T2DM patients can receive a pancreas transplant, and BMI criteria should be expanded. In such a paradigm, the transplant centers would decide and personalize their patient selection. [2].

Treatment Options:

Traditional management of diabetes has been insulin therapy, antidiabetic agents, or behavioral treatment. These methods typically aren't able to achieve normoglycemia and organ complications typically develop. The only solutions establishing long-term normoglycemia are known to be pancreas transplantation, and more recently, islet cell transplantation. [3]

Only a minority of T2DM patients would require a pancreas transplantation. The ideal T2DM patient is considered as insulin-dependent, suffering from nephropathy, lean/low BMI, and no comorbidities. Solitary pancreas transplantation is extremely rare for T2DM, as T2DM don't typically suffer from sever hypoglycemic unawareness. The rate of SPK is increasing for T2DM patients. [2]

Typically, SPK is performed for T2DM patients as there is currently very little data for solitary pancreas transplant. SPK in such patients has typically similar posttransplant outcomes to T1DM patients – positive, consistent patient survival rate and graft function rate. [3].

T2DM patients with obesity, metabolic syndrome, cardiac disease require an alternative solution. They are less likely to receive an organ transplant, and bariatric surgery is typically a pretransplant alternative. Studies have shown that most postrenal transplant patients with bariatric surgery eventually receive a transplant. An Indiana University study demonstrates similar, positive outcomes for pancreas transplantation following bariatric surgery. [2]

PTx Outcomes in T2DM Patients:

Most data for T2DM patients is regarding SPK transplant, not enough data is available for solitary pancreas transplant. Regardless, the outcomes are promising and noninferior when compared to T1DM recipients [5]. In an IPTR study [1], pancreas transplants in T2DM patients were analyzed over 1995-2001, 2002-2008, and 2009-2015. 1514 pancreas transplants in T2DM patients were identified, being mostly SPK. In this analysis, there was an increase in SPKs for T2DM patients over the three eras, with the increase being greater than that for T1DM patients. SPK patient survival also improved, as the patient survival rates increased from 91.4% at 1-year in 1995-2001 to 97.6% at 1-year in 2009-2015. Pancreas graft survival improved from 80.2% at 1-year in 1995-2001 to 89.0% at 1-year in 2009-2015. [1]

The rate of recurrence of T2DM was rare and only due to excessive weight gain posttransplant. There was no difference or disparity in graft loss for high BMI, overweight or obese, patients when compared to normal BMI patients. Such findings suggest that the UNOS current regulations are preventing eligible recipients for an SPK, and should be reevaluated. [1, 2]

Conclusion:

Analyses have proven that outcomes for SPKs in T2DM patients have promising results, and improvements quite similar to T1DM recipient outcomes. UNOS regulations seem to lack justification for restricting patients with high C-peptide and high BMI from receiving an SPK, and such debates will continue. Solitary pancreas transplant for T2DM recipients should only occur for those with severe

metabolic disturbances and problems with exogenous insulin therapy. Using this new paradigm regarding T2DM recipients, centers should consider transplant to be valid and acceptable treatment, and decide on a personalized, case-to-case basis whether to accept a transplant patient. UNOS regulations for pancreas transplant should be reconsidered, and insulin dependent patients with ESRD should be evaluated for PTx based on predicted morbidity. Expanding the criteria can help ensure that those T2DM patients with the correct profile who can benefit from a transplant, are able to receive a transplant.

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