

Pancreas and Beta Islet Cell Transplantation - Evidence Base and Outcomes

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Abstract

From a humble experimental debut in 1966, pancreatic transplantation has undergone significant advances undoubtedly becoming the gold standard endocrine replacement therapy for diabetes in our current time. With more than 37,000 surgeries registered with the international pancreas transplantation registry (IPTR) in the year 2010, it is fair to assume that transplantation of the pancreas has become an established therapeutic modality. Of the three major types of transplantation surgeries; simultaneous pancreas and kidney transplantation (SPK) is the most commonly performed surgery, followed by pancreas after kidney transplantation (PAK), and finally pancreas transplantation alone (PTA) being the least commonly performed. For patients with contraindications to both exogenous insulin and whole pancreas transplantation; less invasive beta islet cell transplantation presents a viable therapeutic modality.

This review article aims to explore the evidential base that supports whole pancreatic and beta islet cell transplant as therapeutic modalities in diabetes mellitus, as well as describing the indications, contraindications, advantages, disadvantages and outcomes associated with these forms of treatment.

Keywords: Pancreas transplantation; Beta islet cell transplantation; Diabetes mellitus

Introduction

The first successful pancreas transplantation surgery by WD Kelly and Richard Lillehei in 1966 [1], saw the beginning of an era of a new form of endocrine replacement therapy that would greatly benefit patients suffering from labile/brittle diabetes. The surgical technique and immunosuppressive regimen used, has ever since undergone significant improvements over the decades, and currently, pancreatic transplantation is the gold standard endocrine replacement therapy for diabetes [2].

In the past 48 years, Pancreatic transplantation has evolved from being entirely experimental to becoming a well established therapeutic modality [3], with more than 37,000 surgeries worldwide, being reported to the international pancreas transplantation registry (IPTR) in the year 2010 [3]. Most of the pancreas graft recipients usually have type 1 diabetes; however, about 7.7% have type 2 diabetes [2].

Indications for pancreas transplantation

Optimal glycemic control, as was established by findings from the DCCT (Diabetes Control and Complications Trial) and the UKPDS (United Kingdom Prospective Diabetes Study) trials [4], is fundamental in the short term and long term care of diabetes mellitus patients; however, for a particular subset of patients, adequate glycemic management fails to be accomplished despite best efforts with exogenous insulin therapy. Similarly, there is also a cohort of patients who present with continuous progression of diabetes related complications despite ongoing intensive insulin therapy; while for others, frequent severe hypoglycemic episodes and hypoglycemia unawareness preclude continuation of treatment with exogenous insulin. For all these patient categories, pancreas transplantation

presents a last resort endocrine replacement therapy worthy of consideration during their management [2]. The contraindications to pancreatic transplantations are usually the general contraindications to anesthesia and surgery [2]. Age is not a contraindication; and on the contrary, older patients tend to have lower graft rejection rates than younger patients [2]. But patients older than 50 years tend to have higher rates of surgical complications [5].

Types of pancreas transplantation

There are three types of pancreas transplantation surgeries [6]. These are:

1. Simultaneous Pancreas and kidney transplantation (SPK)
2. Pancreas after kidney transplantation (PAK)
3. And Pancreas transplantation alone (PTA)

SPK: SPK transplantation accounts for 80% [6] of all pancreatic transplantations conducted, and is usually conducted in uremic diabetic patients with a GFR range of <50-60 mmol/l [7]. Both the pancreas and the kidney are often obtained from the same deceased donor; although at times a pancreas may be obtained from a deceased donor with the kidney from a living donor [2,8].

Quite occasionally both organs (segmental pancreas) may be obtained from a living donor [2,9]. "About 2% of pancreatic transplantations have been conducted with other organs, including enbloc transplantation with a liver or a lung" [2].

SPK is popular due to the benefit of achieving dual organ transplantation in patients already obligated to lifelong immunosuppression for a kidney graft; although this comes at an added surgical risk of transplanting two organ grafts in one single operation [7]. In addition to being the most cost effective form of pancreas transplantation [10], SPK's major advantage lies with lower

pancreas rejection rates, which is largely due to easier recognition of acute rejection of both organs via the concomitant rise in serum creatinine levels [2]. Long waiting times due to worldwide shortage of deceased donors presents one of the main disadvantages of SPK (due to the need for two organs simultaneously) in comparison to PAK and PTA [2]. A factor that has negatively impacted on the survival of patients placed on waiting lists [2].

PAK: PAK transplantation involves a second surgical operation where a pancreas is transplanted in diabetic patients who were prior recipients of a renal graft due to uremia [6]. The procedure accounts for 15% of all pancreatic transplantations [6], and has the advantage of an overall reduced waiting time for a kidney transplantation. This results in improved health during the subsequent future pancreatic transplantation surgery [2]. It is however important to note that transplantation of a pancreas in recipients of kidney allografts, results in transient GFR reduction by up-to 20% during the first year post surgery [11].

Also equally important is the observed progressive renal deterioration following solitary pancreas transplantation surgeries, which occurs despite resolution of diabetes related morphological lesions in native kidneys of pancreas transplanted patients. This observation has been attributed to the nephrotoxic effect of calcineurin based immunosuppressive regimens used [2].

PTA: PTA accounts for ~5% [6] of all pancreas transplantations. The recipients are usually non uremic insulin dependent patients with labile/brittle diabetes marked by frequent episodes of severe hypoglycemia or hypoglycemia unawareness [7].

Pancreas and beta islet cell transplantation: This procedure is comparatively less popular than the other categories of pancreas transplantations due to initial poorer outcomes associated with the surgical technique, as well as complications associated with the prior immunosuppressive regimen that was used [2]. However, since the introduction of calcineurin based immunosuppressive therapy (especially tacrolimus), the improved surgical outcomes and graft survival has resulted in an increase in the number of PTA's conducted, which as of December 2011 accounted for 7.7% of all US pancreas transplantations reported to the IPTR [3]. PTA is usually reserved for patients with a GFR of >80 ml/min/1.73 m², without proteinuria (or with mild stable proteinuria) [2]. But the nephrotoxic effects of cumulative calcineurin based immunosuppression, results in approximately 30% progression rate to renal failure in about 9-10 years post PTA [12,13]. Mainly as a result of the nephrotoxic effects of cumulative calcineurin based immunosuppression, PTA is usually reserved for specially selected individual cases, where the benefit outweigh the theoretical risks associated with the procedure; hence the low numbers being conducted.

Evidence

Survival and sustained function of pancreatic grafts has been demonstrated by reports from pancreas transplantation registries. For instance, according to the cumulative data collected by the IPTR from the year 2005, both PAK and SPK transplantations demonstrated remarkable outcomes. The former achieved a 5 year graft survival rate of 83%; whereas the latter attained a 5 year graft survival rate of 72% for the pancreas and 80% for the kidney, with overall 10 year survival rate of up-to 60% [14]. Unfortunately for PTA, outcomes have been marred by progressive renal decline which has been attributed to the use of calcineurin based immunosuppressive therapy. Scalea et al. [15],

for instance, while following 123 subjects who underwent PTA surgery; demonstrated a progressive decline in GFR in 107 subjects, 13 of whom eventually required renal transplantation after a mean follow up period of 4.4 years [16]. However, albeit the good graft survival observed with SPK and PAK, no randomized control trial (RCT) has been conducted to assess the long term effect of pancreas transplantation towards glycemic control, or prevention of cardiovascular complications. Current knowledge and practice has mainly been informed by data from smaller studies, which in addition to showing a survival benefit and improvement in quality of life, have also suggested improved glycemic control and benefit towards prevention of secondary diabetes complications. Tyden et al. [17] for instance, while following up a homogeneous group of diabetes mellitus patients with renal failure, demonstrated that simultaneous combined transplantation of both the pancreas and the kidney resulted in improved 10 year survival as compared to kidney.

Pancreas and beta islet cell transplantation alone. Similarly, in 2001, Ojo et al. [18] demonstrated a doubling of life expectancy following SPK transplantation as compared to kidney transplantation alone among diabetes patients with renal failure, although patients were not matched for age or morbidity. To the same regard, Speigh et al's study [19] showed improved quality of life among recipients of pancreas transplantation for whom the main indication for the procedure was hypoglycemia unawareness.

Outcomes

Glycemic control

The beneficial effects of pancreas transplantations in restoring HBA1c to normal levels, has been documented to persist even up to 10 years post transplantation [13]. When compared to intensive insulin therapy administered during the DCCT trial, pancreas transplantation resulted in HBA1c levels of 6% at 6 years in 54 subjects, versus an HBA1c of 7% with intensive insulin treatment [2,20,21]. In addition to improved glycemic control among successful transplant cases, pancreatic transplantation also results in improved hypoglycemic response, through restoration of glucagon secretion, and normalization of hepatic glucose output [2,22,23].

Retinopathy

Diabetic retinopathy poses a significant challenge in most type 1 diabetes patients, and it is estimated that approximately 75% will develop retinopathy at 10 years [2]. Pancreatic transplantation has demonstrated modest benefits towards ameliorating progression of diabetic retinopathy in the long term [19,24,25]; however, in about 10-35% of pancreas transplant patients with unstable eye disease, there has been reports of deterioration of retinopathy shortly after the surgery [2,26,27].

Additional insults stem from the calcineurin and steroid based immunosuppressive regimen which have been found to result in further deterioration of cataracts [2].

Nephropathy

Diabetic nephropathy is characterized by mesangial, glomerular basement membrane, tubular basement membrane, and interstitial matrix deposition [2] which is usually persistent in most instances; however, there are reports of improvement and even resolution of

glomerular and tubular diabetes related structural defects 10 years post SPK surgery [28]. It is however impractical to routinely monitor diabetic nephropathy by tracking structural changes within the kidney due to the invasive nature of the testing involved.

In addition, renal biopsies tend to monitor more of the long term diabetes effects as opposed to short term changes. As a result; physiological parameters of renal function such as blood pressure, urinary protein excretion and creatinine clearance seem better and more practical assessment tools of renal function in the short term. To this regard, SPK has been found to result in improved blood pressure, and urinary protein excretion, but creatinine clearance doesn't seem to be favorably affected [2]. This may probably be due to the cumulative effects of calcineurin based immunosuppression.

Neuropathy

"Subtle benefits in neuropathy have been noted after SPK" [2,29-31]. However, "patients with abnormal cardiorespiratory reflexes have reduced rates of death after undergoing a pancreas transplant" [2,32].

In a study conducted by Kennedy et al. [33], stable pancreatic function following transplantation resulted in improvements in neurological function within 24 months post surgery. Improvements were noted in motor, sensory and autonomic functions; which although modest, were persistent at 10 years post surgery.

Cardiovascular effects

Cardio vascular benefits of pancreatic transplantation include regression of coronary artery atherosclerosis, improvement in diastolic dysfunction, left ventricular geometry (as demonstrated by echocardiography) and improved cardiac autonomic function [2].

Rocca et al. [34], through a retrospective analysis of uremic type 1 diabetes patients, reported favorable improvement in ejection fraction and diastolic function at 4 years post SPK when compared to kidney transplantation alone. Whereas Gaber et al. [35] reported sustained improvement in left ventricular geometry post SPK - 75% of patients had improved left ventricular mass post transplant as compared to 31% pre transplant. Similar favorable cardiac effects were also reported by Jukema et al. [36] where type 1 diabetes patients who underwent SPK were found to have a 38% greater regression in coronary artery atherosclerosis as compared to those who did not receive pancreatic transplantation. However, despite the observations noted above, data on hard outcomes such as cardiovascular mortality is currently lacking, necessitating the need for further studies which could evaluate the cardiovascular effect of pancreatic transplantation.

Cerebrovascular

Pancreas and beta islet cell transplantation Improvements in HBA1c and renal function following SPK has been found to correlate with improvements in carotid intimal thickness independent of other cerebrovascular risk factors such as BMI, smoking or changes in lipid concentrations [37].

However, cerebrovascular disease " can worsen after pancreas transplantation, and might continue worsening for years after normoglycaemia, suggesting that it is often far too advanced to reverse" [2].

Survival

Studies have demonstrated increased mortality following pancreatic transplantation in the immediate post surgical period mainly due to the associated surgical complications. For instance, Venstrom et al. [38] demonstrated a 1.5 fold increased mortality risk during the first 90 days post SPK, with greater risk of mortality following PAK and PTA (at 2.83 and 2.27 fold respectively). But in the long run, both SPK and PAK portend an improved overall survival especially when compared to patients who underwent kidney transplantation alone (KTA) surgeries with the renal grafts obtained from deceased donors. However, when compared to KTA with renal grafts obtained from living donors, survival outcomes for KTA are similar to SPK and PAK [2].

Future prospects - Islet cell transplantation: The need for islet cell transplantation was developed as a more viable curative therapeutic option for type 1 diabetes treatment following the drawbacks experienced with exogenous insulin and the surgical complications associated with whole pancreas transplantation. Islet cell transplantation traces its origin to the early 1960's when novel collagenase based cellular isolation techniques were developed [39]. It was however not until the year 2000, when a major breakthrough towards achieving sustained insulin independence was reached. The Edmonton series of beta islet cell transplantation, performed in seven patients with brittle type 1 diabetes reported a 100% success rate, with the subjects achieving a median insulin independence period of 11.9 months. The Edmonton researchers had used a steroid free, non diabetogenic immunosuppressive concoction of tacrolimus, sirolimus and daclizumab [39]. Thereafter the American Food and Drug Administration (FDA) declared islet cell transplantation a biological drug, and reserved it to controlled clinical trials [39,40]. Concurrently the immune tolerance network [41] carried out multicenter clinical trial using the Edmonton protocol, and reported in the year 2006 a 44% insulin independence rate at 1 year.

In the year 2009, the Collaborative Islet Transplant Registry (CITR) [39,42] reported 70% insulin independence at 1 year post-transplantation, 55% at 2 years, 45% at 3 years, and 36% at 4 years. At present, islet cell transplantation still remains an experimental form of therapy.

Conclusion

Pancreas transplantation is at present the gold standard endocrine replacement therapy in diabetes with a profound potential to revolutionize diabetes treatment especially among patients with labile/ brittle diabetes; however, despite the proven beneficial outcomes and independence from exogenous insulin therapy, wide spread application in routine clinical care is marred by limited access to viable pancreas grafts for transplantation, nephrotoxicity of current immunosuppressive regimen, and advanced technical skill required in performing the surgery which is limited to a few centers of excellence worldwide. Bearing in mind the increased mortality risk within the immediate post surgery period, overall improved survival thereafter, argues favorably for pancreas transplantation among specially selected patients who will benefit the most from the procedure.

Future prospects seem promising, where less invasive long term endocrine replacement therapies such as Islet transplantation take center stage. However; while the surgical risks associated with whole pancreas transplantation are subverted through Islet transplantation, the procedure requires harvesting of multiple pancreatic organs in

order to serve one individual patient, adding even more strain on the currently limited availability of grafts. Treatment protocols are mainly formulated in line with the Edmonton protocol, and since its inception, many type 1 diabetes patients have benefited from the procedure with sustained longterm insulin independence.

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