

Simultaneous Pancreas-Kidney Transplantation to Treat End-Stage Renal Disease and Diabetes Mellitus.

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Abstract: Type I Diabetes Mellitus (T1DM), a mostly genetically determined disease, is an important economic and health burden as it leads to long-term complication eventually resulting in end stage renal disease (ESRD). Today, an allogeneic pancreas transplant coalesced with a kidney transplant i.e. simultaneous pancreas kidney transplantation (SPK) has the potential of rendering a Type I diabetic patient completely independent from both insulin and dialysis treatment while reducing further progression of the diabetes and its associated complications. Simultaneous pancreas-kidney transplantation is the most common method for pancreas transplantation. A patient is considered eligible to receive a SPK transplant if they have been diagnosed with T1DM. SPK can be performed via the intraperitoneal approach, the most effective and standard method, or via the extraperitoneal approach, which is the least frequently used. Compared to other techniques and treatments used today, SPK transplantation boasts increased progress in the treatment of neuropathies, nephropathies, retinopathies, macrovascular complications, hyperglycemia as well as quality of life. **Conclusion:** All the positive results and high survival rates for SPK could not but reinforce the fact that SPK is today the best treatment option available for T1DM patients.

INTRODUCTION

Characterized by an absolute insulin deficiency due to destruction of the insulin-producing beta cells of the Islets of Langerhans in the pancreas, Type I Diabetes Mellitus (T1DM) has rapidly become a global phenomenon. Despite accounting only for 8% of all cases of diabetes, the incidence of Type I Diabetes Mellitus is rising on an international scale¹. T1DM has a strong genetic component, which is passed from generation to generation predominantly via the HLA complex¹. T1DM in comparison to its counterpart, Type II diabetes mellitus which is characterized by insulin resistance, has been shown to be more genetically determined².

As of 2013, an estimated 40 million people are living with T1DM worldwide^{3,4} with these numbers expected to rise to nearly 60 million within the coming 15 years^{5,6}. T1DM has been shown to affect both sexes equally and in conjunction with Type II Diabetes Mellitus, is now the world's 8th leading cause of death⁷⁻¹⁰. According to the American Diabetes Association, the global economic burden of T1DM is estimated to have been nearly US \$200 billion in 2012 alone¹¹.

Poorly managed T1DM will eventually lead to long-term complications; these include microvascular conditions such as retinopathy, nephropathy, and neuropathy that are often the result of an accumulation of 'Advanced Glycation End (AGE) Products'¹². Macrovascular complications include ischaemic heart disease, peripheral heart disease, and cerebrovascular disease^{13,14}. These aforementioned micro and macrovascular complications are principally attributable to hyperglycaemia (Oral glucose tolerance test ≥ 11.1 mmol/L or Fasting Glucose ≥ 7.0 mmol/L) due to insufficient insulin secretion¹⁵.

According to a study conducted by the Journal of the American Medical Association, the majority of patients with T1DM will

develop End Stage Renal Disease (ESRD)¹⁶. ESRD is defined as having a Glomerular Filtration Rate of < 15 mL/min¹⁷. ESRD initially manifests itself as microalbuminuria with subsequent evolution to proteinuria. Without severe and effective intervention, 80% of these cases have been shown to progress to nephropathy and ultimately ESRD¹⁸. Current American guidelines for the long-term management of ESRD in eligible patients are dialysis or renal transplantation¹⁹.

There is strong evidence pointing towards the benefit of a pancreas transplant in Type I diabetic patients. Despite our highly innovative modern techniques for insulin delivery, no exogenous insulin delivery source has been able to maintain homeostatic levels of normoglycemia equivalent to that of a functioning human pancreas²⁰. These findings were reiterated by the Diabetes Control and Complication Trial of 2003, which established that a decrease in the progression of T1DM and a reduction in the risk of developing subsequent micro- and macrovascular complications is possible only through strenuous glycaemic control through an intensive insulin therapy regimen²⁰. In accordance with the aforementioned data, pancreas transplantation seems to be the only viable method to achieving euglycemia and insulin-administration independence.

Therefore, an allogeneic pancreas transplant coalesced with a kidney transplant (a simultaneous pancreas kidney transplant) has the potential of rendering a Type I diabetic patient completely independent from both insulin and dialysis treatment while reducing further progression of the diabetes and its associated complications. In other words, a SPK transplant may be the closest thing we have to a cure for patients living with Type I Diabetes and ESRD, in fact it may even reverse progression of certain microvascular complications²².

HISTORY OF SPK TRANSPLANTATION

Dr. William Kelly and Dr. Richard Lillehei performed the first SPK transplant in 1966 at the University of Minnesota in a uremic diabetic patient²². Prior to the 1980s, there was an extraordinarily high mortality and morbidity incidence associated with this SPK transplant procedure²². In the 1980s with the advent of new

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Table 1: Comparing Type I vs. Type II DM

Feature	Type I	Type II
Prevalence	8%	92%
Age of Onset	Children primarily	Adulthood primarily
Onset type	Sudden	Gradual
Presence of Ketoacidosis	Often present	Very rarely present
Presence of Autoantibodies	Very Common	Completely Absent
Endogenous Insulin production	Low or completely absent	Can be either normal, increased, or decreased
Body Size	Thin or Normal	Usually obese (BMI > 30)
Characteristic	Insulin deficient	Insulin Resistant
Selection Criteria for SPK Transplant		
• Nephropathy or ESRD		
• Confirmed diabetic nephropathy on insulin		
• Secondary diabetic complications such as; retinopathy, neuropathy, enteropathy		
• History of medical compliance to prescribed therapies		
• Creatinine Clearance < 15mL/min		

As described by the Dewitt et al, *Journal of the American Medical Association*⁶¹

surgical techniques, such as enteric drainage, and the availability of groundbreaking immunosuppression medications, such as tacrolimus/mycophenolate mofetil-based drugs, there was a significant increase in survival rates²³. With the introduction of these new surgical techniques and the development of improved immunosuppression therapies, 1-year postoperative survival rates increased in the 1980s to over 70%²⁴.

CURRENT METHODS OF SOLID-ORGAN PANCREAS TRANSPLANTATION

Presently, there are 3 practiced methods of complete organ pancreas transplantation. At 83% of total pancreas transplants conducted, the most common method of pancreas transplantation is SPK transplantation²⁵. The second most common method of pancreas transplantation is Pancreas after Kidney (PAK) transplantation, which accounts for 12% of all pancreas transplants conducted²⁶. This procedure involves transplanting a pancreas into a patient who has previously had a kidney transplanted. Finally, the third and least common method of pancreas transplant is a pancreas transplant alone (PTA).

This method is conducted in diabetic patients whom have normal renal function. PTA accounts for 5% of the total pancreas transplants conducted²⁷. The PTA method is usually partaken early on in the course of a patient's diabetes and if performed successfully, has been shown to prevent nephropathy and ESRD²⁸.

ELIGIBILITY FOR PANCREATIC TRANSPLANTATION

A patient is considered eligible to receive a Pancreatic transplant if they have been diagnosed with T1DM. It is important to note the marker used to diagnose T1DM is not insulin levels alone nor blood glucose levels, but rather the more comprehensive C-peptide^{29,30} (PTA). This method is conducted in diabetic patients whom have normal renal function. PTA accounts for 5% of the total pancreas transplants conducted²⁷. The PTA method is usually partaken early on in the course of a patient's diabetes and if performed successfully, has been shown to prevent nephropathy and ESRD²⁸.

ELIGIBILITY FOR SPK TRANSPLANTATION

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diagnosed with T1DM. It is important to note the marker used to diagnose T1DM is not insulin levels alone nor blood glucose levels, but rather the more comprehensive C-peptide^{29,30}; further progression of thereby reducing diabetes and its associated complications. In other words, a SPK transplant may be the closest thing we have to a cure for patients living with Type I Diabetes and ESRD, in fact, it may even reverse progression of certain microvascular complications²².

Table 2: Showing certain selection criteria for patient eligibility for SPK transplant^{25,31}

- Nephropathy or ESRD
- Confirmed diabetic nephropathy on insulin
- Secondary diabetic complications such as; retinopathy, neuropathy, enteropathy
- History of medical compliance to prescribed therapies
- Creatinine Clearance < 15mL/min

SURGICAL TECHNIQUES USED IN SPK TRANSPLANTATION

There are 2 main procedures surgeons use when conducting a SPK transplant. First is the intra-peritoneal approach in which the pancreas graft is often transplanted in the right iliac fossa while the kidney is transplanted in the left iliac fossa³². It is important to note that these locations can be interchanged, with the pancreas being transplanted in the left iliac fossa and the kidney in the right iliac fossa³². This intra-peritoneal approach has been shown to result in fewer post-operative complications such as peri-pancreatic fluid accumulation and infections³³.

Secondly, an alternative surgical approach is used in which both the pancreas and kidney grafts are transplanted in an extra peritoneal and ipsilateral manner³⁴⁻³⁵.

The SPK transplant's arterial anastomosis is formed by fringing the donor's splenic artery with the superior mesenteric artery and anastomosing it to a Y-graft of the recipient's external iliac artery³⁶. Venous anastomosis is formed between the donor's portal vein and the recipient's external iliac vein, with this system using the systemic venous drainage. An alternative venous anastomosis can also be formed using the donor's portal vein and the recipient's superior mesenteric vein to avail of portal venous drainage³⁷. Originally, the portal venous drainage method was believed to cause a reduction in graft rejection rates and lipid deregulation, however recent studies have found no conclusive evidence of such statements³⁸.

SPK TRANSPLANTATION OUTCOMES

Neuropathy

Numerous published studies have shown the positive outcomes of SPK transplantation on the improvement of diabetic associated neuropathy. One study in particular, conducted by Allen et al, demonstrated the beneficial effects of a pancreatic transplant on autonomic, sensory, and peripheral motor nerve function³⁹. This study closely analysed a cohort of 44 Type I diabetic patients, all with significant to severe nephropathy. Over a period of 1 year, Allen and colleagues conducted over 219 electrophysiological studies in these patients and found a significant improvement in all desired motor and sensory indices with improved long term glycaemic control^{39,40}. These results were further reinforced by

numerous studies such as *White et al.*, which was conducted in accordance with the Royal College of Surgeons of England, Kennedy et al, and Martinenghi et al⁴⁰⁻⁴².

Nephropathy

SPK transplantation is conducted in patients living with T1DM and ESRD to replace the near-dead kidney(s) with a more capable kidney. The principle objective of SPK transplantation is to provide a sustainable, long-term euglycemic state with complete insulin independence. Maintaining a long-term euglycemic state has been shown to not only stop the progression of diabetic nephropathy, but to even cause amendments of certain aspects of the nephropathy⁴³. Improvements observed in diabetic nephropathy post SPK transplant included; reduced glomerular basement membrane thickness, reduced thickness of mesangial matrix, and improved condition of glomerular and tubular lesions⁴⁴. As expected renal function was also noticeably improved post SPK transplant as evidenced by a decrease in the amount of urinary albumin present (20 mg/day vs. 103 mg/day)⁴⁵. However, it is important to state that improvements in diabetic nephropathy post SPK-transplant are affiliated with the possibility of nephrotoxicity associated with the use of immunosuppressive therapies, principally from Tacrolimus and Cyclosporine based therapies⁴⁶.

Retinopathy

Diabetic retinopathy is by far the most controversial complication associated with T1DM. Numerous studies have reported vastly conflicting results on the benefits of PTA or SPK transplantation on the treatment of diabetic retinopathy. Nonetheless, after the turn of the century many major studies have shown a normalization or even improvement in the number and state of retinal lesions/retinal micro aneurysms in diabetic patients post SPK transplant⁴⁷⁻⁵⁰. According to a study conducted by Chow and colleagues, there was improvement in 14% of eyes with at least partial vision, 76% of eyes remained stable with no further regression of the retinopathy, and in 10% of eyes the retinopathy progressed to a more severe state⁴⁸. The same study reported a 32% increase in visual acuity and a 46% decreased chance of vitreous haemorrhage post-SPK transplant.

Macrovascular Complications – Post SPK transplant

There is no published evidence that an SPK transplant can reverse the progression of macrovascular diseases associated with T1DM. The main role of SPK transplant in managing macrovascular complications is the stabilization of these complications and a possible slight decrease in the risk of these complications progressing further⁵¹.

Glycaemic Control- Post SPK transplant

In patients living with T1DM and ESRD, SPK transplant has been shown to be the best available therapy for producing normoglycemic levels both in the short and long-term⁵². Stable HbA1C levels were better-achieved post SPK transplant than both post-islet cell therapy and via insulin pumps⁵³. A 15 year follow up study conducted by Kissler et al on SPK transplant patients gave invaluable insight onto the homeostatic properties of SPK transplantation⁵⁴. Over the course of 15 years, HbA1C levels remained stable within the homeostatic range with only a minimal difference between the 1st year and 15th year (4.68% / 4.73%)⁵⁴. Fasting glucose levels were also found to have remained stable within the homeostatic range over the course of the study with a

difference of 0.44 mmol/L between the 1st and 15th year (3.94 mmol/L vs. 4.38 mmol/L)⁵⁴.

Patient and Graft Survival Rates

According to the American Journal of Transplantation, the post operative 5 and 10-year survival rates for SPK transplantation are 87% and 70% respectively as of 2009⁵⁵. These survival rates are exceptional when compared to the survival rates of type I diabetic patients with ESRD on dialysis, with 5 and 10-year survival rates a mere 34% and 23% respectively⁵⁶. With recent improvements in surgical techniques and immunosuppression therapies, graft survival rates are exceptional. Renal graft survival rates are greater than 95% after 1 year post-operation and greater than 60% after 10 years post-operation⁵⁷. 1 and 10-year pancreatic graft survival rates are 86% and 53% respectively⁵⁷⁻⁵⁸.

Quality of Life-Post SPK transplant

Using the 36-item short form health survey, Smith et al evaluated the quality of life for diabetic recipients of SPK transplants with ESRD pre and post-operatively⁵⁹. Using the questionnaire, Smith et al found a significant enhancement in all patient's quality of life post-operatively⁵⁹. Smith et al also used the Physical Component Summary to gage the patient's quality of lives pre and post-operatively and found similar results to that of the 36-item short form health survey⁶⁰. The 36-item short form health questionnaire scores were suggestively higher in the long-term post SPK transplant when compared with pre-transplant, 51.8 vs. 46.8 respectively⁵⁹. Similar results were also observed post-SPK transplant in European patients with ESRD⁶⁰.

CONCLUSION

Not only does SPK transplantation return the patient's renal function, it also provides a means by which the patient can achieve both a short and long-term normoglycemic state without insulin dependence. SPK transplantation greatly improves the survival rate of a Type I diabetic patient with ESRD as opposed to other conventional disease-management options available such as islet-cell transplantation and dialysis. Taking into account published literature, in our opinion, SPK transplantation is the only and best treatment option available for Type I diabetic patients with ESRD. We believe if the patient meets all criteria and is fully aware of the risks associated with a transplant surgery of this calibre, they should be considered for the life saving procedure.

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