SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION FOR END-STAGE RENAL FAILURE SECONDARY TO DIABETIC NEPHROPATHY : PRINCIPLES AND PRACTICE

Shrestha B M*

* Sheffield Kidney Institute, Herries Road, Sheffield S57AU, UK

ABSTRACT

Diabetic nephropathy is the second most common cause of renal failure in the United Kingdom where majority of the patients were managed by renal transplantation and insulin therapy in the past. Over the last three decades, increasing number of patients are undergoing simultaneous pancreas and kidney transplantation (SPKT) because of its advantages, which renders the patient both dialysis and insulin-independent, halts the progression of complications of diabetes, thereby improves the quality of life, survival and has proven to be cost-effective. This article presents a review on the principles and contemporary practice of SPKT worldwide and highlights the future

Key Words: Pancreas, Transplantation, Diabetes, Renal Failure.

INTRODUCTION

Diabetes mellitus (DM) is the leading cause of end-stage renal disease (ESRD) in the United States, and is the second most common cause in the United Kingdom. Diabetic nephropathy (DN) severe enough to cause renal failure usually develops 20-30 years after the diagnosis of type I diabetes (insulin-dependent diabetes mellitus-IDDM) and is preceded by microalbuminuria, proteinuria and hypertension before eventual ESRD. It is an important cause of proliferative retinopathy and neuropathy carrying a mortality rate about five times greater than general population.[1] The options for renal and insulin replacement therapy in patients with ESRD and IDDM is shown in Table I.[2] Simultaneous pancreas and kidney transplantation (SPKT) has been established as a preferred choice of treatment for selected patients with ESRD secondary to DN as this renders patients insulin and dialysis-independent, improves quality of life and patient survival and is cost-effective.[3,4] This article presents a review on the principles and current practice of SPKT and highlights the recent developments in the fields of islet transplantation, stem cells and gene therapy.

Address for correspondence :
Dr. B. M. Shrestha
Sheffield Kidney Institute, Herries Road, Sheffield S57AU, UK
Email: shresthabm@doctors.net.uk

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Table I : Choices of therapies for ESRD and DM

- Haemodialysis
- Peritoneal dialysis
- Kidney transplantation
- Simultaneous pancreas and kidney transplantation (SPKT)
- Kidney after pancreas transplant (KAPT)
- Pancreas after kidney transplant (PAKT)
- Pancreatic islet and kidney transplantation (PIKT)

RATIONALE FOR SPKT

Renal transplantation (RT) in patients with DM was associated with excessive morbidity and mortality in the past from sepsis and cardiovascular complications, however with careful regulation of immunosuppressive drugs, hypertension and hyperglycaemia, the peritransplant and post-transplant outcome has improved significantly to the extent that RT is viewed as the preferred therapy for ESRD.[5] Further extension of RT in ESRD patients with IDDM is SPKT, which retards or halts the progression of microvascular and macrovascular extrarenal complications and protects the transplanted kidney function from the deleterious effect of uncontrolled hyperglycaemia. SPKT is associated with increased perioperative morbidity, but the immediate postoperative mortality remains same.[6] Prospective studies have confirmed that SPKT has a protective effect against cardiovascular mortality in diabetic recipients affected by ESRD.[7] SPKT makes patients insulin-independent and dialysis free, which improves sense of well-being and quality of life significantly.[8]

TIMING FOR SPKT

Timing for SPKT is important to achieve satisfactory outcome. The optimum time to offer a patient SPKT is before dialysis is needed, when the serum creatinine is in the region of 300-400 μmol/l and the GFR is 15-20 ml/min. SPKT before starting dialysis has proven beneficial in prospective studies.[9] Diabetic patients with established diabetic autonomic neuropathy, particularly with impaired gastric emptying compounded by cachexia and uraemia do not cope well with the rigours of SPKT, hence necessity of transplanting preferentially.[10]

ASSESSMENT FOR SPKT

A general assessment plan for SPKT is outlined in Table II. Diabetic patients with ESRD need careful evaluation of cardiovascular system as asymptomatic coronary artery disease may manifest with myocardial infarction in the perioperative period when heart is placed on stress by deliberate intravascular volume expansion during the surgical procedure.[11] Contemporary cardiac evaluation, including a thorough history and physical examination, should include an electrocardiogram, echocardiogram, thallium stress test, and if needed Holter monitoring and coronary angiogram. Coronary revascularisation in the form of angioplasty or coronary artery bypass graft surgery is needed preoperatively in cases with severe coronary artery disease.[11,12]

Symptomatic peripheral vascular disease should be evaluated preoperatively with plain abdominal x-ray, Doppler flow studies and in some instances with CT angiography with 3-D reconstructions or conventional angiograms to help determine where the renal and pancreas allografts should be placed. Compromised blood flow to the lower limbs from atherosclerotic stenoses puts the limbs at risk of acute ischaemia following placement of allografts.[13]

Table II : Assessment for SPKT

- Thorough history and physical examination
- Heart: ECG, echocardiogram, exercise stress test, coronary angiogram
- Lower limbs: X-ray pelvis, Doppler flow study, CT angiogram and conventional angiogram
- Gastrointestinal tract: abdominal radiography and ultrasound scan
- Respiratory system: chest x-ray and lung function tests
- Vision: visual acuity, fundoscopy and fluorescein angiography
- Bones: DEXA scan
- Bladder function: Urine culture. residual volume, and cystometrogram
- Evaluation of potential for self care through social workers

RETRIEVAL OF PANCREAS

Retrieving the donor pancreas and preparing for subsequent transplantation is the most challenging and technically difficult part of the surgical procedure of PT. Whole pancreas is harvested from deceased donor with its intact blood supply based on the arterial arcade around the head formed by the superior and inferior pancreaticodudenal arteries supplying the head and uncinate process, and splenic artery supplying the body and tail.[14] Venous drainage is maintained through preservation of portal vein. Meticulous dissection and minimal handing of the pancreas is mandatory to prevent acute pancreatitis, pseudocyst and fistula development in the postoperative period which contributes to mortality. A Y-segment of the bifurcation of the common iliac artery harvested from the donor is used to reconstruct the arterial inflow.[15] The common bile duct is ligated and the second part of the duodenum is stapled and harvested with the pancreas to provide a conduit for drainage of the exocrine secretion.[16] The preservation of the pancreas is carried out using University of Wisconsin solution, which allows an acceptable cold ischaemia time up to 24 hours.[17]

Sutherland et al. from University of Minnesota have pioneered in popularising living related donor PT, where distal segment of pancreas is harvested from a living donor.[18] Tan et al. from the same institute have successfully harvested distal pancreas and kidney simultaneously from the same donor using laparoscopic technique.[19] This is primarily intended for the recipients who are highly sensitised and have a low probability of receiving a cadaveric allograft, diabetics who should avoid high immunosuppression, and those recipients with a donor who is non-diabetic non-identical twin. There has been no mortality and the incidence of surgical complications has been 15%. Whole-organ pancreas transplantation has the advantage over segmental pancreas because of technical ease of the donor and recipient operation and the larger dose of islet available for the recipient.[20]

RETRIEVAL OF KIDNEY

In cases of SPKT, kidney is harvested simultaneously from the same donor with preservation of the aortic patch on the renal artery and renal vein with adequate length in case of deceased donor. Kidneys from live donors are harvested and transplanted in some cases prior to undergoing PT, which is preceded by several years.[20]

THE RECIPIENT PROCEDURE

The first vascularised pancreas transplant (PT) was performed by Kelly and Lillehei et al. on 17th December 1966 at the University of Minnesota, USA.[21] They harvested body and tail of the pancreas from a cadaveric donor, ligated the pancreatic duct and transplanted in the left iliac fossa, and simultaneously kidney was transplanted in the opposite iliac fossa. The patient became normoglycaemic and insulin independent immediately.

These days, the pancreas and kidneys are placed intraperitoneally after gaining access through a long midline incision. The pancreas is placed on the right iliac fossa and kidney on the contralateral iliac fossa. The arterial inflow to the pancreas is established from external iliac artery and venous drainage to the external iliac vein.[22] Venous drainage to the portal system is a more physiological operation as the surge of high blood insulin is avoided; however the procedure is associated with high rate of venous thrombosis and has shown no metabolic advantage over the systemic drainage.[23,24] The technique for management of the pancreatic duct and the exocrine secretion are enteric drainage into small intestine, urinary bladder, and to a lesser extent, obliteration of the duct by injection with polymer neoprene. Bladder drainage was introduced by Cook et al. by performing duodenovesical anastomosis.[25] It was possible to measure urinary amylase level to assess ongoing rejection in the pancreas allograft. However, activation of pancreatic enzyme in the urinary bladder leading to intense cystitis and chronic loss of bicarbonate in some recipients led to conversion to enteric drainage.[26] More lately, evaluation of large groups of PT recipients have suggested that enteric drainage provides a trend towards increased long-term survival without bladder-related complications such as dysuria, haematuria ad metabolic acidosis.[26, 27]

Postoperatively, frequent monitoring of blood glucose and glycosylated haemoglobin (Hb A1c) provides useful

information on the function of PT.[28] Measurement of urinary amylase (60000-200000 IU/24 hours) in patients with bladder drainage is useful in detecting early rejection which is reflected with significant reduction in amylase level.[29]

COMPLICATIONS OF PANCREAS TRANSPLANTATION (PT)

Vascular complications after PT have been common in the past which include thrombosis, haemorrhage, stenosis, aneurysm and arterio-venous fistula formation. Refinements in vascular surgical techniques and newer immunosuppressive agents have reduced this complication to less than 5 percent.[13,30] Loculated collection around pancreas secondary to pancreatitis, particularly with associated infection, requires percutaneous drainage and antibiotics. Leak from the duodenal segment can be problematic requiring revision or prolonged period of treatment with somatostatin analogue such as octreotide.[31]

Infectious complications in the form of cytomegalovirus and BK virus infections are frequently encountered which is related to escalated immunosuppression in SPKT.[32] Mortality of 3-5% in the first year following SPKT is reported from experienced centres, which results from overwhelming sepsis due to over-immunosuppression and cardiovascular causes. Occasionally, the transplanted pancreas needs to be sacrificed to save patient's life.[18]

IMMUNOSUPPRESSIVE REGIMENS (IR)

The optimal IR for SPKT still remains to be established. The traditional immunosuppression protocol for SPKT in the US consisted of induction with antithymocyte globulin together with ciclosporin, azathioprine and prednisolone.[33] More lately, tacrolimus, mycophenolate mofetil and prednisolone with and without induction with antithymocyte globulin or anti-IL2 receptor antagonists have shown identical rate of acute rejection, glycaemic control, long-term allograft survival, and reduced rate of infectious complications and post-transplant lynphoproliferative disorders.[34-36]

REJECTION

Rejection of PT can be hyperacute, acute or chronic as in renal allograft and they are reflected simultaneously in both organs. Rejection of the PT is manifested with inadequate glycaemic control and that of RT with rising serum creatinine.[37] Percutaneous ultrasound-guided biopsies of PT are being carried out routinely prior to treating rejection, however as there is legitimate interpretation of kidney biopsy as an indicator of pancreatic rejection, pancreatic biopsy is avoided on most occasions.[29]

Acute cellular rejection is treated with pulses of steroids with success. Antibody mediated rejection is diagnosed by biopsy and demonstration of C4D deposition in the peritubular capillaries which is treated successfully with intravenous immunoglobulin (IVIg), rituximab and plasmapheresis.[38] Chronic allograft changes in both pancreas and kidney as evidenced by progressive deterioration in allograft function, once confirmed histologically, is treated with reduction or withdrawal of calcineurin inhibitors and substitution with sirolimus.[39]

OUTCOMES

The world's largest cumulative experience on SPKT is available from International Pancreas Transplant Registry (IPTR) and includes a total of 23208 transplants performed worldwide as of 31st December 2003. The 1, 5 and 10 year PT graft survival was 85%, 61%, and 46%, respectively. Likewise, the patient survival at 1, 5 and 10 years was 95%, 90% and 63%, respectively.[40] PT failure was from vascular thrombosis, infection, pancreatitis, anastomotic leak, bleed leading to removal, rejection and death from cardiovascular causes. There is significant improvement in the quality of life following SPKT as the threat of hypoglycaemia, and risk of hyperglycaemia are removed.[8] There is reduction in the incidence of recurrent DN in the transplanted kidney, which is a major advantage in prolonging the survival of the transplanted kidney.[41] Significant improvement in the autonomic symptoms, particularly postural hypotension, indicates axonal regeneration and partial recovery of DN.

PANCREATIC ISLET TRANSPLANTATION (PIT)

Shapiro el al. have shown excellent outcome following

PIT, where purified islets is injected into the portal vein under radiological control, which continues to grow within liver and render patient insulin-independent and freedom from recurrent severe hypoglycaemia in labile diabetics.[42,43] Significant advances in islet isolation and purification technology, the development of more specific and less diabetogenic immunosuppressants have made PIT successful. In comparison to SPKT, PIT is only a minor surgical procedure, but islet isolation requires advanced technology. Accessing the portal vein via the percutaneous hepatic approach carries the risk of bleeding, and the infusion of islets a risk of portal vein thrombosis. IR consisting of sirolimus following induction with anit-IL2 receptor antagonists has shown promising results.[44] The 1-year recipient survival following P IT is 98%, for the islets 82% and for insulin-independency 42%, however there is a significant decline of islet function to 10%, 5 years after PIT.[45] PIT as a potential treatment for diabetes will always be limited mainly because of the difficulty in obtaining sufficiently large numbers of purified islets from cadaveric donors.

STEM CELL THERAPY

In 1998, scientists discovered methods for isolating and growing human embryonic stem cells (ESC) derived from the inner cell mass of the blastocyst, which are clonogenic cells capable of both self-renewal and multilineage differentiation, including the insulin-producing islet cells of the pancreas, which could then be used to control blood glucose levels in people with IDDM.[46] Likewise, adult stem cells present within tissues of adult organisms are responsible for cell turnover or repopulation of tissues under normal or exceptional circumstances and can be exploited for the same purpose. An increasing body of evidence suggests that the pancreatic cell types (islet, acinar and ductal cells) have remarkable plasticity and can de- and trans-differentiate into each other under appropriate conditions.[47] Elucidation of the molecular mechanisms regulating these processes could lead to clinically applicable ways of either inducing pancreatic islet regeneration in situ or to expanding the insulin-producing cells in vitro for transplantation and contribute to mitigate the increasing demand of islet cells.[48] As ESC research involves destruction of embryos, several countries including USA have imposed restriction on stem cell research.

GENE THERAPY

Gene therapy is a technique for correcting defective genes responsible for disease development where a "normal" gene is inserted into the genome to replace an "abnormal" disease-causing gene. Adeno-, herpes simplex, adeno-associated and retrovoruses are used as vectors which deliver the genes to the target cells.[49] Currently, gene therapy is being studied to prevent islet rejection, e.g. local expression of immunosuppressive cytokines or ligands inducing T-cell apoptosis, knock-out of specific animal genes or transfer of human genes into animal tissue donors or to construct "superislets" resistant to apoptosis or oxidative stress, which is in experimental stage and has not proven successful in clinical trials.[50]

CONCLUSIONS

SPKT has stood the test of time and shown to provide the best form of rehabilitation for patients with ESRD from DN as this not only renders patient dialysis and insulin-independent, but also improves survival and quality of life. Proper selection of patients, meticulous retrieval and implantation of pancreas followed by careful postoperative management is the way forward in achieving satisfactory outcome. PIT has emerged as alternative to SPKT and multicentre studies are underway to examine its efficacy. Stem cell therapy would provide a definitive treatment solution for patients with IDDM, but this therapeutic option is still at an infancy stage of development, so is the gene therapy.

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