Recent Developments and Future Prospects in Pancreatic Transplantation

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Pancreas transplantation is not a life-saving procedure, so the benefits should be sufficient in terms of quality of life to outweigh the risks. Successful transplants give patients more positive health perceptions, improved social interaction, more satisfaction with diet and increased vitality. Studies are unanimous in finding that patients with successful transplants rate their lives better after transplantation than before. The effect of a double transplant in uraemic diabetic patients can be dramatic; patients rate their quality of life higher than diabetics who receive a kidney transplant alone.

Keywords: *Diabetes; pancreas; insulin; quality of life*

Diabetes mellitus is the principal cause of kidney failure and blindness in adults and leads to more cases of amputations and impotence than any other disease. It is one of the most common chronic diseases of childhood. In the United States, diabetes costs $138 billion each year, that is one out of every $7 spent on health care [1].

Pancreas transplantation is an important option for consideration in the treatment of severe diabetes and remains under-utilised in this respect. It has proved to be very successful, with good patient and graft survival rates and the establishment of insulin independence in the recipients (Table 1).

Benefits of Pancreas Transplantation

In addition to correcting dysmetabolism and freeing the patient from exogenous insulin therapy, there is evidence that it has a beneficial effect on the course of secondary diabetic complications. In some studies with follow-up of 4 years or more

Table 1. Criteria for pancreas transplantation

Exclusion criteria
Insufficient cardiovascular reserve:
a) Angiography indicating non-correctable coronary artery disease
b) Ejection fraction below 50%
c) Recent myocardial infarction
Current significant:
a) Psychiatric illness
b) Psychological instability
c) Drug or alcohol abuse
d) Non-compliance with treatment
Active infection
Malignancy
Lack of well-defined secondary diabetic complications
Extreme obesity (>130% of ideal body weight)
Inclusion criteria
Presence of IDDM
Well-defined secondary diabetic complications
Ability to withstand:
a) Surgery
b) Immunosuppression
Psychological suitability
Good understanding of:
a) Therapeutic nature of pancreas transplantation
b) Need for long term immunosuppression and follow-up

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after successful pancreas transplantation, stabilisation of retinopathy was better than one observed in patients followed for the same period of time but whose pancreas transplants had failed.

Both prospective and cross-sectional studies have suggested that pancreas transplantation prevents recurrence of diabetic nephropathy in a newly transplanted kidney, and studies have reported improved motor and sensory nerve function as assessed by nerve conduction velocity in pancreas-kidney transplant recipients when compared to recipients of kidney transplants alone or patients with pancreas graft failure. Studies of autonomic function following pancreas transplantation are less clear. In some studies, pancreas transplantation was associated with greater improvements in autonomic symptoms even if they were accompanied by little objective evidence of change (Table 2).

Future Improvements in Pancreas Transplantation

At this stage, there are still some areas of pancreas transplantation, which could be investigated and improved upon: Donor Pool, Preservation, Transplant Technique, Graft Imaging, Rejection Markers and Immunosuppression.

Due to a worldwide shortage of donor organs, it is important to liberalise the donor criteria as much as possible in terms of age of the donor and condition of the donor pancreas [2]. We can also look at alternative methods of preservation of the organs, patient selection and better intra-operative and post-operative management.

For example, a supplement of nitric oxide during reperfusion has been shown to be effective in attenuating exocrine microvascular reperfusion injury [3], and the use of Octreotide perioperatively has achieved good results in patients, with no post-operative pancreatitis [4]. Bladder drainage is becoming less and less popular due to a high percentage of post-operative complications and enteric drainage is now gaining in popularity [5]. In a comparison of portal venous drainage and systemic venous drainage of the graft, there were no differences in graft or patient survival, major complications, fasting glucose or glycosylated haemoglobin, but portal venous drainage was shown to prevent hyperinsulinaemia and to improve lipoprotein composition [6]. Extraperitoneal placement of the kidney in SPK transplants has been performed in cases where there is no intraperitoneal space for both organs. This prevents any kidney damage in the case of a complication from the pancreatic graft and also facilitates kidney biopsy [7].

Table 2. Criteria for Simultaneous pancreas/kidney (SPK), Pancreas transplant alone (PTA) and Pancreas after kidney transplants (PAK)

Criteria for SPK:
Diabetic nephropathy: creatinine clearance <20ml/min
Patient on dialysis or very close to starting dialysis
Failure of previous renal allograft

Criteria for PTA
The presence of two or more diabetic complications:
Proliferative retinopathy
Early nephropathy; creatinine clearance >70ml/min, proteinuria >150mg/24 h but <3g/24h
Presence of overt peripheral or autonomic neuropathy
Vasculopathy with accelerated atherosclerosis
Hyperlabile diabetes with:
Severe episodes of ketoacidosis
Severe and frequent episodes of hypoglycaemia
Hypoglycaemia unawareness
Severe and frequent infections
Impairment of quality of life

Criteria for PAK
Patients with stable function of previous renal allograt that meet the criteria for PTA

The Use of Vascular Closure Staples

As part of an international team, we have used vascular closure staples (VCS) in pancreatic transplantation. The advantages of this procedure are that the staples do not penetrate the vessel, do not disrupt the endothelium and they do not have an intraluminal component. The VCS technique allows for shorter warm ischaemia time with equal or possibly improved operative outcomes. In our series, all organs were well perfused after revascularisation, and Doppler scan performed immediately post-operatively demonstrated no anastomotic abnormalities. Follow-up between 6 and 24 months revealed the recipients to be insulin independent with no complications. A prospective randomised clinical trial is now required to further evaluate the VCS technique in pancreas (and other organ) transplantation [8].

Monitoring of Rejection

In the diagnosis of pancreatic graft rejection, Duplex Doppler Ultrasonography (DDU) is a useful aid [9]. In our research into pancreas recipients, we have compared the volume flow (VF) in the splenic artery of the graft to the VF of the splenic artery of the native pancreas. The results show that when VF in the graft splenic artery is less than 11% of the VF in the native splenic artery, a graft biopsy is indicated [10].

Magnetic Resonance Angiogram (MRA) imaging is now becoming more popular than angiography as it is not invasive, is not associated with allergic reactions, does not cause renal dysfunction and can be repeated frequently with minimal patient discomfort. In a study to evaluate gadolinium-enhanced MRA with conventional angiography for imaging of the pancreatic graft, MRA provided excellent information on flow in the splenic and superior mesenteric arteries and perfusion of the pancreatic parenchyma. However, MRA did not provide sufficient information on the veins of the graft [11].

Recent studies of rejection markers in the canine model have shown that, during rejection, nitric oxide reaches peak levels much earlier than the elevation of serum glucose, and that the detection of an elevated nitric oxide level can be an early indicator of rejection [12]. Also it has been found in the canine model that peripancreatic fluid cytology can reliably give an early indication of graft rejection and can help to differentiate acute rejection from graft pancreatitis [13]. A rise in serum lipase is the best marker for acute rejection in enterically drained pancreas transplants [14].

Another study in the rat model demonstrated that liver allografts were more readily tolerated in this model than pancreas, heart and kidney allografts. Combined pancreas and liver transplantation protected the pancreatic graft from rejection, and liver transplantation following pancreatic transplantation reversed ongoing pancreatic rejection [15].

Immunosuppression

The immunosuppression for pancreas transplantation is similar to that for other solid organs. The idea is to maximise the immunosuppressive effects and minimise immunodeficient complications and toxicity by employing multiple agents at low doses. Since the mid-1980s, almost every programme has used Cyclosporin in combination with Azathioprine and Prednisone for maintenance immunosuppression. Currently, however, Prograf (Tacrolimus) has replaced Cyclosporin, and Mycophenolate Mofetil (MMF) has replaced

Azathioprine in most centres.

Rejection is the major cause of graft loss due to difficulties in its early detection. While rejection rates used to be 60%, a number of centres are reporting figures of 10 – 40%. Transplantation of a pancreas and a kidney from the same donor allows manifestation of kidney allograft rejection to guide treatment: kidney graft rejection is believed to precede or occur concurrently with pancreas rejection.

Immunosuppressive Usage is an important area on which to concentrate in an attempt to discover safer and cheaper alternatives. There has been a gradual decline in the use of antibody induction from 90% (in 1987-93) to 83% (1994-97). Triple therapy maintenance (Prograf, MMF and Prednisone) is now widely used and pancreas transplant alone (PTA) is becoming an accepted option [16]. There are many ongoing trials of drugs including Tacrolimus, Neoral and Mycophenolate Mofetil [17].

Islet Transplantation

Advantages and Problems

As previously mentioned, islet transplantation is, in theory, an ideal solution for patients with IDDM since it is not a major procedure, can be performed radiologically and can be repeated several times without any major discomfort to the patient. Unfortunately, there are many problems related to islet transplantation, the most difficult being the availability of human organs for islet allotransplantation. Indeed, of approximately 5000 donors available each year in the USA, only a small proportion is suitable for pancreas or islet transplantation and most of those are used for whole organ pancreas transplantation. The technique for islet isolation has to be meticulous in order to obtain a good yield of viable islets. There is great difficulty in early detection of islet allograft rejection, even when they are transplanted simultaneously with a kidney. Finally, the islets are very sensitive to the currently used drugs in the standardised immunosuppressive regimens such as steroids, cyclosporine and tacrolimus.

Technique of Islet Isolation

Islet isolation is currently performed using the semi-automated method described by Ricordi. The pancreas is initially distended with a mixture of Hanks balanced salt solution and collagenase (concentration usually of 1mg of collagenase/ml of Hanks solution), which is injected into the main pancreatic duct. The pancreas is placed in a stainless steel chamber with a 400m screen filtering the outlet. The collagenase solution is circulated in a closed system at 37°C. The progress of pancreas digestion is monitored by microscopic examination of aliquots taken from the circuit. When islets become free from acinar tissue, digestion is stopped by diluting and cooling the collagenase solution with large volumes (4-5 litres) of Hanks solution at 4°C. The resultant dispersed pancreatic islet tissue is collected, washed three times with cold Hanks solution, diluted in plasma (>10:1 v/v, diluent: tissue), and placed in sterile 60cc syringes prior to transplantation. Islet counts are estimated from aliquots of the final preparation, either by measurement of tissue insulin content (acid alcohol extraction) and calculation of the islet number from an estimated average insulin content/islet, or by a counting of islets stained with dithizone.

Previous techniques consisted of injection of a collagenase solution into the main pancreatic duct and incubation at 37°C for a fixed (approximately 20 minutes) period of time without monitoring of the digestion process. Therefore some islets that were free at some point before completion of the digestion time were exposed to prolonged effects of collagenase activity, while others that were still intact with the pancreas at the end of the 20-minute period were never 'liberated' from the pancreas. The distinct advantage of the Ricordi method is that as soon as some islets are free from the pancreas they can be collected and the incubation continues until there are no more islets to be extracted. Using this method, the islet yield retrieved after pancreatic digestion has increased by more than 50% compared to older methods.

Another step that can be added to the islet isolation method is the purification of the islet tissue which involves the separation of the islets from the acinar tissue. This is done by centrifuging the islet tissue through various gradients of a polysaccharide, such as dextran. Purification offers the advantage of minimising the amount of transplanted islet tissue, reducing therefore the possibility of portal hypertension which is the commonest side effect following transplantation. In addition, it is thought that the purification of islets reduces their immunogenicity and their potential for rejection. However, the disadvantage of purification is that many islets are lost with the acinar tissue, leading to a less successful transplant. Transplanting a large volume of unpurified islets into the portal system can be done successfully by proper dilution of the islet tissue followed by a very slow infusion into the portal vein. Purification therefore is not considered an important step for islet transplantation.

Human Islet Allografts

After many years of research, it was only in the late 1980s that it became possible to perform islet allotransplants with some success. The islets obtained from cadaveric donors were transplanted into the liver via the portal vein. Initial results were encouraging, but were later disappointing as it became obvious that most recipients remained hyperglycaemic. By the end of 1995, 270 patients with IDDM who received adult islet allografts were reported to the International Islet Transplant Registry (IITR) [18]. Of these, only 27 (10%) became insulin independent for more than 1 week, 14 (5%) were insulin independent for more than 1 year, and 1 patient was insulin independent for more than 4 years. Factors related to short term insulin independence are detailed in Table 3.

In addition to the classical immunosuppressive protocols, induction therapy with 15-deoxyspergualin is an important factor for achieving relatively long term insulin independence. The reason is the ability of 15-deoxyspergualin to minimise the macrophage-mediated attack that islet allografts (as well as autografts) undergo post-transplant and which causes the phenomenon of islet primary non-function [19]. Although the IITR results for long term insulin independence are not good, it is important to emphasise that many of the insulin-dependent islet recipients have had persisting C-peptide secretion, a reduction of insulin dose, and improvement in stability of glucose control, which correlated with less dangerous hypoglycaemic episodes. This means that

Table 3. Factors related with insulin independence after islet allotransplantation

Preservation time < 8 hours
Transplantation of >6000 islet equivalents (number of islets if all had a diameter of 150 μm)/kg of body weight
Transplantation into the liver via the portal vein
Induction immunosuppression with anti-T-cell agents and 15-deoxyspergualin

it is possible for some of the transplanted islets to survive a long time and, with improvements in islet isolation techniques, as well as improvements in detection of rejection and immunosuppression, long term insulin independence with islet allotransplantation might become a reality. The very encouraging results of the recent report from Edmonton showing complete insulin independence up to 14 months post transplant give us hope.

Patients who underwent pancreatectomy and hepatectomy for extensive abdominal cancer followed by simultaneous islet and liver grafts had very good islet function post-transplant [20]. Indeed, 9 out of 15 (60%) became insulin independent. Ultimately, all patients succumbed to their malignancy, one of them having remained insulin independent for 5 years until her death. The reasons for these better results compared to the results of islet transplants in patients with insulin dependent diabetes mellitus (IDDM) are not clear. A possible explanation is that islets only had to overcome allograft rejection and not the autoimmune response associated with IDDM. The fact that these patients had cancer could have compromised their immunity and finally, the simultaneous liver transplant could have had a protective element.

Human Islet Autografts

Islet autotransplantation is performed for patients who undergo near-total pancreatectomy for relief of intolerable pain due to chronic pancreatitis. The risk of becoming diabetic is very high and transplanting the islets from the patients' own pancreas is a good option for avoiding it. Minneapolis has published the greatest experience (48 patients) with islet autotransplantation [21]. More than 80% of patients experienced significant pain relief after pancreatectomy. Unpurified islets were transplanted into the portal vein. 74% of patients who received more than 300 000 islets were insulin independent for more than 13 years. Of interest, as few as 65 000 islets were able to produce insulin independence while even more than 500 000 can fail in allotransplantation. This obviously reflects the detrimental effect of the autoimmune diabetic process, allo-rejection, and toxicity of the immunosuppressive drugs on islet allotransplants.

Islet Xenografts

There are approximately 30 000 new cases of IDDM in the USA each year but only 5000 available cadaveric donors of whom only a small proportion are suitable for pancreas procurement. The gap between organ demand and availability is increasing for all organs and there is therefore a need to develop another source of potential donors. Xenotransplantation is theoretically an ideal solution.

For physiological as well as ethical reasons, the pig is the animal most likely to be used for xenotransplantation, especially for islet xenotransplantation since porcine insulin only differs by one amino acid from human insulin and has been used for many years in the treatment of diabetics. Serum glucose levels in pigs are very similar to those of humans.

The major barrier for xenotransplantation from pigs to humans is the hyperacute rejection initiated by the reaction of human naturally occurring IgG and IgM antibodies against porcine antigens mainly expressed on vascular endothelial cells. Pig antigens recognised by human natural antibodies are carbohydrate antigens terminating with Gal α 1-3 Gal epitope [22]. It has also been demonstrated that humans have natural antibodies against the pig Thomsen-Friedenreich (TF) and

P^k antigens [23]. We have demonstrated that in the solid porcine pancreas, 100% of islets express Gal α 1-3 Gal, 97% express TF and 21% express P^k. The Gal α 1-3 Gal, TF and P^k antigens are expressed in the intra-islet capillaries before digestion. In some animals the TF antigen is also expressed by islet cells. After digestion with collagenase and isolation, only 12% of islets expressed Gal α 1-3 Gal, 13% expressed TF and 10% expressed P^k (all statistically significant, $p<0.001$) [24]. The significantly reduced expression of Gal α 1-3 Gal, P^k and TF antigens on adult porcine pancreatic islets after collagenase digestion, and the fact that vascularisation of transplanted islets seems to come entirely from recipient endothelial cells [25] which do not express porcine xenoantigens, may increase the possibility of a successful pig to human islet xenotransplantation. We have also demonstrated that cryopreservation can eliminate the residual expression of Gal α 1-3 Gal after collagenase digestion, increasing even more the possibility of success [26].

Immunoprotection of Islets

An interesting approach for immunoprotection of islet allo- and xenografts is their inclusion in a semi-permeable membrane, a procedure called microencapsulation. The idea is that the membrane would allow for nutrients and oxygen to reach the islets and for insulin to be released into the systemic circulation, but would prevent immune cells and antibodies from reaching the islets. Many studies have demonstrated that, although separated from normal vascular supply, the islets can survive and function well inside such membranes [27].

Many materials have been used for islet microencapsulation. The most commonly used is a bead of alginate gel and then coating of the bead with poly-L-lysine or some other material to provide hyperselectivity and strength. A successful study in this field reported that monkeys with spontaneous diabetes were transplanted with adult porcine islets contained in alginate/polylysine capsules and remained insulin independent for as long as 803 days without immunosuppression [28]. Despite these successful results, there are still major questions about how best to design microcapsules. A very important issue is the biocompatibility of the capsule material with host tissue and the contained islets. Another concern is the potential release of antigens and debris of the capsular material into the liver, the peritoneal cavity, or other sites of transplantation, which could cause an inflammatory reaction that would be difficult, if not impossible, to control, since the capsules cannot be easily removed. Finally, research continues for the development of capsule materials that would not provoke an inflammatory reaction by the host, resulting in pericapsule fibrosis and failure of the islets.

The Future of Pancreas and Islet Transplantation

The advances in immunosuppressive strategies and diagnostic technology will only enhance the already good results achieved with pancreas transplantation. Further documentation of the long term benefits and effects of pancreas transplantation may lead to wider availability and acceptance. Prevention of rejection and effective control with earlier diagnosis may soon permit solitary pancreas transplantation to become an acceptable option in diabetic patients without advanced secondary complications or diabetes. During the past decade, significant advances have been achieved in islet transplantation. The success of islet autografts indicates that successful engraftment and function of human islets is possible and, with some advancements in rejection monitoring and immunosuppression, results of islet allotransplantation will also improve. The recent developments in the field of islet xenotransplantation and microencapsulation enhance the belief that islet transplantation will become an ideal option for the treatment of IDDM. Currently, however, islet transplantation cannot compete with the results obtained with whole organ pancreas transplantation.

Therefore, while continuing with the tedious but promising research work to improve the results of islet transplantation, every patient with IDDM who meets the criteria should be offered the option of pancreas transplantation [29].

Summary:

The overall outcome for pancreas transplantation is excellent for patient, pancreas and kidney graft survival. The clinical application of islets is clearly more difficult, however the obstacles preventing success appear solvable and the future looks promising.

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