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Pancreas and Islet Transplantation

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Introduction

The syndrome of type I insulin-dependent diabetes mellitus (IDDM) includes not only abnormal glucose metabolism but also specific microvascular complications such as retinopathy, nephropathy and neuropathy. Diabetes mellitus is currently the leading cause of kidney failure and blindness in adults, the number one disease cause of amputations and impotence, and one of the leading chronic diseases of childhood associated with poor quality of life.
The aim of pancreas and islet transplantation is to establish the same status of glucose control that is provided by endogenous secretion of insulin from a healthy native pancreas in order to improve the quality of life and ameliorate secondary diabetic complications in patients with IDDM.
The first pancreas transplant in a human was performed by Kelly and Lillehei on 16 December 1966 at the University of Minnesota (1).
Islet transplantation is, theoretically, 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. Islet transplantation in humans has been performed systematically since 1974 and, as with pancreas transplantation, the University of Minnesota pioneered the field (2). However, despite tedious experimental and clinical efforts over the past 25 years, long term and consistent insulin independence has not yet been achieved.

Indications

Pancreas transplantation is indicated for patients with IDDM and additional selection criteria are listed in Table I. Patient selection is aided by comprehensive multidisiplinary pre-transplant evaluation with additional work up according to the specific problems of each patient. The evaluation initially confirms the diagnosis of IDDM, establishes the absence of any exclusion criteria, determines the patient's ability to tolerate a major operation (based primarily on the patient's cardiovascular status), and documents end-stage organ complications for future tracking following transplantation.

Riassunto

TRAPIANTO DI PANCREAS E DELLE INSULE PANCREATICHE

Lo scopo del trapianto di pancreas e quello delle insule pancreatiche isolate è quello di ristabilire lo stesso tipo di controllo glicemico determinato dalla increzione endogena di insulina da parte di un pancreas sano e normale, al fine di migliorare non solo la qualità di vita ma anche le complicanze secondarie nei pazienti con diabete mellito di tipo I insulino dipendente.
Il trapianto di insule rappresenta teoricamente la soluzione ideale per pazienti con diabete mellito insulino dipendente, perché non si tratta di un procedimento maggiore, può essere realizzato con tecnica radiologica e può essere ripetuto più volte senza particolare impegno per il paziente. Purtroppo però, nonostante gli sforzi sperimentali e clinici per oltre 25 anni, non è stata ancora raggiunta un'indipendenza di lungo termine dall'insulina. Il trapianto di pancreas è indicato per pazienti con diabete mellito insulino dipendente considerando anche altri parametri di selezione. In un candidato proponibile è necessaria anche una valutazione per definire il tipo di trapianto di pancreas soprattutto in rapporto al tipo di nefropatia.
Vengono esaminati analiticamente particolari dell'intervento sul ricevente insieme con i metodi anti-rigetto ed i risultati globalmente ottenuti allo stato attuale.
Analoghe considerazioni sono riservate ai procedimenti per il trapianto di insule.
Parole chiave: Trapianto di pancreas, trapianto di insule

Abstract

The aim of pancreas and islet transplantation is to establish the same status of glucose control that is provided by endogenous secretion of insulin from a healthy native pancreas in order to improve the quality of life and ameliorate secondary diabetic complications in patients with type I insulin-dependent diabetes mellitus (IDDM). Islet transplantation is, theoretically, 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, but despite experimental and clinical efforts over the past 25 years, long term and consistent insulin independence has not yet been achieved. Pancreas transplantation is indicated for patients

with IDDM following also additional selection criteria. In a suitable candidate, the evaluation is also needed to determine the type of pancreas transplantation, based mainly on the degree of nephropathy. Details of the recipient operation together with the anti-reject procedures and actual global results are described analytically. Similar considerations are dedicated to the islet transplantation procedure.
Key words: Pancreas transplantation, islet cells transplantation.

In a suitable candidate, the evaluation is also needed to determine the type of pancreas transplantation, based mainly on the degree of nephropathy. The degree of renal dysfunction (creatinine clearance below 20 ml/min) is used to select patients for simultaneous pancreas-kidney transplantation (SPK) versus pancreas transplant alone (PTA) (creatinine clearance above 70 mls/min). A third option is to transplant a pancreas after a kidney (PAK) in patients with IDDM who have already had a kidney transplant and who meet the criteria for pancreas transplantation. The criteria for SPK, PTA and PAK transplants are summarised in Table II.

Criteria for PAK

Patients with stable function of previous renal allograft that meet the criteria for PTA

Tab. I

Exclusion criteria
Insufficient cardiovascular reserve:
a) Angiography indicating non-correctable coronary artery disease
b) Ejection fraction below 50%
e) 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

Tab. II

Criteria for SPK
Diabetic nephropathy: creatinine clearance <20mls/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:
a) Proliferative retinopathy
b) Early nephropathy; creatinine clearance >70 mls/min, proteinuria >150 mg/24hr but <3 g/24 hr
c) Presence of overt peripheral or autonomíc neuropathy
d) Vasculopathy with accelerated atherosclerosis
Hyperlabile diabetes with:
a) Severe episodes of ketoacidosis
b) Severe and frequent episodes of hypoglycaemia
c) Hypoglycaemia unawareness
d) Severe and frequent infections
e) Impairment of quality of life
Criteria for PAK
Patients with stable function of previous renal allograft that meet the criteria for PTA.

Recipient Operation

The majority of pancreas transplants are performed in conjunction with a kidney transplant from the same donor through a midline incision intraperitoneal approach. The same approach is used for PTA and PAK transplants. The surgical approach to pancreas transplantation is similar to that for the kidney in many aspects. The pancreas is directed with the head towards the pelvis and, usually, the graft vessels are anastomosed end-to-side to the recipient common or external iliac vessels using 5-0 Prolene suture for the venous and 60 Prolene suture for the arterial anastomosis. If possible, the vessels are anastomosed to the right iliac vessels of the recipient, which are more superficial compared to the left iliac, vessels.

This minimises the chances of post transplant graft thrombosis. In order to prevent thrombosis of the portal vein of the pancreatic graft, it is important to ligate and divide the internal iliac vein in order to free the common and external iliac veins prior to the anastomosis with the portal vein. This type of venous anastomosis results in systemic drainage of the venous outflow of the pancreatic graft. More recently, the University of Tennessee (3) has introduced a portal drainage technique where the pancreas is placed head up and the portal vein anastomosed to one of the mesenteric veins. This achieves a more physiological drainage into the portal circulation. This technique is possibly associated with a higher rate of technical complications while there is no clear evidence that it has better metabolic results. The only possible advantage of portal drai-

nage is the absence of systemic hyperinsulinaemia which is characteristic of systemic drainage.
Several surgical techniques have been used to manage the exocrine secretions of the pancreatic graft, including urinary drainage, enteric drainage or polymer injection. Urinary drainage is currently the most popular, but enteric drainage has recently regained popularity. Duct injection is becoming less and less popular even in the European centres where it was first introduced (4).

Urinary Drainage

The creation of the duodenocystostomy starts by opening the bladder anteriorly and longitudinally. The anastomosis is done either manually or using a stapler, the latter being the most popular technique. The major advantage of this technique is the ability to detect pancreas rejection episodes early (before hyperglycaemia) by monitoring urinary amylase. It is, however, associated with significant morbidity including duodenal leaks, cystitis, urethritis, reflux pancreatitis, dehydration, acidosis and electrolyte abnormalities (5).

Enteric Drainage

The duodenum is anastomosed side-to-side in two layers to a loop of proximal ileum while avoiding any tension. The distal duodenum is closed as described earlier. The enteric drainage of exocrine secretions is more physiological in view of the bowel reabsorption. However, urinary amylase cannot be used as a rejection maker and eventual leaks can lead to severe complications.

Duct Injection

The injection of polymer into the main pancreatic duct is a very simple and fast technique, which leads eventually to the atrophy of the exocrine portion of the pancreas. Unfortunately it can lead too to the atrophy of the endocrine tissue, resulting in graft failure.

Immunosuppression

Optimal immunosuppressive strategies in pancreas transplantation aim at achieving effective control of rejection while minimising injury to the allograft as well as risk to the patient. Until recently a standard immunosuppressive protocol consisted of cyclosporine (cyclosporin A), prednisone and azathioprine combined with an induction course of anti-T cell monoclonal or polyclonal antibody (antilymphocyte globulin (ALG), antithymocyte globulin (ATG) or OKT3). Tacrolimus has replaced cyclosporine in 20% of centres and more recently mycophenolate mofetil (MMF) has been used instead of azathioprine (3). Studies have demonstrated higher patient and graft survival rates. Transplantation requires a lifelong commitment to immunosuppression. However, most patients find it easier to adjust to their immunosuppressive medications than to insulin, dietary and activity restrictions.

Results

From December 1966 up to date over 16000 pancreas transplants have been performed worldwide. The latest publication of the International Pancreas Transplant Register (IPTR) data includes 8800 pancreas transplants that had been performed from December 1966 to November 1996, including more than 6400 from the USA and more than 2300 from other countries (6). Most of those transplants (86%) were SPK, 8% were PAK and 5% were PTA. Outside the USA most were performed in Europe (91%). The leading country was France (19%), followed by Germany (16%), Sweden (10%) and Spain (7%).
For the 4592 bladder-drained pancreas transplants performed in the USA between October 1987 and November 1996, the patient survival rates at 1, 2, 3 and 5 years were 92%, 89%, 86% and 81% respectively. Graft survival at 1, 2, 3 and 5 years was 76%, 71%, 67% and 61% for all cases. When only the 4062 technically successful cases were considered, the 1-, 2-, 3- and 5-year graft survival was 85%, 81%, 76% and 72% respectively. When the same data was analysed by recipient category, the 1-, 2-, 3- and 5-year patient survival was 92%, 89%, 86% and 81% for SPK (n = 3989), 91%, 87%, 82% and 74% for PAK (n = 375), and 90%, 88%, 86% and 8 1 % for PTA (n 229) respectively. The patient survival rate was not significantly different ($p > 0.22$) between the three recipient categories. For the same period, graft survival at 1, 2, 3 and 5 years was 79%, 75%, 71% and 65% for SPK, 58%, 45%, 38% and 27% for PAK, and 56%,48%,40% and 32% for PTA, respectively. Graft survival was significanfly different between the three categories ($p = 0.0001$). The outcome was significantly better for SPK than for PTA but there was no difference between PTA and PAK ($p = 0.83$). The technical failure rate was lower in the SPK category compared to PTA. There was no significant difference for 1-year graft survival rates for primary versus retransplants in the SPK (79% vs 77%, $p > 0.10$) and PTA (57% vs 51%, $p > 0.8$) categoreis. In contrast, for PAK transplants, 1-year graft survival was higher in primary transplants than in retransplants (62% vs 47%, $p < 0.0001$).
The results of pancreas transplantation in European and other non-US centres are comparable to those in the USA. One-year patient survival for SPK in the USA, Europe and other countries was 92%, 91% and 86% respectively ($p = 0.08$). One-year graft survival forblad-

der-drained SPK in the USA, Europe and other countries was 79%, 73% and 70% respectively ($p < 0.08$). Likewise, 1-year graft survival for enterically drained SPK in the USA, Europe and other countries was 72%, 63% and 72% respectively ($p > 0.7$).

Effect of pancreas transplantation on secondary complications of IDDM

The results of patient and graft survival after pancreatic transplantation have significantly improved in the last decade. Pancreas transplantation is not a life-saving procedure, and the assessment of its effect on the progress of the secondary diabetic complications as well as the overall quality of life of pancreas transplant recipients is of great importance.

One major problem in studying the effects of pancreas transplantation on halting or, even more, reversing the progress of secondary diabetic complications is that many pancreas transplant recipients have end stage degenerative diabetic complications, for which there is no hope for improvement. In addition, since the majority of pancreas transplants are performed simultaneously with a kidney, it is difficult to differentiate and attribute any positive development after SPK to the effect of the normal status of glucose metabolism rather than to the corrected uraemia. Finally, most of the studies that deal with the effect of pancreas transplantation on diabetic complications are not multicentre prospective randomised trials with large numbers of patients and long-term follow-up from which reliable conclusions could be reached.

Retinopathy

There is some controversy on the effect of pancreas transplantation on diabetic retinopathy. Most of these studies were performed in patients already affected by proliferative retinopathy. In one of these studies with follow-up of 4 or more years after transplantation, stabilisation of retinopathy was observed, more than that observed in patients followed for the same period of time but whose pancreas transplants had failed (7). In another study two groups of diabetic patients were included: in the first group the patients underwent SPK and in the second a kidney transplant alone (8). The status of diabetic retinopathy remained unchanged in 88% and 90% of these patients respectively. The results were similar in another study performed in diabetic patients who underwent PTA; the post transplant euglycaemia did not change the course of diabetic retinopathy (9).

Nephropathy

In one study of diabetic patients who underwent pancreas transplantation after having had a successful kidney transplant, it was demonstrated that pancreas transplantation prevents, to some extent, recurrence of diabetic nephropathy and that the diabetic glomerular lesions were less severe compared to diabetic patients that underwent a kidney transplant alone (10). However, studies performed on patients who received a PTA showed that the diabetic glomerular lesions did not improve even after several years of achieving an insulin-independent euglycaemic state with pancreas transplantation (11).

Neuropathy

A number of studies have reported improvements in both motor and sensory nerve function as assessed by nerve conduction velocity in SPK compared both to recipients of kidney transplant alone and patients with pancreatic graft failure (12, 13). These studies clearly demonstrated that although the correction of uraemia by a simultaneous kidney transplant, or a kidney transplant alone, significantly improves motor and sensory nerve conduction, the presence of a pancreatic graft has an additional and important positive effect in improving peripheral neuropathy. Studies of the effect of pancreas transplantation on autonomic neuropathy were performed in PTA and compared to non-transplanted patients or patients after pancreas graft failure (14). The cardiorespiratory reflexes were evaluated in these patients and analysed in relation to the survival rate. These studies demonstrated that PTA with a functioning pancreatic graft had better survival rates compared to recipients with a failed pancreatic graft as well as compared to diabetics who were not transplanted. However, other studies of autonomic function following pancreas transplantation are less clear. In some, pancreas transplantation was associated with greater improvement in autonomic symptoms, even if they were accompanied by little objective evidence (15, 16).

Quality of life after pancreas transplantation

Patient and graft survival rates, the incidence of morbidity and the effect of transplantation on the secondary diabetic complications are definitely of great significance in evaluating the results. What is perhaps of even greater significance is the effect that pancreas transplantation has on the overall quality of life of diabetic patients. The effect on the quality of life is important for the evaluation of all modem therapeutic interventions, but it is even more important in the case of a non-life-saving organ transplant which carries a non-negligible risk and involves many social and financial aspects. It is encouraging that it is in the field of quality of life that many studies agree that pancreas transplantation has a very positive effect.

A detailed study evaluated the effect of pancreas transplantation on many different aspects of life quality of 157 diabetic patients (17). The results indicated a much better quality of life (satisfaction with physical capacity as well as leisure time activities) in recipients of SPK compared to pre-transplant pre-dialysis diabetic patients. In an interesting study, authors reported on the benefit of SPK compared to kidney transplant alone (18). Of all SPK, 90% had full-time occupations post-transplant compared to 50% of recipients of kidney transplant alone. In addition, lost working days decreased by 44% compared to the pre-transplant situation in the SPK, whereas in recipients of kidneys only there was no change. Furthermore, SPK achieved a better quality of life in physical well being, sole functioning and perception of self.

In another extensive analysis 131 recipients of pancreatic transplant 1 to 11 years post transplant were studied (19). Patients with functioning pancreatic grafts were compared with recipients with failed grafts who had good kidney function. The recipients with functioning graft compared to recipients with non-functioning grafts re-ported more satisfaction with the overall quality of life (68 vs 48%), felt healthier (89 vs 25%) and were able to care for themselves and their daily activities (78 vs 56%).

In a prospective study with 1 year follow-up using the Medical Outcome Study Health Survey 36-Item Short Form (SF-36) and comparing SPK recipients to kidney transplants alone and IDDM patients who did not receive a transplant, improvement of general health perception, social function, vitality and pain was seen in both transplanted groups. However, physical limitations improved only in SPK recipients (20). In addition, financial situation, physical capacity, occupational status, sexual and leisure time activities improved significantly for SPK recipients (21).

Islet Transplantation

Advantages and problems of islet transplantation

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 standardized immunosuppressive regimens such as steroids, cyclosporine and tacrolimus.

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) (22). Of these, only 27 (10%) became insulin independent for more than one week, 14 (5%) were insulin independent for more than one week, 14 (5%) were insulin independent for more than one year, and 1 patient was insulin independent for more than 4 years. Factors related to short term insulin independence are detailed in Table III. 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 (23). 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 it is possible for some of the transplanted islets to survive a long time 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.

Patients who underwent pancreatectomy and hepatectomy for extensive abdominal cancer followed by simul-

Tab. III

Factors related with insulin independence after islet allotransplantation

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

taneous islet and liver grafts had very good islet function post-transplant (22). 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 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.

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 (24). 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.

Conclusion - 8 Key Points for Clinical Practice

1. The aim of pancreas and islet transplantation is to establish the same status of glucose control that is provided by endogenous secretion of insulin from a healthy native pancreas in order to improve the quality of life and ameliorate secondary diabetic complications in patients with IDDM.
2. Optimal immunosuppressive strategies in pancreas transplantation aim at achieving effective control of rejection while minimising injury to the allograft as well as risk to the patient.
3. Pancreas transplantation is not a life-saving procedure, and the assessment of its effect on the progress of the secondary diabetic complications as well as the overall quality of life of pancreas transplant recipients is of great importance.
4. Pancreas transplantation prevents, to some extent, recurrence of diabetic nephropathy and that the diabetic glomerular lesions were less severe compared to diabetic patients that underwent a kidney transplant alone.
5. A number of studies have reported improvements in both motor and sensory nerve function as assessed by nerve conduction velocity in SPK compared both to recipients of kidney transplant alone and patients with pancreatic graft failure.
6. A much better quality of life (satisfaction with physical capacity as well as leisure time activities) in recipients of SPK compared to pre-transplant pre-dialysis diabetic patients.
7. 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.
8. While continuing with the tedious but promising research work to improve the results of islet transpiantation, every patient with IDDM who meets the criteria should be offered the option of pancreas transplantation.

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