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Editorial

Pancreatic transplantation for patients with Type I diabetes

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 USA diabetes costs $138 billion each year; that is one out of every $7 spent on health care. The aim of pancreas transplantation is to improve quality of life of patients with Type I insulin-dependent diabetes mellitus (IDDM) and to ameliorate secondary complications by establishing an insulin-independent euglycaemic state. This aim is achieved by engrafting insulin-producing β cells in the islets of Langerhans.

IDDM includes not only abnormal glucose metabolism but also specific microvascular complications such as retinopathy, nephropathy and neuropathy. Over the last 15 years, it has become increasingly evident that the microvascular complications of diabetes mellitus result from hyperglycaemia. Exogenous insulin therapy prevents acute metabolic decompensation and, when delivered so as to achieve near-normal glucose concentrations, reduces the frequency of many complications. Even in well-controlled patients, exogenous insulin administration does not achieve the level of control effected by endogenous insulin secretion, which responds to moment-by-moment changes in glucose concentration. Pancreas transplantation is the only treatment for IDDM that is able to induce insulin independence consistently and that normalises glucosylated haemoglobin.

Patients who can be considered for a pancreas transplant fall into three categories:

(i) Those who have had a previous kidney transplant and are already on anti-rejection drugs: pancreas after kidney (PAK).

(ii) Those who have failed or failing kidneys and need a kidney transplant. Such patients are on dialysis, or will soon need dialysis unless a kidney transplant is done first. In such patients, a kidney and pancreas can be transplanted simultaneously from a cadaver donor: simultaneous pancreas and kidney (SPK).

(iii) Those who need only a pancreas transplant, pancreas transplant alone (PTA). An individual whose kidneys have not failed can receive a pancreas transplant alone. Diabetic complications such as neuropathy must be present, or there must be extreme difficulty with diabetic control. This restriction is imposed because of the need for immunosuppressive drugs to prevent rejection.

Patient selection is aided by a comprehensive multidisciplinary pretransplant evaluation, with additional work-up according to the specific problems of each patient. Renal dysfunction with a creatinine clearance <20 ml/minute is used to select patients for simultaneous pancreas–kidney transplantation versus pancreas transplantation alone (creatinine clearance >70 ml/minute). If the creatinine clearance is 40–70 ml/minute the patient can be offered a pre-emptive kidney transplant.

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 using multiple agents at low doses. Since the mid-1980s, almost every programme has used cyclosporin in combination with azathioprine and prednisone for maintenance immunosuppression; most (>85%) also use anti-T cell agents for induction, although there is a recent change in practice to no induction at all. Lately, several institutions have achieved promising results using tracrolimus instead of cyclosporin for maintenance therapy. It is currently the primary immunosuppressant in 20% of pancreas transplants. Azathioprine is being replaced by mycophenolate mofetil (MMF).

Although transplantation requires a life-long commitment to immunosuppression, most diabetic patients find that they have fewer dietary and activity restrictions and a much better quality of life after pancreas transplantation. There is no evidence that immunosuppressive drugs are associated with any more complications than diabetes over a 20-year period. Early pancreas transplantation can prevent secondary complications and, even when done late, it has been shown to improve nerve damage caused by diabetes. It would be reasonable for a person with diabetes to choose to have a pancreas transplant with long-term immunosuppression rather than a lifetime with diabetes.

From 1966 to date over 15,000 pancreas transplantations have been performed world-wide, most in the last 10 years. According to the United Network for Organ Sharing (UNOS) Register [1] established in 1987:

- 84% of pancreas transplantations were preformed in conjunction with a kidney transplantation in patients who had imminent renal failure or were on dialysis.
- 8% were performed as a sequential pancreas-after-kidney transplantation.
- 6% were preformed as a solitary transplantation.
- 2% were preformed in conjunction with a single organ transplantation other than the kidney or with multiple organs.

The results of pancreas transplantation have improved progressively since the introduction of cyclosporin and, more recently, tacrolimus, plus the refinement of surgical techniques [2,3]. In an analysis of 4500 cadaver donor cases reported world-wide between 1987 and 1996 [1], the overall one-year patient survival rate was 92% and the one-year insulin-dependent rate was 79%[1]. One-year kidney graft survival rate was 70% in Europe, 78% in the USA and 75% in the rest of the world. In the last decade operative mortality has been 1 to 3 % in most established centres. At St Mary's Hospital, London we have introduced a new technique of whole organ kidney pancreas transplant with synchronous implantation of the two grafts, with an operative time of 120 $\pm$ 15 minutes, 100% patient and graft survival and minimal blood transfusion [4]. This experience should encourage many more centres to start this type of transplant.

In addition to correcting dysmetabolism and freeing the patient from exogenous insulin therapy, there is evidence that pancreas transplantation has a beneficial effect on the course of secondary diabetic complications. In some studies with follow-up of four years or more after successful pancreas transplantation, stabilisation of retinopathy was better then that 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. 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 improvement in autonomic symptoms, even it they were accompanied by little objective evidence of change.

The improvement in success rates has led to increasing interest in PTA in non-uraemic patients. More than 850 PTAs have been carried out so far world-wide. As recently as 1996 there was a big difference in the one-year graft survival between SPK (79%), PAK (60%) and PTA (57%), the main reason being the high incidence of rejection. Indeed, the incidence of late acute rejection was 7% in SPK, 25% in PAK and 41% in PTA.

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.

The advances in immunosuppressive strategies and diagnostic technology will improve the good results achieved with pancreas transplantation so far. Further documentation of the long-term benefits and effects of pancreas transplantation may lead to wider availability and acceptance. Effective control of rejection with earlier diagnosis or better prevention may soon permit solitary pancreas transplantation to become an accepted treatment option in diabetic patients without advanced secondary complications of diabetes. Although there is an appreciable morbidity rate after pancreas transplantation, complications can usually be managed without adversely influencing the outcome. Other strategies for the treatment of IDDM are being actively investigated, including islet cell and fetal pancreas transplants, xenogenetic islet gene therapy, implantable insulin pumps and bio-hybrid artificial pancreas units.

With regard to islet transplantation, since 1989 several groups have succeeded in establishing insulin independence in occasional diabetic recipients by intraportal islet transplantation. Consistent islet allograft success has recently been achieved by using multiple donors and a steroid-free immunosuppression regimen at the University of Alberta in Edmonton. Thus, engrafting an adequate β cell mass appears to be the critical factor for clinical islet transplant to succeed. The challenge now is to achieve consistent success with a single donor. That this goal should be possible is apparent from the fact that islet auto transplantation after total pancreatectomy can sustain insulin independence, as shown by the very first case in the late 1970s.

Perhaps there will be a role for both islet and pancreas transplantation , with islet transplantation reserved for diabetic individuals with a low insulin requirement, while pancreas transplant may be preferable for those with a high insulin requirement or insulin resistance, such as those with Type II diabetes. Pancreas transplantation will also be preferred in individuals who are diabetic as a result of total pancreatectomy, in whom enteric drainage could be used to correct exocrine deficiency, as was first done in the 1980s. Indeed, if an unlimited supply of β cells for transplantation could be obtained (xenografts of human cell lines), the future of pancreas transplantation could primarily be to correct exocrine deficiency, for which the groundwork has already been laid [5].

Although any or all of these methods may have a role in the treatment of IDDM in the future, it will be difficult for these alternative strategies to improve on the metabolic efficiency of the vascularised pancreas transplant. With the improvement in quality of life and the potential reversing effect on diabetic complications, pancreas transplantation may become a more common transplant procedure and may soon become the treatment of choice for IDDM.

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