

Diabetic nephropathy and β -cell replacement therapy

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ABSTRACT

Whole pancreas transplantation can effectively restore endogenous insulin secretion in type 1 diabetes mellitus, and prevent, retard, or reverse diabetic complications. The effect of a simultaneous pancreas and kidney transplantation (SPKT) on diabetic complications is variable. These reports must be interpreted in the light of the fact that most recipients received a pancreas in combination with a kidney graft after having already had diabetes for over two decades. Nevertheless, the potential benefits should also be balanced against the risk of perioperative morbidity and the requirement of long-term immunosuppressive medication. Transplantation of a whole pancreas is currently the only reliable option to achieve long-term normoglycaemia. The success of pancreatic islets transplantation will ultimately depend on the longevity of pancreatic islets, requiring further development of immunosuppressive regimens which are not toxic to the islets and prevent recurrent autoimmune destruction of transplanted pancreatic β -cells.

PREVENTION OF PROGRESSIVE DIABETIC NEPHROPATHY

Type 1 diabetes mellitus is an evolving disease with a rapid increase in incidence around the world and particularly in children under five years of age. According to the World Health Organisation, approximately 1.3 and 1.4 million individuals are affected with type 1 diabetes mellitus in Europe and the United States, respectively. Diabetes is already the most common single cause of end-stage renal disease (ESRD), both in the USA and Europe. About 20

to 30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy. Due to the much greater prevalence of type 2 diabetes, these patients constitute over half of those diabetic patients currently starting on dialysis. In type 1 diabetes, however, a considerably larger proportion of patients progress to ESRD.

The Diabetes Control and Complications Trial (DCCT) demonstrated an approximately 50% reduction in the prevalence of eye, nerve and kidney complications with intensive treatment for hyperglycaemia.¹ This has clearly led to increased interest in reducing blood glucose concentrations to normal to delay the development and progression of diabetic complications. In native kidneys, the earliest clinical evidence of nephropathy (incipient nephropathy) is the appearance of microalbuminuria (>30 mg/day). Without specific intervention, about 80% of type 1 diabetic patients with sustained microalbuminuria progress to overt nephropathy (>300 mg/day) within 10 to 15 years and develop hypertension along the way. Approximately 50% of type 1 diabetics with overt nephropathy will progress to ESRD within 10 years and more than 80% within 20 years. Many studies have shown that in hypertensive patients with type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors can reduce the level of albuminuria and can reduce the rate of progression of renal disease.² It has also been shown that there is benefit in reducing the progression of albuminuria in normotensive type 1 diabetic patients.³ As well as being the earliest manifestation of nephropathy, albuminuria is a strong predictor of greatly increased cardiovascular morbidity and mortality for patients with diabetes mellitus. Approximately 30% of diabetics with ESRD who enter renal replacement therapy have significant

coronary artery disease, which may be asymptomatic or not associated with conventional cardiovascular risk factors.⁴ The excess cardiovascular morbidity is also clearly reflected in a 10% annual mortality rate while on maintenance dialysis.⁵ If despite optimal glycaemic control and aggressive antihypertensive treatment (including the use of ACE inhibitors and/or angiotensin-receptor blocker therapy) progression occurs to overt nephropathy, then virtually all patients with type 1 diabetes will ultimately progress to ESRD and experience significant cardiovascular morbidity and excess mortality.⁶

DIABETES MELLITUS TYPE 1 AND PANCREAS TRANSPLANTATION

Pancreatic transplantation was first used for the treatment of diabetes in humans in 1966. The introduction of better immunosuppressive agents (calcineurin inhibitors and anti T cell antibodies), new surgical techniques, and the selection of healthier recipients has resulted in markedly improved outcomes over the past decades. As a result, the number of pancreatic transplantations has steadily increased each year. By the end of 2001, well over 16,000 pancreas transplants had been recorded in the International Pancreas Transplantation Registry. Pancreas transplantation is most commonly performed in three settings: pancreas transplantation alone in the nonuraemic diabetic patient with minimal or no evidence of diabetic nephropathy (PTA); pancreas transplantation after a successful kidney transplant (PAKT) and, in over 80% of cases, as a simultaneous pancreas and kidney transplant (SPKT) in uraemic patients.

The options for insulin-dependent patients with diabetes mellitus type 1 (IDDM) and ESRD include dialysis, a kidney transplant (deceased or living donor), or a SPKT.⁷ After three decades of controversy surrounding the therapeutic validity of pancreas transplantation, a SPK transplantation has become the preferred treatment option for IDDM patients with advanced diabetic nephropathy and (or approaching) ESRD.⁸ Kidney transplants accompanied by pancreas transplants from cadaver donors have similar, if not better, long-term survival rates than those of cadaver and haplo-identical living donor kidneys transplanted alone.^{9,10} Proper patient selection is crucial to the success of SPKT. In general, type 1 (C-peptide deficient) insulin-dependent diabetics younger than 50 years of age are considered potential candidates and patients with significant uncorrected coronary artery disease are excluded. Recipient age and obesity appear to affect patient survival more than immunological graft loss.¹¹ The principal consideration in the selection of candidates, however, remains the balance between cardiovascular risk and the benefits of long-term normoglycaemia with regard to quality of life, end-organ

disease, and mortality rates. Major amputations secondary to severe peripheral vascular disease or severe visual impairment are not considered absolute contraindications. These patients will benefit from reversing uraemia, but are less likely to derive improved function at the end-organ level from restitution of normoglycaemia. Studies on the efficacy of pancreas transplantation on diabetic microvascular and macrovascular disease must therefore be interpreted in the light of the fact that most recipients received a pancreas in combination with a kidney graft after having already had diabetes for over two decades. Perhaps even more important, pancreas transplantation seems to be a treatment option that can improve survival rates in type 1 diabetes with advanced, often irreversible, end-organ damage.⁵

The goals of pancreas transplantation have developed beyond simply restoring normoglycaemia for a period of time and improving quality of life.¹² Pancreas transplantation, as simultaneous pancreas-kidney transplantation, is nowadays a functional and effective therapy that can reverse metabolic abnormalities and prevent or minimise many of the secondary complications of diabetes, including coronary artery disease, amputation and blindness.^{13,14} We can expect that also the lesions of diabetic retinopathy will be prevented or their progression slowed if β -cell function is restored when eye disease is still at an early stage. Recent results suggest that, with the newer immunosuppressive agents, pancreas transplantation alone in nonuraemic type 1 diabetic patients may be as successful as SPKT.¹⁵

DIABETIC NEPHROPATHY AND EARLY PANCREAS TRANSPLANTATION

The obvious benefits of normoglycaemia would theoretically be even more profound if it becomes possible to perform pancreas transplantation or islets transplantation alone for patients without significant renal dysfunction, early in the course of diabetic nephropathy and other complications.^{13,14} Single pancreas transplantation has generally been reserved for patients in whom glucose control is extremely difficult to achieve without frequent episodes of life-threatening hypoglycaemia. Nowadays, the circumstances where the risk-benefit equipoise could potentially favour pancreas transplantation may well include patients with diabetes mellitus type 1 and sustained overt diabetic nephropathy despite aggressive early intervention.^{6,16} While the risks of immunosuppression are not to be underestimated, it should also be recognised that short-term morbidity and mortality after pancreas transplantation are due primarily to the chronic complications of diabetes, that rejection rates with current immunosuppressive regimen are low and that pancreas transplantation is currently the only reliable option to achieve long-term restoration of normal glucose metabolism.

IS PANCREAS TRANSPLANTATION SUPERIOR TO INTENSIVE INSULIN TREATMENT?

There are at least three reasons why pancreas transplantation is superior to intensive insulin treatment with regard to glycaemic control and the course of diabetic complications. First, the mean glycosylated haemoglobin levels in patients long term after pancreas transplantation (5.5% at five years and 5.5% at ten years) were lower than the target value of 6.0% defined in the Diabetes Control and Complication Trial (DCCT), a value that was reached at least once in only 44% of the patients in the intensive treatment group.¹ It is noteworthy that, after pancreas transplantation in nondiabetic patients, normoglycaemia was achieved despite long-term immunosuppressive treatment, which may cause insulin resistance and impaired glucose tolerance.

Secondly, in patients with intensive insulin treatment, progressive reductions in glycosylated haemoglobin values are achieved at the expense of more hypoglycaemic episodes, whereas pancreas transplantation maintains normoglycaemia without causing severe episodes of hypoglycaemia. In this context it is important to know that patients with frequent hypoglycaemic episodes were excluded from participation in the DCCT trial.¹ Finally, whole pancreas transplantation is currently the only reliable option to achieve long-term euglycaemia and prevent (or reverse) diabetic nephropathy and other diabetic complications. Recurrent diabetic nephropathy develops in almost all diabetic patients undergoing renal transplantation. Glomerular basement thickening and mesangial expansion are seen by two years, followed by hyalinisation of the afferent and efferent arterioles by four years. Moreover, the extent of the coronary angiographic findings in candidates evaluated for transplantation had a strong predictive value for subsequent vascular events occurring within three years after a successful SPKT.¹⁷ Intensive treatment with insulin can only delay progression of the morphological changes of early diabetic nephropathy, while approximately ten years of normoglycaemia were found to be necessary to reverse established nephropathy.¹⁸

PANCREAS TRANSPLANTATION, AUTOIMMUNITY AND ALLOIMMUNITY

The results reported after SPKT continue to improve. For instance, the transplant group at the North-Western University recently reported 100% patient and graft survival following SPKT in 40 consecutive recipients.¹⁹ The incidence of rejection at one year was reported at 2.5%, which is remarkable considering this was accomplished with a steroid-free regimen. Unlike autoimmune diabetes mellitus, acute rejection of the pancreas is usually directed principally

against acinar tissue, not the islets. In IDDM patients, a transplanted pancreas should be as susceptible to the autoimmune process as the native pancreas. Indeed, insulin-dependent diabetes can recur in an immunocompetent or a minimally immunosuppressed recipient of a pancreatic transplant from an identical twin or human leucocyte antigen (HLA) identical sibling. When a portion of the pancreas of a normal twin is transplanted into a diabetic twin, recurrent autoimmunity with selective β -cell destruction occurs in the recipient.²⁰ The donor and recipient of a pancreatic graft do not have to share HLA antigens for recurrent autoimmune destruction of the graft.²¹ The recipient must therefore receive immunosuppressive therapy, not only to prevent alloimmunity (rejection of transplanted tissue from a genetically different person) but also to prevent recurrent autoimmune islet destruction. Immunotherapies, including those specifically directed against T cells, have been shown to delay disease progression in patients with IDDM of recent onset but did not prevent β -cell dysfunction.^{22,23} This delay was not accompanied by changes in autoantibody levels, providing evidence of the immunological memory of islet-specific T cells.²⁴ It is most likely that the degree of immunosuppression required to prevent acute rejection is also sufficient to prevent recurrent autoimmune damage in the majority of recipients of a vascularised pancreas.

WHAT ARE THE DRAWBACKS FOR PANCREAS TRANSPLANTATION?

The drawbacks for whole pancreas transplantation are the necessity of major surgery, with perioperative and postoperative morbidity, as well as the lifelong need of immunosuppressive medication. It is hoped that the less invasive procedure of islets cell transplantation will convey the same benefits, with respect to survival rates and diabetic complications, as do PTA and SPKT at the present.^{12,15} This approach with percutaneous, transhepatic portal vein transplantation of pancreatic islets is minimally invasive and relatively safe, but requires long-term immunosuppression as well.²⁵ Another limitation of human islets transplantation continues to be the variability with which viable human islets can be obtained from the human cadaver pancreas. The majority of patients who achieved insulin independence required several infusions of islets isolated from at least two donors per infusion. The increasing shortage of organs available for transplantation demands further refinement in single donor islets transplant protocols or ultimately the use of xenogeneic or stem cell sources before islets transplantation can be routinely introduced. In contrast to most studies of transplantation of islet allografts in diabetic patients, islets autograft transplantation has been remarkably successful in nondiabetic patients

after total pancreatectomy for chronic painful pancreatitis. Many of these patients have been documented with normoglycaemia and normal HbA_{1c} values for up to 13 years after transplantation.²⁶ Immunosuppressive drugs, and steroids in particular, given to the allograft recipients may have an adverse effect on the function of transplanted islets.²⁵ Ultimately, the success of human islets transplantation will be dependent in obtaining a more reliable source of β -cells, the longevity of pancreatic islets, and further development of immunosuppressive regimens which are not toxic to islets but prevent recurrent autoimmune destruction.

PANCREAS TRANSPLANTATION AND LONG-TERM INSULIN INDEPENDENCE

The key issue in preventing progression or reverse diabetic complication is the longevity of insulin independence following transplantation. The largest series of pancreatic islets transplantation performed at the University of Alberta has reported insulin independence up to three years following islets transplantation, but most patients have required further infusions of pancreatic islets to obtain insulin independence again.²⁷ Whole pancreas transplantation is currently the only reliable option to achieve long-term insulin independence. Between 1986 and 2002 more than 150 simultaneous pancreas-kidney transplants were performed in the Leiden University Medical Centre. The five-year and ten-year pancreas survival in this cohort of patients, defined as freedom from exogenous insulin, was 74 and 71% respectively. In contrast to islets transplantation, these results were obtained using a single pancreatic graft.

CONCLUSION

Intensive treatment with insulin can only delay progression of the morphological changes of early diabetic nephropathy, and up to ten years of normoglycaemia were found to be necessary to reverse established nephropathy. At the present whole pancreas transplantation is the only reliable option to achieve long-term insulin independence and an SPK transplantation has become the preferred treatment option for selected IDDM patients with advanced diabetic nephropathy and (or approaching) ESRD. Another option one may consider, especially if the waiting time for a pre-emptive (i.e. before initiation of dialysis) SPKT is prolonged, is a cadaver pancreas graft after a living (un)related kidney transplantation.

The American Diabetes Association strongly endorses pancreas transplantation in diabetic patients who have received prior kidney transplants and who have life-threatening metabolic instability. As results improve, isolated

pancreas transplantation will be offered with increasing frequency to diabetics with preserved renal function. Nowadays, the circumstances where the risk-benefit equipoise could potentially favour pancreas transplantation may well include patients with diabetes mellitus type 1 and sustained overt diabetic nephropathy (albuminuria >300 mg/day) despite aggressive early intervention using ACE inhibitor and/or angiotensin-receptor blocker therapy.

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