Pancreas transplantation

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Abstract

Pancreas transplantation is now standard of care for selected patients with diabetes and end-stage renal failure or life-threatening diabetic complications. The morbidity and mortality of pancreas transplantation is higher than other transplant types, and for this reason selection criteria for both donors and recipients are more stringent. Meticulous organ retrieval technique and back-table preparation, and a standard implantation technique using enteric drainage are central to good outcomes. Modern immunosuppression has reduced acute rejection rates and lowered the need for long-term corticosteroids. Results have improved over time and recipients of a simultaneous kidney–pancreas transplant can now expect 5-year transplant survival of around 75%. The addition of a pancreas to a kidney transplant for suitable recipients has clear benefits in both length and quality of life, and there is increasing evidence that pancreatic transplantation can reduce or halt the progression of diabetic nephropathy, neuropathy, retinopathy and cardiovascular disease. In patients with normal renal function, pancreatic islet transplantation offers an alternative with reduced peri-procedural morbidity and mortality, at the expense of lower rates of long-term insulin independence.

Keywords Diabetes; islet transplantation; pancreas transplantation

Introduction

Clinical transplantation of the pancreas was first performed in December 1966 at the University of Minnesota Hospital. Since then over 35,000 pancreases have been transplanted worldwide with an annual rate of approximately 2000.[1] In the UK, where there has been central NHS funding of pancreas transplantation since 2004, there were 463 pancreas donors in the financial year 2015/2016, resulting in 185 solid-organ pancreas transplants (90% of which were transplanted simultaneously with a kidney) and 30 islet transplants. Pancreas transplantation has evolved from being an experimental to a routine procedure, but these relatively small numbers also reflect that transplantation of the pancreas does not yet have the impact of kidney or liver transplantation. Indeed, annual numbers of pancreas transplants worldwide have been declining over recent years, with falls of around 10% in the past decade mainly resulting from a decrease in pancreas-alone transplants in the US.[2]

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Indications

Pancreas transplantation is the only curative treatment for patients with diabetes mellitus. Traditionally, only patients with type-1 diabetes were candidates for pancreas transplantation. This disease is characterized by immune-mediated destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas leading to complete insulin deficiency. However, this accounts for only about 10% of all cases of diabetes mellitus in a Caucasian population. In such patients pancreas transplantation can restore the physiologic hormone balance and, if performed at early stage, pancreas transplantation probably has the potential to stabilize or improve the complications of long-term diabetes (e.g. retinopathy, nephropathy, and neuropathy).

In contrast, type-2 diabetes is often characterized by obesity and peripheral insulin resistance and, until recently, it was generally accepted that pancreatic transplantation would not be of benefit. However, it is increasingly clear that there is a wide spectrum of conditions with the label of type-2 diabetes and several recent reports have demonstrated improved glycaemic control after pancreas transplantation in subsets of type-2 diabetic patients. Thus, the old paradigm is no longer generally applicable, and 7% of pancreas transplants are performed in type-2 diabetic patients.[1,3] Suggested criteria for suitable type-2 diabetic patients include longstanding insulin dependence with requirements less than 1 unit/kg/24 h, BMI less than 32 kg/m^2 and absence of cardiovascular disease.[4]

Solid organ pancreas transplantation

Three main types of solid organ pancreas transplant are commonly performed.

Simultaneous transplantation of pancreas and kidney

SPK is the most common type of pancreas transplant, accounting for around 90% of all procedures. A combined kidney and pancreas transplantation is generally recommended for patients with type-I diabetes and chronic renal failure. These patients receive both a kidney and pancreas from a single deceased organ donor.

Pancreas transplantation after kidney transplantation

PAK is performed in diabetic patients who have had a successful kidney transplant. This type of transplant is particularly relevant to the growing number of diabetic patients who initially undergo kidney transplantation from a living donor. Today 8–15% of pancreas transplants are performed as PAK.

Pancreas transplantation alone (PTA)

Patients with type-I diabetes with (yet) normal kidney function but life-threatening diabetic complications (e.g. hypoglycaemic unawareness) or rapidly progressing and severe side effects of type-I diabetes (neuropathy, retinopathy, etc.) may be suitable to receive a pancreas transplant alone. The decision is based on a risk-benefit analysis, comparing the risks of on-going diabetes

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with those of transplantation (particularly long-term immunosuppression). Historically, this type of pancreas transplantation has been associated with inferior outcomes when compared to SPK, and most of the recent decline in transplant numbers is in this group.

Islet transplantation

Islet transplantation is the transplantation of a purified preparation of isolated pancreatic islets. In order to achieve insulin independence, transplantation of two or more donor organs may be needed sequentially. In most, if not all, clinical programmes, the islets are infused via the portal vein, which is accessed by a radiological, trans-hepatic approach, into the liver. The strategy of transplanting only the endocrine component of the pancreas is highly attractive — this comprises only about 2% of the gland and excludes the exocrine component that is responsible for much of the morbidity of the whole organ transplant. At present, however, the medium-term results of islet transplantation are inferior to those of the whole organ, with many transplanted patients reverting to insulin by 5 years. Nevertheless, islet transplantation continues to reduce the need for insulin, improves blood glucose control, and greatly reduces the risk of episodes of severe hypoglycaemia (hypoglycaemic unawareness) in the selected group of diabetic patients.

Recipient selection

Whilst pancreatic transplantation may potentially benefit any type-1 (and selected type-2) diabetic patients in the categories defined above, the risks of transplantation must be weighed against the potential benefits for each recipient. An assessment must be made of the potential additional benefit of a pancreas transplant over that of a kidney alone. Transplantation of the pancreas is associated with greater perioperative morbidity and mortality than renal transplantation, and the diabetic patient population have a high incidence of cardiovascular and peripheral vascular disease. The importance of adequate pre-transplant assessment cannot be overemphasized, which may include 12-lead ECG, echocardiogram, myocardial perfusion studies and cardiac stress testing depending on local protocol. Any cardiac disease that is detected should be treated prior to addition to the waiting list; untreatable cardiac disease is a contraindication.

The usual contraindications to transplantation apply to this population, including recent history of malignancy and active infection. Most units have an upper age limit of around 60 years of age, and would exclude patients with a body mass index (BMI) or greater than 30, although there is a tendency to widen recipient selection criteria over time.[1]

Donor selection

Whilst selection criteria for recipients have relaxed over time, the criteria for selection of potential donors have tended to become more restrictive in recent years. This trend has occurred on the realization that the penalties of transplanting a substandard organ are severe, and pancreas transplantation is not an immediately life-saving operation. This represents a significant challenge in light of the increasingly marginal donor population, with more donors after cardiac death (DCD) and older, obese donors.

Absolute contraindications include donor diabetes, acute or chronic pancreatitis, transmissible infection and malignancy. The ideal donor is a donor after brain-stem death (DBD), less than 45 years of age, haemodynamically stable, BMI less than 30 and with only a short period of intensive care treatment. However, most pancreas centres transplant organs from donors with a broader limit of inclusion criteria. The upper age limit varies, with differences between transplant centres, between 50 and 60 years. Grafts from older donors and a cerebrovascular cause of death have a higher risk of primary non-function. Signs of fatty infiltration or fibrosis of the organ are markers for poor outcomes. Fatty infiltration, in particular, increases the risk of reperfusion pancreatitis and for this reason most units have an upper limit for donor BMI of 30 kg/m^2. However, recent evidence suggests that carefully selected donors with BMIs between 30 and 35 kg/m^2 may have equivalent outcomes.[5] The risk factors for poor outcome are likely to be additive, which has led to the development of tools to assess donor risk and guide organ use.[6]

Organs which qualify for islet separation share many of the requirements with whole organ grafts; however, some differences exist: isolation of the islets of young donors (<18 years) is technically challenging, whereas these are excellent whole pancreas donors. In contrast to solid organ transplantation, older donors may make good islet donors. Pancreases from obese donors have a higher β-cell mass and may be good islet donors. However, there is substantial overlap between the solid organ and islet groups with respect to suitable donor organs and the system of allocation may be controversial.[7]

Surgical technique

The donor operation

Technique: almost every pancreas retrieval is part of a multi-organ retrieval. After an initial period of dissection in the warm phase, the abdominal organs are then perfused in situ with ice-cold preservation solution. The pancreas is usually retrieved together with the spleen after removal of the liver; alternatively, the pancreas can be retrieved en-bloc with the liver and the organs then separated during back-table preparation. The advantage of the latter is a faster organ removal and shorter warm ischaemic time; however, this procedure might be technically more challenging. The pancreas is very easily injured and any parenchymal damage can render the organ unusable.

The nature of the in situ perfusion is important. If the liver is perfused via the portal vein as well as the aorta, it is important to avoid obstruction to the portal venous outflow of the pancreas as this leads to venous distension. This situation is most likely to apply when a portal cannula is inserted via the superior or inferior mesenteric veins. Pancreas outflow can be secured by insertion of the portal vein cannula above the pancreas after the initial aortic cold flush and complete transection of the portal vein after insertion of the cannula.

Commonly occurring pathology, particularly fatty infiltration or fibrosis, cannot be detected before retrieval surgery; this highlights the importance of an experienced surgical team for evaluation of the organ during surgery. The lack of clarity in quantifying 'donor quality' significantly contributes to the high number of pancreases being discarded for transplantation.[8]

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