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Review

The current challenges for pancreas transplantation for diabetes mellitus

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ABSTRACT

Pancreas transplantation is an accepted treatment for a subset of patients with diabetes mellitus, in particular those with renal failure who also require a kidney transplant and those with life-threatening hypoglycaemic unawareness. As results have improved and demand has risen, attention has focused on increasing the availability of pancreas transplantation by utilising pancreases from less than ideal donors, as well as addressing factors that limit the longevity of graft survival. The development of islet transplantation has posed additional demands on donor pancreas availability, as well as posing new challenges for donor organ allocation. This review focuses upon some of the current areas of interest in pancreatic transplantation.

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Introduction

In the 47 years since Lillehei's pioneering work [1], pancreas transplantation has become accepted as an effective treatment for diabetes mellitus, restoring good glucose control and so reducing the progression of, or permitting the reversal of some of the secondary complications of diabetes [2–4]. It remains limited by the availability of donor organs, the need for continued immunosuppression, and the magnitude of the initial surgical assault. While the early results of pancreas transplantation have improved over time (one-year survival 85% for the era 2005–2007, compared to 77% for 1987–1989, UNOS data), the long term survival has shown less variation [5]. This paper reviews the current status of pancreas transplantation, and looks at some of the areas of recent innovation and other areas of continued uncertainty.

Types of pancreas transplantation

The pancreas is transplanted either in combination with a kidney, commonly called simultaneous pancreas and kidney transplantation (SPK), or by itself as a solitary pancreas transplant. Solitary pancreas transplantation is usually performed in patients already on immunosuppression following a previous kidney transplant (pancreas after kidney, PAK), but may be performed in isolation (pancreas transplant alone, PTA).

Solitary pancreas transplantation

The need for immunosuppression, with its side effects and attendant risks from infection and malignancy, have generally restricted pancreas transplantation to those patients who will also need immunosuppression for the purpose of kidney transplantation in order to treat their end-stage diabetic nephropathy. Otherwise the hazards of immunosuppression, coupled with its nephrotoxic nature, are considered to outweigh the benefits of pancreas transplantation [6]. This is not the case in patients with life-threatening hypoglycaemic unawareness, who have a much higher mortality without islet replacement [7]. It is this group of patients who are candidates for a solitary pancreas transplant, but are equally good candidates for islet transplantation. However, the differing magnitudes of the procedures have meant that patients and clinicians prefer the less invasive islet transplantation, even though it requires more donor pancreases to produce a successful transplant and insulin independence is not certain (albeit may not be required) [8]. One of the unintended consequences of repeated islet transplants is the development of antibodies to human leukocyte antigens (HLA-antibodies) [9–11], which may limit access to future transplants of either islets, whole pancreas, or kidney. The latter is particularly relevant since the immunosuppression commonly used for islet (and pancreas) transplantation is nephrotoxic, and may hasten renal failure in patients with early nephropathy.

The results of solitary pancreas transplantation, like islet transplantation, are inferior to those of combined kidney and pancreas transplantation [12]. One reason may be the delay in recognising acute rejection. Rejection in combined pancreas and kidney transplantation (SPK) is usually concordant, that is, the kidney and pancreas are rejected at the same time; a rise in creatinine is a relatively early event in renal rejection, prompting renal biopsy, early diagnosis and treatment, often at a time when there are minimal features of pancreatic dysfunction such as a raised amylase or lipase. Most rejection in the pancreas component of an SPK is thus detected and treated by default when renal rejection is treated. Moreover the kidney is an easy organ to biopsy, in contrast to the pancreas. Absence of a kidney to act as surrogate results in delayed recognition of rejection in the solitary pancreas recipient, and delayed diagnosis makes successful treatment more challenging. The occurrence of hyperglycaemia in a patient with pancreatic rejection is a late and usually irreversible feature. Nevertheless improving results from solitary pancreas transplantation have resulted in expansion of its indications to include severe retinopathy and early nephropathy as the balance between the long term benefits of euglycaemia and the side effects of immunosuppression changes [13].

Combined kidney and pancreas transplantation or pancreas after kidney?

Renal failure carries a high mortality in patients with diabetes and, while a combined kidney and pancreas transplant may be the ideal treatment for a diabetic patient with end stage renal failure, the period of time spent waiting for organs to become available is associated with significant mortality, particularly if that wait extends beyond a year [14–16]. The best results for SPK transplantation come when the transplant occurs before dialysis had started [16].

The waiting time for an SPK varies within and between countries depending upon the allocation schemes in place. Much of the variation relates to the relative priority given for a donor kidney to accompany the pancreas rather than be allocated to a patient awaiting a kidney alone; until recently in the USA it was left for the organ procurement organisation to decide on the priority given for SPK versus pancreas or kidney transplant alone for all but the best matched, most highly sensitised recipient (HLA 0-0-0 mismatch, cPRA$\geq$80%) [17]. In the UK recipients awaiting an SPK have priority for a kidney above all but the best matched and most sensitised renal recipients [18,19]. Since there is a preference to use a younger donor pancreas for transplantation, priority to allocate a kidney for SPK transplantation, rather than kidney transplantation alone, not only results in younger donor kidneys being lost to the pool of patients awaiting solitary kidney transplantation, but also to shorter waiting times for an SPK than for a solitary kidney transplant [20]. The argument in favour of such a system is that the survival of a diabetic patient on the waiting list for an SPK is much poorer than a non-diabetic awaiting a kidney alone, and hence the relative priority to get a transplant if you have diabetes is balanced. Nevertheless such a priority has been perceived as unfair by some allocation systems, and in particular in parts of the US where the pancreas was not until recently given priority for a kidney, resulting in longer waits for an SPK [21].

An alternative to waiting on dialysis for a deceased donor is to have a kidney transplant alone, preferably from a live donor since this can often be arranged prior to requiring dialysis, followed some time later by a deceased donor pancreas transplant [22,23]. There is a definite short term survival benefit in favour of a live donor kidney transplant compared to SPK because it is an elective procedure of lesser magnitude. An SPK in contrast is a bigger procedure but, beyond a year, the benefit in patient survival is in favour of an SPK with its superior diabetic control; both are superior to a deceased donor kidney alone [22,24–27]. However while patient survival is superior when undergoing sequential living donor kidney followed by deceased donor pancreas transplantation, the outcomes of the pancreas remain inferior to those achieved when it is transplanted as part of an SPK [24,25]. One deficiency in currently published data are the paucity of studies where patient survival is quoted from the point of wait listing or starting dialysis, rather than from the point of transplantation, making it difficult to assess the overall benefit of each strategy to the recipient in different healthcare settings.