



PANCREAS TRANSPLANTATION – BENEFITS AND RISKS FOR DIABETIC PATIENTS

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Abstract

Pancreas transplantation is considered a valuable therapeutic option in diabetic patients, either alone or combined with renal allografts in transplant candidates with imminent or established end-stage renal disease. Improvements in transplant techniques, diverse immunosuppression regimens, a better donor -recipient HLA matching and frequent post-transplant monitoring have resulted in increased number of pancreas recipients, with increased graft survival and a better quality of life. The benefits consist of normalization of glucose metabolism, insulin independence and elimination of acute complication such as hypoglycemia, marked hyperglycemia or ketoacidosis. In addition, pancreas transplantation partially reverses or stabilizes secondary complications of diabetes. This is a review of the current literature regarding the types of pancreas transplantation, their indications and the novel immunosuppressive regimens used.

keywords: *pancreas, transplant, diabetes, kidney, immunosuppression*

Introduction

In the last decades, pancreas transplantation in Type 1 diabetes mellitus (T1DM) gained a lot of interest. As per American Diabetes Association, pancreas allotransplantation (PT) is considered an

acceptable therapeutic alternative to continued insulin therapy in diabetic patients with imminent or established end-stage renal disease (ESRD) who had or plan to have a kidney transplant [1].

First whole organ pancreas transplantation was performed in 1966 by the University of

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Minnesota [2]. It was a simultaneously pancreas - duodenum - kidney transplant which was performed in a patient with diabetic nephropathy. Early outcomes were poor since the procedures were complicated by high mortality rates due to the lack of immunosuppression. However, constantly improvements in transplantation techniques, immunosuppression regimens, understanding the importance of allo-immune response including HLA matching and post-transplant monitoring of graft function and rejection have resulted in increased number of pancreas transplants with reduced mortality and better quality of life for these patients [3].

The benefits are significant, since this therapeutic method remains the only one that restores glucose metabolism to normal in diabetic patients. However, transplantation has been restricted to those with extremely labile diabetes or established life-threatening complications. Important advantages are: a) exogenous insulin independence, b) elimination of acute complications such as hypoglycemia, marked hyperglycemia and ketoacidosis, c) abolition of daily blood glucose monitoring and d) more permissive diet for transplant patients. In addition, PT partially reverses or stabilizes the secondary complications of diabetes and also significantly improves the quality of life. These advantages overcome the patient peri-operative and procedural risks, the side effects of immunosuppression and the risk of graft loss, that might require a return to insulin dependence.

In 2005, according to the latest International Pancreas Transplant Registry (IPTR) report (see http://www.iptr.umn.edu/annual_reports/2004_annual_report/home.htm

1), over 23 000 pancreas allo-transplants had been registered worldwide. The majority of transplants were performed in USA (n=17132). In non-USA countries were reported 5294 transplants, majority (89%) were performed in Europe [3].

There are three categories of pancreas transplantation: 1. simultaneously kidney and pancreas (SKP), 2. pancreas after kidney transplantation (PAK) and 3. pancreas transplant alone (PTA).

In USA, SPK are the majority (78%) of cases, while PAK represents 16% and PTA only 7% of PT. Since 2003, the number of SKP in US has been constant, though there were significant augmentations in PAK and PTA [4].

The differences between USA and Europe PT demographics are multi-factorial, to cite a few: 1) variances in the reporting system/registry - while the transplant activity in the USA is regulated and reported to UNOS (United Network for Organ Sharing), outside USA, the reports are made rather on a voluntary basis; 2) clinical criteria for inclusion on PT waiting list vary between countries, or even amongst transplant centers in the same country or Euro-regions; 3) the availability/ recovery / prevalence of deceased organ donation; 4) higher prevalence of T1DM or end-stage renal disease (ESRD) secondary to T1DM in USA; 5) different insurance reimbursement policies [5].

Simultaneously Kidney-pancreas transplantation (SKP)

SKP is mainly indicated in diabetic patients with ESRD, since forty percent of these patients will develop ESRD as a secondary complication [6]. The transplant is often performed from a cadaveric kidney

donor. While the kidney transplant ameliorates the renal function and abolishes the dialysis, the pancreas allograft will set an euglycemic state in these patients [1]. It has also been shown that patients who received a simultaneously kidney-pancreas allograft exhibited a better medium and long term survival [7]. Furthermore, many authors reported improvement of diabetic neuropathy [8], lower prevalence of coronary artery disease [9], stabilization of diabetic retinopathy [10], and significant reversal of renal anatomic-pathological changes [11, 12].

Pancreas after kidney transplant (PAK)

PAK is usually considered when a living donor kidney is available. First, the patient receives a kidney living allograft which ameliorates the renal function, which allows, at a second time point the pancreas transplantation. Unlike the SKP, which attributes two organs from the same cadaveric donor (identical HLA antigens), PAK requires two donors living for kidney, cadaveric from the pancreas [1]. The immunosuppression regimen used is very similar to the kidney transplant alone.

Pancreas transplant alone (PTA)

PTA is indicated in non-uremic patients with life threatening hypoglycemic unawareness. These patients have little/ no renal damage. The American Diabetes Association criteria are: history of frequent, acute, and severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis); clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating; and consistent

failure of insulin-based management to prevent acute complications [1].

Outcomes in pancreas transplantation

The surgical procedure of PT is complex and may expose patients to operative and post-operative complications. In recent era, the rate of complications such as thrombosis of allograft vessels, intra-abdominal hemorrhage, pancreatitis, fistulas or sepsis was significantly reduced [13]. In USA, recipients transplanted between 1987-1992 and 2001-2003, showed a progressive improvement in graft outcomes with survival rates at one year post-transplant rising from 76% to 85% for SKP, 57% to 79% for PAK and from 55% to 76% for PTA [3]. Improvements in organ preservation, surgical technical aspects and newer immunosuppressive drugs may be responsible for a better outcome. In a retrospective study, Gruessner et al. [4] assessed the mortality of PT recipients and of transplant candidates on the pancreas waiting lists. They reported a significantly lower survival rate in candidates on the waiting list when compared to pancreas transplanted patients. Thus, survival rates on the waiting lists (vs. post-transplant), in the SPK category, were 58.7% (vs. 90.3%); in the PAK category, 81.7% (vs. 88.3%); and in the PTA category, 87.3% (vs. 90.5%) [4]. Furthermore, the overall mortality in all three PT categories was not increased after transplantation, while for SKP recipients the mortality was significantly decreased [4].

Our days challenge remains the ongoing shortage of organ donors. An UNOS database analysis [14] showed that living donor kidney transplants, in patients with type 1 diabetes, were associated with superior outcomes compared to SKP transplants, despite more

older donors and older recipients. Furthermore, these patients were less exposed to dialysis and spent less time on the waiting list [14].

As in all solid organ transplants, HLA compatibility plays a decisive role in the short and long term survival of the graft. In 2005, the European SKP study revealed that patients with 0-3 HLA mismatches will exhibit less rejection episodes compared to those with 4-6 HLA-A, -B, -DR mismatches [15]. A higher rate of acute rejection was correlated with poor HLA matching and does impact the long-term survival of the graft [15].

Acute and chronic rejection in pancreas transplantation

In 2008, a Banff consensus has established the criteria for the diagnosis of acute cell-mediated allograft rejection and chronic rejection/graft sclerosis in PT. Tentative criteria for the diagnosis of antibody-mediated rejection were also proposed [16].

Acute rejection is diagnosed based on clinical criteria and histopathological changes. Diagnosis relies on increase in serum amylase and/or lipase which correlates with biopsy-proven rejection in approximately 80% of cases [16, 17] or abnormalities in the exocrine or endocrine functions (decrease in urine amylase in bladder-drained grafts or hyperglycemia). Hyperglycemia occurs only in severe, most often irreversible, forms of acute rejection [18]. In SPK recipients, serial serum creatinine levels and renal allograft biopsy are used to monitor the allograft rejection [18].

PTA is commonly associated with earlier rejection episodes and higher rate of graft loss in comparison to SPK (9% and 30% in PTA

vs. 2% and 7% in SPK transplants at 1 and 5 years, respectively) [3].

In a retrospective analysis of SPK recipients, Pascual et al. established the incidence of antibody mediated rejection (AMR) as being 15% [19]. However, prompt and aggressive treatment of early AMR episodes (< 3 months post-transplant) was successful, while late AMR (>3 months) episodes were associated with significant graft loss. This study revealed female gender as an independent risk factor for AMR and for graft loss [19]. Donor kidney function (high serum creatinine) was also found as an independent risk factor for both kidney and pancreas graft loss [20]. AMR is diagnosed by allograft dysfunction, C4d positive staining in pancreas biopsy, and detectable donor specific antibodies (DSA) in recipient serum [21]. DSA surveillance and diffuse C4d positive staining may guide early treatments in rejection episodes of isolated pancreas grafts [21].

Introduction of newer immunosuppressive agents reduced the incidence of acute rejection and graft loss, though the prevalence of chronic rejection was to a lesser extent. In a retrospective study, performed by University of Minnesota, Humar et al. established the risk factors for chronic rejection [22]. Of the 914 cadaver pancreas grafts, 70.3% were still functioning at 3 years of follow-up. Chronic rejection accounted for 8% of failed grafts, second to graft loss due to technical failure (12%). The highest incidence of graft loss due to chronic rejection was reduced in PTA, followed by PAK, with the lowest incidence SPK recipients. The risk factors for chronic rejection were: previous episode of acute rejection, isolated (vs. simultaneous)

transplant, post-transplant cytomegalovirus infection, retransplant (versus primary transplant), and antigen mismatches at the HLA-B locus [22, 23].

Immunosuppression regimens in PT

To prevent rejection of the graft and potential recurrence of the autoimmune process that might destroy pancreatic islet β -cells, PT recipients require life-long immunosuppression. Currently, the treatment protocol includes induction and maintenance therapy. The induction protocols contain anti-lymphocytic antibodies, such as Thymoglobulin (polyclonal) or OKT3, Campath® (monoclonal), and/ or non-depleting antibodies (anti-CD25 directed, Zenapax®) [23].

The most common maintenance protocol used in USA consists of a combination of calcineurin-inhibitor (Cyclosporine or FK506/ Tacrolimus®) and Mycophenolate Mophetil (MMF) with or without the addition of corticosteroids [23]. There is a trend toward “steroid-free” protocols as an attempt to avoid their side effects (hyperglycemia, dyslipidemia, osteoporosis). In addition, Sirolimus® appears to be effective in preventing acute rejection, though its combination with a calcineurin-inhibitor may

accentuate its nephrotoxicity [24, 25]. In order to eliminate the undesired calcineurin inhibitor- and steroid-related side effects, Gruessner et al. tested the combination of Campath® and MMF in SPK recipients and found that this protocol was associated with a lower rejection rate, a favorable safety profile, and good kidney function [25]. Large randomized trials in all PT categories, with long-term clinical and biopsy follow-up, are mandatory to establish new guidelines for immunosuppressive regimens.

Conclusions

Pancreas transplantation is usually performed after many years of established type 1 diabetes. Currently, type 2 diabetes patients are also candidates for PT. This procedure, though invasive, is the only treatment that restores and maintains euglycemic levels. There are no research data to determine whether transplantation performed earlier in the course of the disease would prevent secondary complications. The risk of morbidity and mortality in the first months post-transplant and also the side effects of the immunosuppressive regimens are counteracted by the long term perspective and the better quality of life in these patients.

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