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Management of Hyperglycaemia After Pancreas Transplantation

Are New Immunosuppressants the Answer?

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Abstract

Pancreas transplantation is considered the optimal therapy for patients with diabetes mellitus who reach end-stage renal disease. Despite achievement of euglycaemia after this procedure, the progression to impaired pancreatic function and metabolic exhaustion still represents one of the major concerns that increase the risk of graft loss. This paper reviews the possible mechanisms that can induce post-transplant hyperglycaemia, including those related to immunosuppression and those non-related, and the new strategies available for minimising or preventing this complication.

Different aetiologies can induce pancreatic dysfunction. Technical complications, acute pancreatitis and delayed graft function, mostly related to impaired insulin secretion, are considered the early causes for abnormal glucose control. In general, acute rejection does not affect the endocrine portion of the pancreas graft because islet destruction occurs later than the inflammation of the exocrine components. Hyperinsulinaemia and insulin resistance represent the main concern for the progression of blood glucose intolerance. The anastomotic techniques of the exocrine portion of the pancreas and the immunosuppressive regimens are of critical importance for the development of impaired glucose metabolism. Hyperinsulinaemia, as a result of the fact that systemic-enteric or systemic-bladder drainages reducing the hepatic clearance of insulin, has led to the introduction of more physiological techniques using portal drainage of the endocrine secretions. Experimental and clinical data have shown that many of the current immunosuppressants account, to a large degree, for the increased risk of the development of post-transplant hyperglycaemia. The most common maintenance regimen in pancreatic transplantation still consists of triple therapy with a combination of corticosteroids, calcineurin inhibitors (either ciclosporin [cyclosporine] or tacrolimus), and mycophenolate mofetil (MMF).

The diabetogenic effects of corticosteroids and calcineurin inhibitors have resulted in the need for protocols able to minimise their use. Recent studies have shown the safety and efficacy of steroid-sparing or -free regimens. Sirolimus has shown powerful immunosuppressive potency in absence of nephrotoxicity and diabetogenicity. Multicentre and single-centre reports have demonstrated that both calcineurin inhibitor withdrawal and avoidance were possible when sirolimus was used in a concentration-controlled fashion, with low-dose cortico-

steroids and MMF. Although the experience with sirolimus in pancreatic transplantation is still limited, the results are promising. Patients affected by diabetic gastroparesis seem to better tolerate a regimen with sirolimus and low-dose tacrolimus than one with tacrolimus in combination with MMF.

For successful, long-term results of pancreatic transplantation, it is crucial to combine donor selection, technical aspects, modified anastomotic techniques and new therapeutic approaches designed to minimise the metabolic and non-metabolic adverse effects of the immunosuppressive regimens.

An estimated 16 million individuals in the US are affected by diabetes mellitus, a number that is expected to double by 2030. Nearly 35 000 new cases of type 1 diabetes are diagnosed each year, and the incidence is increasing.[1] Worldwide, the incidence of type 2 diabetes is also increasing. This entity represents a major health problem of growing magnitude among young adults and children.[2,3] The microvascular and macrovascular complications of type 1 and 2 diabetes cause pronounced morbidity and mortality.[4] In the past decade, significant progress has been achieved in the field of pancreatic transplantation, which is now considered the optimal therapy for patients with diabetes who have end-stage renal disease (ESRD).[5] Pancreatic transplantation offers the possibility of inducing euglycaemia and, therefore, the possibility of preventing long-term complications secondary to diabetes. In the past, pancreatic transplantation was indicated only for type 1 diabetes, but now this procedure can also be performed in patients affected by type 2 diabetes who have reached insulin dependency and ESRD. Recent studies have shown that contrary to the previous theory, type 2 diabetes is related to an impaired β-cell function rather than insulin resistance.[2] These findings can explain the rationale and the current success with pancreatic transplantation in patients with type 2 diabetes, where a new graft restores the insulin production and secretion with no or minimal concern relating to the insulin resistance.[6,7]

Despite improved results in all the categories of pancreatic transplantation (simultaneous pancreas-kidney for patients in ESRD, pancreas alone or pancreas after kidney), mostly related to refined surgical techniques and new powerful immunosuppressive regimens, the progression to impaired pancreatic function and metabolic exhaustion still represents one of the major concerns that increase the risk of graft loss.[8-10] It is important to realise that interplay among different aetiologies can induce metabolic dysfunction.[11,12] Adverse metabolic effects of immunosuppressants are of critical importance. Efforts should be directed towards new therapeutic approaches that minimise or exclude use of corticosteroid- or calcineurin inhibitor-containing regimens in order to prevent β-cell mass exhaustion and decrease the degree of peripheral insulin resistance. Both calcineurin inhibitors, ciclosporin (cyclosporine) and tacrolimus, are diabetogenic, whereas mycophenolate mofetil (MMF), sirolimus and the emerging compounds, FTY 720 and leflunomide, do not appear to affect glucose metabolism.[13-17]

1. Post-Pancreatic Transplantation Hyperglycaemia

Pancreatic transplantation is considered a treatment for diabetes because of its role in the normalisation of glucose metabolism; therefore, the term post-transplant diabetes (PTDM) can only partially apply to this procedure. Hyperglycaemia and glucose intolerance are the appropriate terms used when abnormal blood glucose control occurs in pancreatic transplant recipients.[18,19]

PTDM occurring as a complication of organ transplantation has been recognised for many years and is considered an adverse effect of corticosteroid, ciclosporin or tacrolimus treatment. The incidence of PTDM varies between 4% and 50% across different studies because no consensus has been reached

regarding its definition and diagnostic criteria. Among the transplant community, consensus has recently been achieved about the clinical diagnosis of PTDM, which should be made on the following American Diabetes Association recommendations:[20]

- fasting plasma glucose >126 mg/dL on two separate occasions; or
- 2-hour post-prandial glucose values ≥200 mg/dL after a 75g glucose load (the glucose tolerance test); or
- two random plasma glucose tests ≥200 mg/dL and symptoms of diabetes, which include polyuria, polydipsia and unexplained weigh loss.

Different studies indicate that the development of PTDM imparts additional long-term mortality risk to renal allograft recipients.[21]

PTDM is also a complication in liver transplant recipients. An association between cirrhosis and abnormalities of glucose metabolism has been recognised for over 30 years.[22] Several studies have suggested a link between hepatitis C virus (HCV) infection and the risk for development of PTDM.[23,24] Because HCV infection is the leading cause of end-stage liver disease and can also be acquired in ESRD patients during dialysis treatments, mandatory interest should be given to these patient categories, in which HCV reactivation together with the immunosuppressive regimens play a diabetogenic synergistic role. The impact of HCV on patient and graft survival has also been evidenced in pancreas transplant recipients.[25]

Heisel et al.[26] performed a meta-analysis of 16 studies, which included patients receiving either tacrolimus (n = 1636) or ciclosporin (n = 1407). PTDM was reported in 13.4% of solid organ transplant recipients with a higher incidence in patients receiving tacrolimus than ciclosporin (16% vs 9.8%). The trend was observed across kidney, liver, heart and lung transplant groups.[26] Recently, an International Expert Panel Meeting presented recommendations and guidelines to avoid or minimise the incidence of new-onset diabetes and management options.[27] Interestingly, pancreas transplant recipients seem to be more resistant to hyperglycaemia development than recipients of other solid organ transplants.[28] Whether the lack of innervation of the pancreas or the careful selection of pancreatic donors has a role in this discrepancy has not been determined yet.

Most transplant centres define post-pancreatic transplantation hyperglycaemia as plasma glucose levels >200 mg/dL during the day from randomly taken samples and insulin requirement according to a sliding scale. Generally, blood glucose levels that are slightly elevated during the day are consistent with an early and transitory phenomenon related to an initial high dosage of corticosteroids. A more worrisome situation is related to the detection of fasting blood glucose levels consistently >110 mg/dL which might indicate the development of insulin resistance. Because of these differences in the definition of post-pancreatic transplantation hyperglycaemia it is important to consider a different number of aetiologies, including those related to the pancreas graft itself rather than immunosuppression (table I).

1.1 Early Causes for Impaired Pancreatic Transplantation Function

Improved donor management, organ procurement and surgical techniques have significantly reduced the incidence of pancreas thrombosis and primary nonfunction in pancreatic transplantation.[29] Attention to donor selection has also limited the number of complications related to severe post-transplant pancreatitis and the risk for anastomic

Table I. Hyperglycaemia after pancreas transplantation

Early causes	Late causes
Technical complications	Acute/chronic rejection
Vascular thrombosis	Chronic pancreatitis
Pancreatic leak	Drug toxicity[a]
Primary nonfunction	Hyperinsulinaemia related to the
Preservation-injury	exocrine duct technique
ischaemia	Recurrence of autoimmunity
Acute pancreatitis	
Acute rejection	
Drug toxicity[a]	

a Direct pancreatic structure damage vs impaired insulin synthesis or secretion.

leaks, ischaemia and damage to the endocrine component of the pancreas graft.[30,31] The inspection of the graft is the most important determinant of its suitability. In the case of major traumatic injuries, calcifications, fibrosis or fatty infiltration, whole organ transplantation should be avoided. Donated pancreas are considered marginal if they were retrieved from patients >45 years of age or who were haemodynamically unstable at the time of harvest. Several studies have shown that pancreas from older donors are associated with graft pancreatitis, technical failure rates and abdominal infections.[32,33] Donor hyperglycaemia and hyperamylasaemia are not considered contraindications for pancreas donation.[32]

Whereas in renal transplantation the criteria for delayed graft function (DGF) has been delineated and histologically proven, there is no well accepted definition for delayed endocrine graft function in pancreas transplant recipients. Pancreatic β cells can begin releasing insulin immediately after reperfusion. The correlation between blood glucose levels and C-peptide release has been demonstrated as early as 30 minutes after transplantation. However, it is not clear what level of islet cell function is adequate to restore euglycaemia immediately after pancreatic transplantation. The aetiology of DGF in pancreas transplant recipients can be related to impaired insulin secretion, a possible consequence of insufficient functional reserve rather than an early development of insulin resistance.[34] Troppmann et al.[35] analysed qualitative aspects of endocrine pancreas graft function during the first 2 weeks after transplantation to determine the incidence of DGF in pancreas transplant recipients, defined as a total insulin requirement of >30 units between days 5 and 10 post-transplantation and/or >15 units between days 11 and 15, irrespective of the insulin dose administered during the first 5 days after transplantation. The incidence of DGF in pancreas transplant recipients was 69% (37 of 54). By univariate analysis, significant risk factors for DGF in these pancreas transplant recipients were recipient pre-transplant weight >80kg, older donor age and donor cause of death (such as cardiocerebrovascular or non-traumatic events). Although the incidence of acute pancreas rejection episodes was similar for recipients with or without DGF in pancreas transplant recipients, this complication affected the 1- and 3-year graft survival (76% and 59% vs 94% and 82%, respectively, for recipients with immediate endocrine function; $p = 0.03$). The study also showed that, in simultaneous pancreas-kidney transplant recipients, the DGF of one organ does not have implications for the early function of the other.[35] Similar results were obtained by the Minnesota group that reviewed the incidence of DGF in pancreas transplant recipients in 531 primary pancreatic transplantations. Comparable incidence of DGF in pancreas transplant recipients was found in simultaneous pancreas-kidney (36%), pancreas alone (31%) and pancreas after kidney (32%) transplants. As no correlation was found between DGF in pancreas transplant recipients and rejection, the decreased graft survival was considered to be more related to non-immunological causes.[36]

Although insulin independent, there is still a relatively small number of pancreatic transplant recipients who experience unsatisfactory blood glucose control. These patients can present during the day with glycaemic values >200 mg/dL. Generally, blood glucose control improves within a few days in conjunction with the corticosteroid dose reduction. However, those patients in whom this does not resolve, should be carefully managed with the understanding that this scenario will induce progressive glucose intolerance and a requirement for insulin replacement. An early detection of elevated C-peptide levels would suggest the premature development of insulin resistance and the need for agents able to improve this feature.[10,37,38] In the initial post-transplant period, the predictive value of intravenous or oral glucose tolerance tests (IVGTT and OGGT), stimulated insulin secretion and the glucose disappearance rate have been controversial because they are affected by different variables, including immunosuppression levels and diet.

If the recipient exhibits persistent hyperglycaemia, the immunosuppressive drugs could be cautiously modified since each of them is able to gener-

ate impairment in insulin production, secretion and utilisation.

1.2 Pancreatic Transplant Rejection

Pancreas allograft monitoring and the diagnosis of rejection have been difficult problems because of a lack of non-invasive diagnostic markers. Hyperglycaemia is not a useful sign for diagnosis of acute rejection because the endocrine pancreatic deterioration occurs later than the inflammation and destruction of the exocrine component. A decrease in urinary amylase in recipients with bladder-drained pancreas or an increase in serum amylase and lipase levels in those with enteric drained pacreas may precede the rejection, but unfortunately this is nonspecific.[39,40] A multitude of other serum markers have been proposed for the prompt diagnosis of rejection, but none have reached a level of clinical relevance. Serum creatinine in the context of simultaneous pancreas-kidney transplantation can be used as a possible indicator of both organ rejections. However, dyssynchronous rejection episodes have been documented.[41] In the past, this lack of reliable markers has impaired the early diagnosis of rejection and, consequently, the number of immunological graft losses has been higher in pancreas after kidney and pancreas alone transplant recipients than in recipients of other organs.

Currently, most centres employ ultrasound-guided percutaneous biopsy, performed under local anaesthesia for all types of pancreatic transplantation. Both acute and chronic rejection can be graded histologically and differentiated from other aetiologies of dysfunction such as drug toxicity and recurrence of diabetes. The criteria for the histological diagnosis of pancreatic rejection have been established and published.[42,43] Fine needle aspiration biopsy has been also proposed for monitoring the intra-graft events.[44]

The combination of stronger immunosuppressive regimens and sequential pancreas biopsies have allowed improved and comparable results in terms of patient and graft survival in all pancreatic transplantation categories, as shown by current data from the International Pancreas Registry (table II).

Table II. International Pancreas Transplant Registry annual report 2003 mid-year update

1 Year	All categories	Type of transplant		
		SPK	PAK	PTA
Patient survival (%) [n = 5140]	94.9	95.0	94.9	98.4
Graft survival (%) [n = 5129]		P 84.6 K 92.0	78.5	78.2

K = kidney; **P** = pancreas; **PAK** = pancreas after kidney; **PTA** = pancreas alone; **SPK** = simultaneous pancreas-kidney.

1.3 Recurrence of Autoimmunity

Although extremely rare, the possibility of type 1 diabetes recurrence after pancreatic transplantation, regardless of the immunosuppressive therapy, is supported by clinical and experimental data.[45,46]

Recurrent disease is diagnosed when there is a combination of a sudden or progressive loss of glycaemic control associated with selective destruction of β cells in the graft generated by mononuclear cell infiltration (isletitis). In addition to hyperglycaemia and the histological findings, recurrent autoimmunity can be determined by the presence of islet cell autoantibodies (GAD 65 and IA-2) in the serum that proceed the clinical picture in some patients.[47,48] These events are in contrast to the paradoxical effects of immunosuppressive drugs on the autoimmune component of diabetes demonstrated in different animal models and uncontrolled clinical trials. Unfortunately, most studies showed that ciclosporin or tacrolimus did not have a beneficial effect on preservation of β-cell function in patients with new onset diabetes because the positive response was transient and dose dependent. Nephrotoxicity was a major concern because of irreversible kidney damage in a significant number of patients.[49,50] Sirolimus has been effective in preventing the onset and severity of autoimmune disorders in several animal models, suggesting its possible therapeutic application in diseases such as diabetes, systemic lupus erythematosus, uveoretinitis, arthritis and psoriasis.[51]

1.4 Hyperinsulinaemia and Insulin Resistance

The complete diversion of pancreatic venous flow from the portal to the systemic venous circuit,

and the possible metabolic consequences, has generated enormous interest and discussion among transplant experts.

Despite achievement of euglycaemia following pancreatic transplantation, concern arises regarding hyperinsulinaemia because of its potential role as an independent factor for dyslipidaemia and accelerated atherosclerosis. Luzi et al.[52] evaluated glucose and free fatty acid (FFA) metabolism in simultaneous pancreas-kidney transplant recipients with systemic drainage and confirmed that, despite hyperinsulinaemia development, these patients had normal inhibition of FFA turnover and oxidation. Diem et al.[53] compared basal levels of insulin and C-peptide and their changes after intravenous glucose and arginine administered to pancreatic transplant recipients with different anastomotic techniques and to two control groups (non-diabetic kidney transplant recipients and non-diabetic healthy volunteers). They concluded that pancreatic transplantation with systemic venous drainage produces greater basal and stimulated insulin levels than any of the other groups studied.[53] Widerman and colleagues,[54] employing the hyperglycaemic challenge (clamp), found that simultaneous pancreas-kidney transplant recipients had significantly elevated basal and glucose-stimulated insulin levels compared with a renal transplant and a healthy control group. Despite marked systemic hyperinsulinaemia in the simultaneous pancreas-kidney transplant recipients, hepatic glucose production was normal in the basal- and glucose-stimulated states. The authors concluded that the portal vein insulin was not essential for normal control of the hepatic and peripheral disposal of glucose.[54]

Hyperinsulinaemia, as a result of the fact that systemic-enteric or systemic-bladder drainages reduce the hepatic clearance of insulin, led to the introduction of more physiological techniques using portal drainage of endocrine secretions and enteric drainage of exocrine secretions.[55,56] Shokouh-Amiri et al.[55,57] described the portal drainage technique in a porcine model and a few years later this technique was introduced in whole pancreatic transplant recipients. To date, several transplant centres are routinely using this procedure.[54] Portal drainage has also generated definitive interest among transplant centres because of the possibility of 'immunological' advantages related to the passage through the liver. The liver has been shown experimentally and clinically to alter the immune response to the allograft when donor-specific antigens are introduced via the portal vein.[58,59]

Although chronic hyperinsulinaemia and the long-term use of immunosuppressive agents have been suggested to contribute to insulin resistance, the complete pathogenetic mechanisms are not entirely understood. The reduction of peripheral glucose utilisation rather than resistance to suppression of hepatic glucose production and the decreased capacity to store glucose as glycogen are among the mechanisms hypothesised for the generation of insulin resistance in pancreatic transplantation.[52,60] Several groups reported that corticosteroids, calcineurin inhibitors and, perhaps, limited β-cell mass, were similarly responsible for abnormal insulin secretion and reduced peripheral sensitivity, both of which are progressive over time. The denervation of pancreatic transplants might be responsible for the lack of feedback inhibition for insulin secretion and, consequently, the hyperinsulinaemic condition.[28,61,62] Early studies of pancreatic autograft and allograft models suggested that elevated peripheral insulin levels were attributed to a combination of denervation and systemic venous drainage.[63]

1.5 Drug-Related Hyperglycaemia

Experimental and clinical evidence suggests that most currently used immunosuppressive regimens account for a large degree of the increased risk for the development of diabetes after transplantation.[12,18] However, different agents vary in the extent to which they induce diabetes. Interestingly, the incidence of drug-induced hyperglycaemia appears to be less in pancreatic transplantation patients than recipients of other organ allografts, who may have a native pancreas already compromised or a family history of diabetes.[64] Furthermore, the deceased donors selected for pancreas allocation are those who are euglycaemic during the terminal phases and

will offer an adequate β-cell mass sufficient for their insulin needs.

Whether the denervated pancreas, with a consequent increase of insulin secretion because of a lack of neurally mediated inhibition is less susceptible to immunosuppression-related glucose intolerance than the native pancreas has not been completely determined.[44,61]

1.5.1 Corticosteroids

Corticosteroids have been an integral part of immunosuppressive regimens for a long time. Their use in transplantation, and particularly in diabetic patients, has been less than optimal because of their adverse effects. The association between corticosteroid therapy and the development of diabetes after transplantation is clearly established in solid organ transplantation.[65-67] The incidence of corticosteroid-induced diabetes is related to the dosages used and the duration of therapy. The predominant effect of corticosteroids in causing PTDM seems to be the induction of insulin resistance. Other mechanisms for corticosteroid-induced PTDM that have been suggested are decreased insulin receptor number and affinity, impaired peripheral glucose uptake in the muscle and impaired suppression of endogenous of insulin secretion.[37]

In the past, attempts at minimising or discontinuing corticosteroid therapy have been limited by the increased risk for rejection. The introduction of calcineurin inhibitors and other newer immunosuppressant drugs has allowed the withdrawal of corticosteroids in kidney and liver transplant recipients and, more recently, in simultaneous pancreas-kidney transplant recipients. Corticosteroid avoidance in pancreas after kidney and pancreas alone transplantation has not received a complete consensus and reported data are sporadic and anecdotal. At present, the non-uraemic and, therefore, more immunogenic condition of pancreas alone transplant recipients might represent the only patient category with a need for corticosteroids. Several trials of corticosteroid withdrawal in kidney transplantation have been reported with mixed results.[68,69] Corticosteroid withdrawal in regimens using ciclosporin therapy demonstrated either increased rejection episodes or differences in long-term outcomes that favoured patients remaining on corticosteroids. More recent protocols that include thymoglobulin induction, tacrolimus, MMF and very early corticosteroid withdrawal or complete avoidance appear to be more successful in maintaining rejection-free graft survival.

Until recently, the acute rejection rates had discouraged attempts at eliminating corticosteroids in pancreatic transplantation except for sporadic reports in smaller groups of patients. Jordan et al.[70] achieved excellent patient and graft survival in 58 of 124 pancreatic transplant recipients receiving tacrolimus, in which the corticosteroids were discontinued within a mean time of 15.2 ± 8 months. Biochemical parameters were identical in both patients who were off and those who were on corticosteroids except for glycosylated haemoglobin (HbA_{1c}) and serum creatinine levels, which were statistically better in patients off corticosteroids.[70] A smaller but similar favourable experience was reported by MacDonald,[71] who used a combination of tacrolimus and sirolimus following thymoglobulin induction and were able to discontinue corticosteroids over a 6-month period with only one rejection episode. A Northwestern University group has reported similar results.[72]

The earliest successful report of corticosteroid avoidance in simultaneous pancreas-kidney transplant recipients came from the study by Cantarovich et al.,[73] which documented not only excellent survival rates but also a rejection rate of <10% with a regimen consisting of thymoglobulin induction followed by ciclosporin and MMF.[73] The possibility of complete corticosteroid avoidance, even in patients receiving polyclonal anti-T-cell therapy, was confirmed in a prospective study performed by Kaufman et al.[72] in which patients treated with antilymphocyte globulin induction were given corticosteroids for only 6 days and maintained on tacrolimus and MMF or tacrolimus and sirolimus. Importantly, in the absence of long-term corticosteroid use, full doses of thymoglobulin were not associated with increased incidence of cytomegalovirus or other infections.[72] The difference between the success

rates associated with rapid withdrawal or avoidance protocols and those from older trials utilising later, gradual corticosteroid withdrawal led Kaufman et al.[72] to suggest that their avoidance may be successful in part because of the absence of immune activation events related to long-term use. This opinion was based in part on the results from Almawi et al.[74] which demonstrated that corticosteroids not only decrease cytokine production but also upregulate proinflammatory cytokine receptor expression on T cells, particularly interleukin (IL)-1R, IL-2Rα and IL-6R, and that these changes are associated with enhancement of T-cell proliferation.[74] More recent data have confirmed excellent outcomes using corticosteroid-free regimens not only in pancreatic transplantation but also in islet transplantation.[75,76]

1.5.2 Calcineurin Inhibitors

Hyperglycaemia in pancreatic transplantation was first described in 1983, but it was not until 1991 that it was convincingly reported to occur in primate transplants involving the use of tacrolimus.[77]

The diabetogenicity induced by calcineurin inhibitors has been evidenced by experimental and clinical experience.[12,78,79] The mechanism by which calcineurin inhibitors induce diabetes is a reduction of insulin secretion and inhibition of insulin synthesis. Calmodulin may have a role in insulin secretion, and ciclosporin binds to calmodulin, which may have an inhibitory effect on insulin secretion. A calmodulin inhibitor can restore the insulin secretory capacity of pancreatic islets suppressed by ciclosporin. It is known that the enzyme cis-peptidyl-propyl-isomerase A is a major binding site for tacrolimus and ciclosporin. In the case of tacrolimus, toxic effects on the endocrine pancreas may be due to selective localisation of FK-binding protein-12 and calcineurin in the islets.[80,81]

Although ciclosporin and tacrolimus are both diabetogenic, clinical studies indicate that tacrolimus is associated with a higher risk of impaired glucose tolerance in kidney, liver, pancreas, allogenic stem cell and heart-lung transplantation.[82-84]

In a number of studies involving adult kidney transplant recipients, the risk for developing PTDM was found to be up to five times higher with tacrolimus at 1 year after kidney transplantation compared with ciclosporin.[82,85] However, the long-term incidence of PTDM is likely to remain similar for ciclosporin and tacrolimus. Because tacrolimus is 10 to 100 times more potent than ciclosporin, tacrolimus may have lesser detrimental effect on glucose metabolism because the total corticosteroid requirement is markedly less when compared with ciclosporin-based regimens.

Elmer et al.[86] investigated the metabolic effects of tacrolimus versus ciclosporin in pancreatic transplantation with portal drainage. The impetus for the investigation came from the clinical observation that, although rejection rates were decreased with tacrolimus therapy, there was a higher rate of hyperglycaemia. However, portal drained pancreatic transplant recipients treated with tacrolimus or ciclosporin and a corticosteroid did not show significant differences in any endocrine outcome at 1, 3, 6 and 12 months post-transplant.[86] More recently, Dieterle and coworkers[87] compared glucose metabolism in 136 simultaneous pancreas-kidney transplant recipients who received ciclosporin (group 1, n = 71) and tacrolimus (group 2, n = 65) as maintenance immunosuppression with the addition of azathioprine or MMF and a corticosteroid. Glucose and insulin levels during an OGGT as well as HbA_{1c} were analysed at 3 months and 3 years after transplantation. There was no difference in any of the metabolic parameters evaluated in the early post-transplant period. After 3 years the incidence of a normal OGGT tended to be lower (70% vs 78%), whereas HbA_{1c} (5.3% vs 5.0%) and fasting glucose (81 vs 78 mg/dL) levels had a trend to be higher in tacrolimus-treated patients. The authors concluded that, concerning glucose metabolism and secretory capacity of the pancreas graft, no significant differences were found between tacrolimus- and ciclosporin-treated pancreatic transplant recipients. Because of the lack of information relating to the causes of graft loss in either cohort, it is not possible to draw any conclusions on the immunosuppressive efficacy of the chosen calcineurin inhibitor.[87]

The question arises as to whether calcineurin inhibitor-induced hyperglycaemia relates to the different anastomotic techniques. According to our experience at the Tennessee Health Science Center, the three different anastomotic techniques (systemic-enteric, portal and systemic-bladder drainages) had no apparent effect on glucose control, suggesting that portal drainage does not lead to impaired blood glucose control, despite elimination of hyperinsulinaemia.[88]

Until recently calcineurin inhibitor withdrawal was not considered possible in pancreatic transplantation, even in patients with hyperglycaemia and unsatisfactory glucose control, because of the elevated risk for rejection and lack of other powerful immunosuppressants. In the case of established nephrotoxicity or glucose intolerance, patients were usually converted from one calcineurin inhibitor to another. In the past few years a number of new immunosuppressive agents have been introduced that have been used in combination with a low-dose calcineurin inhibitor or with complete calcineurin inhibitor avoidance in renal transplantation either in *de novo* or conversion studies.[89,90] Pancreatic transplant recipients are always started on calcineurin inhibitor maintenance immunosuppression and eventually converted to other regimens when there is severe calcineurin inhibitor intolerance.

2. New Immunosuppressive Agents

Tolerance remains the ultimate goal of transplantation and, indeed, progress has been made. However, it is likely that some form of immunosuppression will be required for the foreseeable future. The ideal combination of medications with the least adverse effects should be balanced against the possibility of graft loss and rejection.

Consensus exists about the need for an induction agent in pancreatic transplantation. Despite anti-T-cell agents such as thymoglobulin and muromonab CD3 (OKT3) being neither diabetogenic nor nephrotoxic, their use has been controversial mostly because of the concern related to increased risk for infections deleterious in diabetic patients. The anti-IL-2 receptor monoclonal antibodies, basiliximab and daclizumab, have shown excellent results in different experiences in renal and pancreatic transplant recipients.[91] Induction with a thymoglobulin course is still mainly used for pancreas alone transplant recipients.[92,93] On the basis of successful results in kidney transplantation with the humanised CD52-specific monoclonal antibody alemtuzumab, which is able to produce profound T-cell depletion and reduce the need for maintenance immunosuppression,[94,95] the Minnesota group has recently introduced this agent in all pancreatic transplantation categories. Two or three doses of alemtuzumab are given for induction in combination with MMF and then alemtuzumab is continued for maintenance immunosuppression with re-administration occurring whenever the absolute lymphocyte count rises above 200/mm^3, with a limit of eight doses during the first year post-transplant. The long-term results of this immunosuppressive regimen, including post-transplant infections and lymphoproliferative diseases, have not been determined yet.[96]

The most common maintenance regimen in pancreatic transplantation still consists of triple therapy with a combination of low-dose corticosteroids, tacrolimus and MMF.[97] In past years, the immunosuppressive superiority of MMF when compared with azathioprine has been confirmed by several trials and has allowed calcineurin inhibitor dose reduction or avoidance in low immunological risk, renal recipients.[98]

New immunosuppressants, such as leflunomide and FTY 720, hold great promise for their possible use in pancreatic transplantation. Leflunomide has heightened interest in renal transplantation not only because its lack of nephrotoxicity and diabetogenicity, but also because of its antiviral properties and the possibility for polyomavirus nephropathy treatment.[16,99] Whereas leflunomide has been only sporadically used in pancreatic transplant recipients, the results in animal islet allografts appear to be very promising.[100,101] In several animal models FTY 720 has been shown to inhibit mixed lymphocyte reactions and IL-2-dependent proliferation, and to prolong the survival of skin, heart and liver allografts. There was no toxicity on the endocrine

pancreas in these studies.[102] FTY 720 is under trial in kidney transplant recipients and early results are encouraging in demonstrating immunosuppressive efficacy.[13,17]

Several m-TOR inhibitor-based protocols have been used in kidney transplant recipients utilising both everolimus and sirolimus in either sparing or avoiding calcineurin inhibitor protocols.[103,104] Multicentre and single-centre reports in kidney transplant recipients have demonstrated that both calcineurin inhibitor withdrawal and avoidance were possible when sirolimus was used in a concentration-controlled fashion in combination with low-dose corticosteroids and MMF.[104,105] The advantages of sirolimus include its mechanism of action which blocks cytokine-mediated proliferative signalling without interfering with calcineurin pathways and activation-induced apoptosis.[106] Recent studies have proven that rapamycin-sensitive pathways are able to down-regulate insulin signalling and effects.[107,108] Although lipid and haematological abnormalities are frequent in sirolimus-treated patients, the overall lack of nephrotoxicity and diabetogenicity has resulted in considerable interest in this drug.[109,110] A recent study did not find increased cardiovascular complications in a large cohort of kidney transplant recipients receiving sirolimus treatment despite abnormal lipid values.[111]

Since 2000, sirolimus has been introduced with outstanding results in pancreatic transplantation in combination with tacrolimus and corticosteroids.[112-115] To date, there have been no reports of pancreatic transplantation initiated with calcineurin inhibitor-free regimens. The current standard of care in pancreatic transplantation maintenance immunosuppression is either tacrolimus plus MMF or tacrolimus plus sirolimus. Recently, our group has published a long-term experience with conversion from a calcineurin inhibitor to sirolimus in kidney, pancreas and liver transplant recipients. Patients were abruptly discontinued from the calcineurin inhibitor, loaded with a single oral dose of sirolimus 6–8mg and maintained in a triple regimen consisting of sirolimus (target level 10–12 ng/mL), MMF and a low-dose corticosteroid. Indications for sirolimus conversion were biopsy-proven calcineurin inhibitor nephrotoxicity, chronic allograft nephropathy, thrombotic microangiopathy, and PTDM or glucose intolerance for pancreatic transplant recipients. Most patients evidenced stabilisation, if not improvement, of the renal and glycaemic dysfunction without rejection episodes and with an acceptable adverse effect profile.[116] On the basis of excellent results in kidney transplant recipients treated with sirolimus and MMF from the beginning,[117] it is now our policy to consider sirolimus in combination with low tacrolimus doses or MMF for pancreatic transplant recipients affected by early glucose intolerance. Some of those patients have been able to tolerate a corticosteroid-free regimen after a >5-year follow-up.

3. Conclusions

The question of whether new regimens can prevent or minimise the post-pancreatic transplantation hyperglycaemia has a positive answer because of the promising results with new immunosuppressive drugs, which are less diabetogenic than older agents or, in some cases, not diabetogenic at all. Nevertheless, for the successful management of pancreatic transplant recipients it is crucial to combine a therapeutic approach with several other aspects, including donor selection, organ preservation, intrinsic graft factors and physiological conditions determined by the selected exocrine drainage. Increasingly, sophisticated studies have allowed analysis of the performance of pancreatic transplantation and have enhanced the basic understanding of the complex interplay of insulin in the peripheral process of glucose regulation.[10]

The ideal non-diabetogenic immunosuppressive regimen proposed for pancreatic transplant recipients should probably include an effective and short-term induction period followed by a combination of at least two agents. At present, the tacrolimus plus sirolimus association appears to offer a reliable alternative to the standard regimen of tacrolimus plus MMF. This strategy would not only expose the patient to reduced dosages of calcineurin inhibitor

but might also offer immunosuppressive efficacy combined with a minimal adverse effect profile, with particular benefits for patients affected by severe gastroparesis who are, therefore, intolerant of MMF. Excellent results from different studies have confirmed that long-term corticosteroid exposure is not necessary in pancreatic transplant recipients.[72,73,93,113]

Finally, a maintenance regimen consisting of an anti-T-cell agent (such as alemtuzumab) and MMF would be very intriguing if it was able to achieve adequate immunosuppression without diabetogenicity, nephrotoxicity and other adverse effects.[96]

In conclusion, the immunosuppression regimen in pancreatic transplant recipients should be designed and appropriately modified according to the graft immunological and non-immunological conditions with particular regard to the control of the metabolic pattern.

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