The Immunological Implications of Renal Transplantation in Diabetes

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Abstract

Over the past years immunosuppressive regimens have been a key component in improving short term outcomes for solid-organ transplantation. However, the prevention and treatment of chronic transplant nephropathy is still an issue. Immunosuppressive agents are given at a cost to patients with renal transplants, increasing the risk of infections and cardiovascular morbidity and mortality. One of the main ways through which these drugs cause harm is through the development of post transplant diabetes or the worsening of previously present diabetes. Corticosteroids and calcineurin inhibitors play major roles in the development of post transplant diabetes, infections and other metabolic complications. Another important immunological implication for renal transplantation occurs with combined kidney and pancreas or islet cell transplantation. Beta cell replacement is an attractive cure for patients with diabetes undergoing renal transplantation. Improvement of blood glucose levels helps reduce development of complications. However an important immunological mechanism may adversely affect this procedure. In patients with Type 1 diabetes a memory autoimmune response to islet autoantigens may occur with re exposure to these antigens. Keeping these issues in mind, we ask, are new drugs improving the lives of these patients? Is there a solution to these problems?

ABBREVIATIONS

TH Cell - T helper lymphocyte cell
MHC - major histocompatibility complex
PTD - post transplant diabetes
IHD - ischaemic heart disease
LDL - low density lipoprotein
GAD - glutamic acid decarboxylase
HLA - human leukocyte antigens
KA - kidney alone
KP - kidney-pancreas

INTRODUCTION

In the absence of immunosuppression, transplanted organs invariably undergo progressive immune-mediated injury. Immunosuppressive drug regimens have evolved greatly and transformed solid-organ transplantation, helping to obtain impressive short term results. By contrast long term graft and patient survival remains a major problem.

Transplant recipients have an increased risk of cardiovascular morbidity and mortality and have an increased possibility of developing infections[1]. Patients originally suffering from diabetes mellitus or those developing diabetes post transplant are among the main determinants of this increase. The natural history of post-transplantation diabetes shares many similarities with that of type 2 diabetes. Excess cardiovascular and overall mortality occurs not only in patients with diabetes but also in those with nondiabetic hyperglycaemia[2]. In practice, the objectives of primary prevention in diabetic patients should be those of secondary prevention in non-diabetic patients[3]

Immunosuppressants are used in all patients with renal transplants. This helps prevent rejection of the graft, but at the expense of deleterious side effects which are an insult to patients with diabetes. Nephrotoxicity, abnormal glucose metabolism, hypertension, hyperlipidaemia and infection all increase morbidity and mortality in any individual especially in a patient with long standing diabetes with a renal transplant.

Another important immunological implication for renal transplantation occurs with combined kidney and pancreas or islet cell transplantation. Type 1 diabetes mellitus is an autoimmune disease in which the beta cells of the islets of Langerhans are selectively destroyed. Pancreatic/islet transplants for patients with Type 1 diabetes potentially face two distinct types of immune destruction: one generated by

the allogeneic response to foreign tissues and the other generated by the recurrence of the tissue-specific autoimmune process that caused the disease in the first place. Indeed, Type 1 diabetes mellitus can recur in a patient if this autoimmune reaction takes place[4].

IMMUNOLOGICAL MECHANISMS IN RENAL TRANSPLANTATION

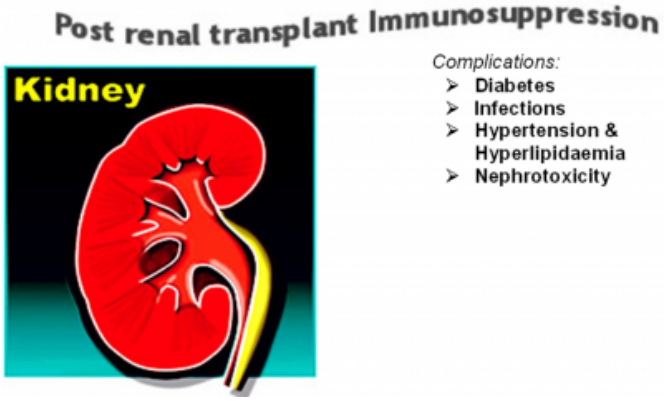
Implantation of any solid organ allograft results in a series of immunological events.[5] Donor lymphoid cells travel from the allograft into the recipient, simultaneously with an influx of recipient cells into the allograft. Acute rejection would occur as antigen presenting cells in the graft mainly directly stimulate TH1 cells with resultant maturation of cytotoxic T cells; expansion and maturation of B cells; and recruitment of macrophages, eosinophils, neutrophils and other effector cells, all of which have the potential to damage the organ[6].

In chronic rejection an indirect mechanism exists. Here recipient antigen presenting cells uptake donor allopeptides, and through MHC-restricted presentation, stimulate recipient T cells, especially TH2 helper cells. This reaction has been strongly implicated in indirect allopresentation, tissue injury, upregulation of adhesion molecules, alterations in blood flow, and release of fibrogenic growth factors, a basis for chronic rejection[7].

IMMUNOSUPPRESSANTS AT A COST!

Metabolic complications such as post transplant diabetes, hypercholesterolemia, and hypertension occur as a direct result of immunosuppressive medicines and increase the risk of cardiovascular disease, a major cause of death late after transplantation. Even when current immunosuppressive therapy is effective, as it is in most patients receiving solid organ transplants today, this treatment is also associated with a significantly increased risk for infection, cataracts, and renal dysfunction; all conditions with increased prevalence in patients with diabetes.[8]

Figure 1



POST TRANSPLANT DIABETES AND IMMUNOSUPPRESSION

New-onset diabetes and impaired glucose tolerance are among the most serious metabolic complications of solid organ transplantation. Montori et al [9] in a systematic review on post transplant diabetes declare that immunosuppression is the factor most strongly associated with this disease. Glucocorticoids, cyclosporine, and tacrolimus have been shown to impair insulin secretion and insulin action through dose-dependent, complex, and imperfectly understood mechanisms. Development of insulin resistance in patients with PTD occurs due to impaired nonoxidative glucose disposal. This is similar to that observed in patients with Type 2 diabetes in the general population. In this study by Ekstrand et al [10] glucose utilization, primarily storage of glucose as glycogen, was reduced by 34% in kidney transplant patients with normal glucose tolerance when compared with healthy control subjects (18.2 +/- 2.9 vs. 27.5 +/- 2.7 microM/L; $p < 0.05$). Development of transplantation diabetes was associated with only minor further deterioration of glucose storage (14.7 +/- 2.7 microM/L; $p < 0.001$ vs. control subjects), whereas insulin secretion became impaired as compared with nondiabetic kidney transplant patients (769 +/- 216, 3084 +/- 545, and 6293 +/- 533 pM; $P < 0.05$).

Corticosteroids play a major role in the development of post transplant diabetes and are the immunosuppressive agents associated with the greatest risk. The hyperglycaemic effect of corticosteroids is primarily related to induction of insulin resistance, which manifests as an increase in glucose production by the liver with a decrease in glucose uptake by the peripheral tissues, i.e., muscle and fat, which are the targets of insulin effects.

The incidence of new-onset diabetes in transplant recipients receiving prednisolone has been reported to be as high as

46% and is related to both the dose administered and the duration of therapy. Hjelmesaeth et al [11] proved this by revealing a significant relationship between the 2-hr serum glucose and prednisolone dose. The risk of developing PTD was 5% per 0.01 mg/kg/day of increase in prednisolone dose.

In a study by Arner et al [12] persistent steroid diabetes developed in 25% of the patients and transient diabetes in another 22%. When antidiabetic therapy was required, insulin had to be given in 50%.

The introduction of calcineurin inhibitors permitting the use of cyclosporine based regimens with lower dosages of corticosteroids decreased the rate of occurrence of diabetes but did not exclude it. These drugs are also diabetogenic. The insulin secreting -cell is the main target involved in the hyperglycaemic effect of calcineurin inhibitors, which reversibly decrease the synthesis and secretion of insulin[13]. The intensity of histological abnormalities in this study depended on the dose of calcineurin inhibitors and these changes improved on cessation of drug treatment. Tacrolimus is reported to be up to five times more diabetogenic than cyclosporine. In a meta analysis by Webster et al [14] at one year, tacrolimus treated patients had less acute rejection (RR = 0.69, 0.60 to 0.79) and less steroid resistant rejection (RR = 0.49, 0.37 to 0.64) but more diabetes mellitus requiring insulin (RR = 1.86, 1.11 to 3.09). The relative excess of diabetes increased with higher concentrations of tacrolimus (p = 0.003).

The greater diabetogenicity of tacrolimus versus cyclosporine was confirmed by Woodward et al [15] who investigated the incidence of new-onset diabetes before and after kidney transplantation; diabetes mellitus had an incidence of approximately 6% per year among those waiting for transplant, whilst over the first 2 years post-transplant its incidence increased to almost 18% and 30% among patients receiving cyclosporine and tacrolimus respectively.

THE IMPACT OF POST TRANSPLANT DIABETES

Why do we give so much importance to post transplant diabetes? This condition has serious consequences for transplant recipients. One of the main complications is the increased risk of graft-related problems such as graft rejection and infection. Miles et al [16] found that the 12 year graft survival in diabetic patients was 48%, compared with 70% in control patients (p = 0.04), and revealed diabetes to be a significant predictor of graft loss (p = 0.04, relative risk = 3.72) independent of age, sex, and race. Renal function at 5 years was inferior in diabetic patients compared to control patients (2.9+/-2.6 vs. 2.0+/-0.07 mg/dl, p = 0.05). Histological findings of diabetic nephropathy are observed in allografts of patients with pretransplant diabetes mellitus and in patients who develop diabetes posttransplant. In a study by Bhalla et al [17] of a cohort of renal transplant patients with histological diabetic nephropathy, 69.6% had recurrent diabetic nephropathy and 30.4% had de novo diabetic nephropathy. Besides graft failure, actual patient survival is reduced in transplant recipients. In a study by Friedman et al [18] patient survival in controls was greater than in post transplant diabetics, reaching significance (83 vs. 67%) at 2 years.

The development of new-onset diabetes after transplantation is a major determinant of the increased cardiovascular morbidity and mortality seen in transplant recipients. Lindholm et al[19] in a study of patients who died with a functioning graft, found that 53% were due to ischemic heart disease and 10% were due to other vascular disease. In the 55- to 64-year-old age group, the risk of death from IHD was 6.4 times higher in the transplanted nondiabetic patients and 20.8 times higher in the transplanted diabetic patients than in the general population. Besides this Kasiske et al[20] revealed that in kidney transplant recipients, diabetes was found to be the most important risk factor for developing both cerebrovascular disease and peripheral vascular disease (p < 0.05).

POST TRANSPLANT INFECTIONS

Newer immunosuppressive agents have dramatically reduced the rates of acute graft rejection over the last decade but may have exacerbated the problem of post-transplant infections. In a study on patients transplanted in the year 2000, the post transplant infection-associated hospitalization rate was twice that for acute rejection-associated hospitalization during each time period. In the 6-24-month time period post-transplant, the risk of bacterial and viral infection-related hospitalization rose significantly from 1987 to 2000 (p < 0.001 for trend by transplant year).[21] This is a problem of enormous significance in anyone with diabetes, considering their increased risk of infection related mortality.

HYPERTENSION AND HYPERLIPIDAEMIA

Two other metabolic side effects of immunosuppressive treatment and of significant importance in patients with

diabetes, especially as regards a worsening of cardiovascular risk profile, are hyperlipidaemia and hypertension. Cyclosporine-induced hypertension, and hyperlipidaemia may contribute to the high cardiovascular morbidity in renal transplant patients. In a study by Artz et al [22] when comparing tacrolimus to cyclosporine use, significant reductions in serum LDL cholesterol and triglyceride levels and blood pressure were apparent at 3 months after conversion to tacrolimus and persisted until the end of follow-up.

Hyperlipidaemia and hypertension exacerbated by a post transplant high-dose corticosteroid regimen, among other factors, has been implicated in the prevalence of ischemic heart disease in patients with renal transplants. These findings raise the possibility that steroid withdrawal might reduce the long-term rates of atherosclerosis and consequent coronary artery disease. In a study assessing changes that occur in a steroid withdrawal group patients in the low/stop group had lower blood lipid levels at 6 and 12 months ($p< 0.01$) and also systolic and diastolic blood pressure was significantly lower. ($p< 0.001$).[23]

NEPHROTOXICITY

For the patient with diabetes, renal function is a crucial factor in determining long-term outcome, and calcineurin inhibitors are significantly nephrotoxic. Their use may lead to severe tubular atrophy, interstitial fibrosis, and focal hyalinosis of small renal arteries and arterioles Indeed, Ojo et al [24] have published an analysis indicating that among patients receiving other-than-kidney allografts, 7%–21% end up with renal failure as a result of the transplant and/or subsequent immunosuppression. Bumbea et al [25] recently have revealed that when switching from calcineurin inhibitors to sirolimus there was a significant improvement in renal function, creatinine clearance increasing from 49.4±14.9 to 53±16.3 ml/min at day 30 ($p = 0.01$), and to 54.7±20 ml/min at day 180 ($p = 0.01$), thus confirming the nephrotoxic effects of these drugs. Use of Sirolimus is associated with a deterioration in lipid profiles, but this appears to be controllable with administration of statins.

AUTOANTIBODY RESPONSE TO ISLET BETA-CELLS IN SIMULTANEOUS KIDNEY AND PANCREAS TRANSPLANTATION

Pancreatic transplantation is a therapeutic procedure which has now reached a level of safety sufficient to permit it to be offered as a realistic option to diabetic patients receiving renal grafts. Concurrent transplantation of pancreas and kidney normalizes blood glucose levels reducing progression of coronary atherosclerosis and thus decreasing cardiovascular morbidity and mortality. Beta-Cell replacement through transplantation of pancreas, islets, or even genetically engineered non–Beta-cells remains an attractive cure for patients with diabetes.

However an important immunological mechanism may have a negative influence on this procedure. Transplantation in Type 1 diabetes is performed in the presence of an active or memory autoimmune response to islet autoantigens. Bosi et al [26] have shown that on re-exposure to these antigens, despite being under immunosuppression, a minority of patients who received pancreas plus kidney allografts showed a marked rise in antibodies to glutamic acid decarboxylase and/or protein tyrosine phosphatase IA-2 from 1 to 3 years post transplantation; the rise was associated with subsequent pancreas but not kidney graft failure.

The antibody responses were typical of those seen in the initial stages of autoimmunity, and were invariably associated with a subsequent loss of pancreas function, a finding consistent with autoimmune destruction of the islet beta cells. This reaction is characteristic of that found in preclinical Type 1 diabetes and is independent of donor-recipient HLA matching and autoantibody titer at the time of transplantation[27]. Clinical monitoring of pancreas transplant patients by systematic measurement of islet specific antibodies should help in the early identification of these cases.

FINDING A SOLUTION!

For the past years, the options for immunosuppressive drugs were initial induction with the use of protein immunosuppressive therapy; preadaptation maintenance therapy with three drugs — a calcineurin inhibitor, a second line of drugs (azathioprine and now mycophenolate mofetil), and glucocorticoids; and postadaptation therapy with the same combination of drugs at lower doses. Rejection was reversed with high-dose steroids or depleting antibodies[28]. Alternative drugs are now evolving with less nonimmune side effects. Nonimmune drug toxicity in patients with renal transplant is agent-specific and is often related to the mechanism that is used, because each agent or class of drugs targets molecules with physiologic roles in nonimmune tissues. For example, drugs like mycophenolate do not increase cardiovascular risk[29] while sirolimus may have arterial protective effects.[30]

Cardiovascular risks as previously mentioned are particularly high in patients with uremia and diabetes, even after kidney alone transplantation. Kidney-pancreas transplantation in patients with diabetes seems to play a protective role in the progression of cardiovascular disease in these patients: a statistical reduction in mortality (at 7 years, KP = 76.2% vs. KA = 63.5%) is observed in patients undergoing kidney-pancreas transplantation.[31]

Will other new immunosuppressive agents being developed and different transplantation procedures improve the outcomes of renal transplantation? It is not easy to say, but it is obvious that specific immunosuppressive reagents or manipulations that lead the immune system down the pathway toward immunologic tolerance of tissue antigens in the graft and at the same time causing less adverse effects, especially with regards to cardiovascular risk and infections would go far in giving transplant recipients a normal life.

KEY MESSAGES

- Immunosuppressive agents are given at a cost to patients with renal transplants increasing cardiovascular morbidity and mortality
- One of the worse consequences of immunosuppressive drugs is the development of post transplant diabetes or worsening of previously present diabetes
- Other serious effects of these drugs for the patient with diabetes is the increased risk for infections, and the development of hypertension, hyperlipidemia or nephrotoxicity
- Type 1 diabetes can recur in patients with pancreas/islet cell transplantation
- Development of new immunosuppressive agents and modern transplant procedures should help improve the life of renal transplant patients

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