Post-Transplant Diabetes Mellitus
The Role of Immunosuppression

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Summary

Immunosuppressive agents increase the risk of death due to coronary disease or stroke by their ability to cause 3 different adverse effects: dyslipidaemia, hypertension and hyperglycaemia. Post-transplant diabetes mellitus has emerged as a major adverse effect of immunosuppressants. As recipients of organ transplants survive longer, the secondary complications of diabetes mellitus have assumed greater importance.

There is a need for a precise definition of post-transplant diabetes mellitus to facilitate inter-centre comparison and to study the natural history of post-transplant diabetes mellitus. We recommend broad criteria to define hyperglycaemia, as a fasting blood glucose level of >400 mg/dl at any point or >200 mg/dl for 2 weeks, or a need for insulin treatment for at least 2 weeks. We also recommend serial measurements of HbA1c.

Cyclosporin and tacrolimus cause post-transplant diabetes mellitus by a number
of mechanisms, including decreased insulin secretion, increased insulin resistance or a direct toxic effect on the beta cell. For corticosteroids, the induction of insulin resistance seems to be the predominant factor. However, few studies have examined the mechanism of diabetogenicity at the molecular level. This may hold the key for pharmacological manipulation of current immunosuppressive regimens which may result in decreased metabolic complications.

Corticosteroid sparing regimens have been shown to reduce the metabolic complications of immunosuppressants including post-transplant diabetes mellitus. However, their use should be balanced against the increased incidence of transplant rejections.

Post-transplant diabetes mellitus may be organ-specific, irrespective of the immunosuppressant used. Tacrolimus causes a high incidence of post-transplant diabetes mellitus in recipients of kidney transplants (up to 20% in some reports); the diabetogenicity of cyclosporin-based regimens is comparable with that of tacrolimus-based regimens in recipients of liver transplants. A few clinical studies in which attempts were made to discontinue cyclosporin resulted in an unacceptable loss of the transplant. In the case of tacrolimus, complete withdrawal of immunosuppression may be possible in selected patients with liver transplants. However, post-transplant recipients who may benefit from this approach are difficult to identify.

In some early series, patients received doses of tacrolimus that were approximately 2 to 3 times higher than those currently used, which may have resulted in a higher incidence of post-transplant diabetes mellitus. More recently, it has been shown that tacrolimus was successful in salvaging whole pancreatic grafts which were maintained on cyclosporin. Tacrolimus-based immunosuppression as primary therapy was also used with remarkable success in solitary whole pancreas transplants.

Strategies to reduce the metabolic complications of immunosuppressants should be pursued aggressively as this will directly lead to a decrease in long term cardiovascular adverse effects.

The Diabetes Control and Complications Trial (DCCT) demonstrated that tight control of glucose levels significantly reduced the risk of diabetes-related complications.\textsuperscript{[1]} A 2% difference in average HbA1c between the DCCT standard and intensive treatment groups was associated with a 60% reduction in risk for diabetic retinopathy, nephropathy and neuropathy.\textsuperscript{[12]} Furthermore, there was a continuing reduction in the risk of complications when the HbA1c was reduced below 8%.\textsuperscript{[3]} Although there have not been similar studies in recipients of organ transplants who develop post-transplant diabetes mellitus and the natural history of post-transplant diabetes mellitus is not well defined, the importance of recognising the possible impact of diabetes mellitus induced by immunosuppressive agents follows as a corollary. It was recently suggested that the prediabetic state was also associated with an increased risk of cardiovascular disease.\textsuperscript{[4]} It follows from this hypothesis that even a modest increase in glucose level may be important, and a modifiable cardiovascular risk factor.

1. Definition of Post-Transplant Diabetes Mellitus

A definition of post-transplant diabetes mellitus has not been universally accepted; investigators have either followed the World Health Organization (WHO) recommendation or defined their own criteria. Depending upon the definition, and duration...