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Diabetes Mellitus and Renal Transplantation

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Diabetes mellitus after renal transplantation consists of both pre-existing diabetes and new-onset diabetes or NODM. Previously the term "post-transplant diabetes mellitus" or PTDM was used; however, this condition is distinct from pre-existing diabetes and may have its own underlying pathophysiology and clinical course. NODM is associated with markedly decreased dialysis-free patient survival and the same risk of developing all of the short- and long-term complications of diabetes. Risk factors include advanced age, African American or Hispanic ethnicity, a strong family history of diabetes, use of corticosteroids and tacrolimus, hepatitis C infection, and a history of glucose intolerance. Regular and frequent monitoring for the development of NODM, based on Canadian Diabetes Association (CDA) guidelines, is recommended for all renal transplant recipients and preventative strategies (eg, steroid minimization or avoidance) are becoming increasingly popular. An intensive multidisciplinary approach to patients with NODM is essential to ensure optimal allograft and patient outcomes. This issue of *Endocrinology Rounds* briefly reviews renal transplantation in the patient with diabetes and provides an extensive account of the unique entity of NODM.

Renal transplantation in the patient with diabetes

Over 170 million people in the world have diabetes (World Health Organization [WHO] 2003) and it is expected that the worldwide prevalence of diabetes will double between 1995 and 2010. Approximately 90%-95% of patients will have type 2 diabetes (American Diabetes Association [ADA] 2003). End-stage renal disease (ESRD) will eventually develop in about 40% of patients with type 1 diabetes after 20 years. In those with type 2 diabetes, 5%-10% will progress to ESRD (ADA 2002), although this percentage is expected to increase with time. About 40% of ESRD is due to diabetes, with approximately half of these patients having type 2 diabetes.

Renal transplantation is the therapeutic modality of choice for ESRD. It provides maximum replacement of renal function and offers the greatest potential for restoring a healthy and productive life. Transplantation also prolongs survival when compared to dialysis, even when compared to patients on the organ waiting list who are of presumably equivalent health.¹ Unfortunately, many patients with ESRD do not qualify for renal transplantation because they are too ill as a result of cardiovascular disease, malignancy, and other co-morbidities.

Approximately 30% of renal transplant recipients (RTR) have co-existing diabetes.² However, patients with ESRD and diabetes present a special challenge when being considered for transplantation since they have a higher mortality rate compared to non-diabetic patients due to multiple causes.³ On the other hand, their survival with transplantation is better compared to comparable patients remaining on dialysis and they have an even better incremental survival advantage compared to non-diabetics.^{1,4}

It should be recognized, however, that RTRs with diabetes have a higher mortality rate compared to their non-diabetic counterparts.⁵ Other microvascular and macrovascular diseases will progress post-transplantation, leading to a worsened quality of life and survival.



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Patients with diabetes are also more prone to fractures.⁶ Moreover, recurrent diabetic nephropathy can occur in the allograft, even within 10 years,⁷ and histological changes in the kidney have been documented as early as 3 years post-transplantation.⁸

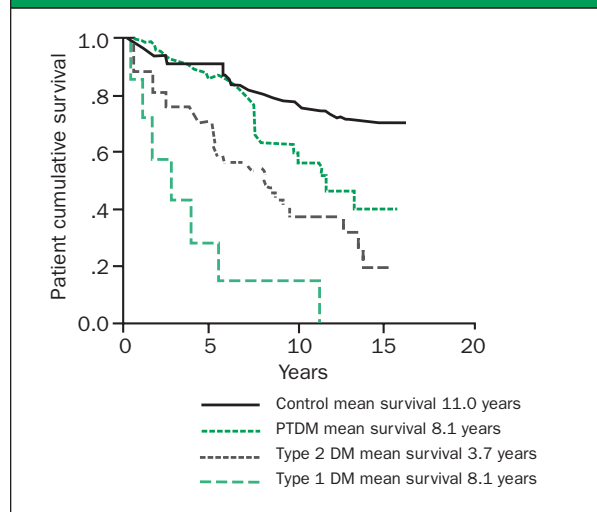
The options available at this time for a patient with diabetes and ESRD include:

- combined kidney-pancreas transplantation in the case of type 1 diabetes, with the kidney coming from a live donor before the cadaveric pancreas becomes available (PAK or pancreas-after-kidney) or
- from a live or cadaveric kidney donor along with a cadaveric pancreas (SPK or simultaneous pancreas-kidney)
- a third option is a live or cadaveric kidney-after-pancreas (KAP)

A live partial pancreatic donation is not considered an option. Kidney-pancreas transplantation improves quality of life by reducing the severity and frequency of hypoglycemic episodes, as well as patient survival compared to kidney transplantation alone;^{9,10} however, in kidney-pancreas transplantation it remains unclear whether there are any clinically relevant benefits to the renal allograft. Patients with type 2 diabetes, on the other hand, may be offered either a live or cadaveric kidney donation, with the live donation being the preferred option.

When a prospective RTR is referred for possible kidney transplantation, the work-up is generally more extensive for the patient with diabetes. A rigorous work-up for cardiovascular and peripheral vascular disease is mandatory. All patients should undergo exercise or similar cardiac stress testing, in addition to a 2-D echocardiogram, regardless of age. Some patients will require cardiac catheterization and subsequent revascularization based on these results, since a perioperative cardiac event may result in poor graft function. They should also have iliac Doppler investigations to examine blood flow within the vessel (which, if diminished, may compromise lower extremity perfusion) and the presence of vascular calcification (that may present technical challenges to performing vascular anastomosis). If the dorsalis pedis and/or posterior tibial pulses are absent on physical examination, full lower extremity Doppler investigations should be considered. Patients with active foot ulcers or osteomyelitis are not candidates for a renal transplant. Likewise, those with severe gastroparesis, in whom retaining oral immunosuppressive medications is compromised, would not be good candidates. Smoking may be a particularly dangerous co-factor for vascular disease and graft survival. Patients should be counseled about increased morbidity risks that include wound infections and delayed healing, as well as higher mortality rates. The older prospective RTR with diabetes may be especially challenging to approve for transplantation.

Figure 1: Kaplan-Meier curves of survival in patients with NODM (PTDM), type 2 DM, and type 1 DM¹¹



New-onset diabetes after renal transplantation

NODM specifically refers to the situation where an RTR with no previous history of diabetes develops this disease after transplantation. NODM is associated with markedly decreased dialysis-free patient survival¹¹ (Figure 1) and patients with NODM have the same risk of developing all the short- and long-term complications of diabetes.

Incidence

The incidence of NODM has been difficult to establish from the published transplant literature since their major data have been from the surgical specialties. Rates from 1% to 53% have been reported.¹² This variation has been attributed to differing periods of follow-up, lack of routine screening, and most importantly, lack of a standard definition. Definitions have included the requirement for insulin or oral hypoglycemic medication 30 days post-transplant, hospitalization for hyperglycemia, and so on. This concern has been addressed with the publication of Consensus Guidelines.¹³ The incidence depends on time elapsed since transplantation and has been estimated to be 9.1% at 3 months, 16% at 12 months, and 24% at 36 months.¹⁴ The incidence may be increasing, even in children,¹⁵ in whom it has been reported to be around 20%. With the adaptation of the CDA definition for diabetes, based on fasting and casual plasma glucose values or an oral glucose tolerance test, the “true” incidence of NODM remains to be determined.

Risk factors

The risk factors for NODM are well-defined and are listed in Table 1. The more significant risk factors are briefly described further.

Table 1: Risk factors for NODM after renal transplantation

- Increasing age
- Family history of diabetes
- Abnormal glucose tolerance pretransplantation
- History of gestational diabetes
- Black or Hispanic ethnicity
- Obesity
- Hepatitis C virus infection
- Corticosteroids
- Calcineurin inhibitors (tacrolimus, cyclosporine)
- Male donor
- Metabolic syndrome
- Genotype (A28, A30, Bw42, B27)

The risk for developing diabetes is enhanced 6.6-fold in RTRs who are >45 years compared to those who are younger.¹⁶ There is an increased risk with increasing age across other studies.^{17,18} A positive family history increases risk 7-fold.¹⁷ Black and Hispanic RTRs have a 5-fold greater risk of developing diabetes compared to white and Asian RTRs.¹⁷ Ethnic differences in risk may be due to genotype, such as A28, which has a higher frequency in African Americans, or it may be due to differences in immunosuppressive pharmacodynamics and pharmacokinetics.¹² African Americans require more of the drug tacrolimus, for example, to achieve therapeutic concentrations. Tacrolimus may also be more diabetogenic in this group.¹⁹

Obesity may increase the risk 4-fold.¹⁶ When defined as a body mass index (BMI) ≥ 30 kg/m², the cumulative incidence was 13.8%, 22.9%, and 35.2% at 3, 12, and 36 months post-transplantation, respectively, in obese RTRs, compared to 8.2%, 14.6%, and 21.8% in non-obese RTRs ($p < 0.0001$).¹⁴ Hepatitis C positivity may predispose to diabetes, especially when tacrolimus is used.²⁰

The association between immunosuppressive therapy and NODM has been the subject of much study and debate in the transplant literature. RTRs are commonly placed on a combination of a “calcineurin-inhibitor” (eg, cyclosporine or tacrolimus), mycophenolate mofetil, and prednisone. Occasionally, other drugs such as azathioprine, daclizumab or basiliximab, sirolimus, or everolimus are used. It is generally acknowledged that corticosteroids are diabetogenic in RTRs. They induce insulin resistance,²¹ may decrease insulin receptor number and affinity, and activate the glucose/free fatty acid cycle.²² The effect is both time- and dose-dependent, and

patients who develop acute rejection, which requires large doses of steroids, are also at high risk. Steroid tapering is associated with a reduction in prevalent diabetes.²³ In fact, it is estimated that the risk of NODM increases by 5% with each 0.01 mg/kg/day increase in prednisolone dose.²⁴ A number of steroid avoidance and minimization clinical trials are in progress, with NODM as an important outcome.

Cyclosporine and tacrolimus are potent immunosuppressives that inhibit calcineurin phosphatase, thereby preventing the dephosphorylation of nuclear factor of activated T cells (NFAT) (and its entry into the nucleus) and causing gene expression for interleukin-2 and other cytokines that mediate rejection. Both cyclosporine and tacrolimus cause NODM among their side effects. However, tacrolimus is associated with an approximately 5-fold increased risk of NODM.^{14,25} RTRs are at higher risk with tacrolimus compared to other organ recipient-types.²⁶ Using less corticosteroids may help reduce the risk,²⁷ since the risk with tacrolimus may be dose-dependent. Mechanisms include pancreatic islet beta-cell toxicity, decreased insulin synthesis, and decreased secretion (via calmodulin).¹¹ Cytoplasmic swelling, vacuolization, apoptosis, and abnormal immunostaining for insulin have all been observed.²⁸ These changes are more severe with tacrolimus. With respect to insulin, while cyclosporine inhibits mRNA synthesis, tacrolimus affects mRNA transcription. Cyclosporine also inhibits DNA synthesis. The end result with both drugs is decreased insulin synthesis.^{11,27} Calcineurin inhibitors also impair corticosteroid metabolism via the P-450 system, and increase their levels.²⁹

Clinical significance

RTRs who develop NODM are most likely to be at the same risk for developing the short- and long-term non-cardiovascular complications of diabetes as people with type 2 diabetes. Unfortunately, there have been no prospective, long-term, observational, or interventional studies with adequate statistical power to support this statement. It is clear, however, from small studies that NODM has an adverse effect on both transplant and patient outcomes.

It has been demonstrated that after 12 years of follow-up post-transplant, graft survival in patients with NODM was only 48% compared to 70% in non-NODM RTRs.³⁰ NODM independently predicted graft loss with a relative risk of 3.72.³⁰ There may also be an association between diabetes and acute rejection.³¹ Even in the shorter term, graft survival was shown to be reduced by 17% after 3 years and 34% after 4 years compared to non-diabetics.³²

Increased patient mortality may be due to the development of a worse cardiovascular disease risk profile,

Table 2: Management principles in diabetes after transplantation¹³

- Define the disease no differently than in the general population
- Identify risk factors for NODM prior to transplantation and correct where possible
- Monitor fasting plasma glucose regularly in all RTRs
- Individualize immunosuppressive therapy before and after the development of diabetes
- Patient education in a multidisciplinary approach
- Specialist and sub-specialist consultation where appropriate
- Achieve adequate glycemic control while preserving renal function

including a higher incidence of hyperlipidemia and hypertension, as well as symptoms of coronary artery disease.¹⁷ The risk of cardiovascular death is increased in NODM RTRs by about 6-fold compared to non-diabetic RTRs, and 20-fold compared to the general population.³³ A 15% reduction in survival at 1 year and 19% reduction at 2 years³³ have been demonstrated.^{16,34} Other outcomes such as enhanced infectious morbidity,¹⁷ sepsis-related mortality,³⁰ and opportunistic infections (eg, cytomegalovirus³¹) may also be higher in RTRs with diabetes.

Management

The principles of management of NODM are outlined in Table 2 and are discussed below. During the initial visit to the transplant clinic when a patient is being evaluated as a transplant candidate, a complete medical history should be documented, along with potential risk factors for NODM, including those shown in Table 1. A fasting plasma glucose (FPG) level should be obtained. Pertinent and modifiable risk factors that are identified should be discussed with candidates and, where feasible, immunosuppressive drug regimens can be discussed. Candidates should be counseled on weight control, a healthy diet, and physical exercise to minimize risk.

After transplantation, it is recommended that FPG be checked weekly for 4 weeks, then again at 3, 6, and 12 months, and annually thereafter. An oral glucose tolerance test (GTT) or additional FPG can be performed at the physician's discretion. Again, CDA definitions must be rigorously applied. Two levels must be obtained. Within the first month, it is

probably reasonable to monitor the FPG without pharmacotherapy as long as metabolic decompensation does not occur and other measures such as dietary counseling are being performed.

Immunosuppressive therapy should be individualized. Very high-risk patients may be considered for a steroid-free protocol and cyclosporine should be considered instead of tacrolimus. If steroids must be used, the dose should be tapered as much as feasible within the first 3 months. Likewise, tacrolimus and cyclosporine blood levels should not be kept unnecessarily high. If an RTR develops NODM on tacrolimus, a switch to cyclosporine may be considered and the steroids tapered more quickly than previously planned. This sometimes results in resolution of NODM, although the patient remains at high risk for the future.

There is some exciting new evidence to suggest that using HMG-CoA reductase inhibitors (statins) after renal transplantation may prevent NODM (see Abstracts of Interest section on page 6). Statins have been shown to prevent diabetes in the WOSCOPS trial³⁵ and are known to modify peripheral insulin resistance. Their benefit for this indication, however, remains to be prospectively shown.

Once NODM has developed, target glucose levels and target lipid levels used for the general population apply. The RTR should be placed in the "very high risk" category for coronary artery disease, with the various target parameters (low-density lipoprotein [LDL], triglycerides, and total cholesterol-to-high-density lipoprotein [HDL] ratio) in the lipid profile prescribed accordingly. HbA_{1c} should be measured every 3 months in the RTR on insulin, and every 6 months in those on oral agents or using dietary modification alone. Self-monitoring of blood glucose is essential. Lifestyle counseling should be reinforced, and then oral agents instituted first, although if acute metabolic decompensation occurs, insulin may need to be started initially. Metformin, a glitinide, or a sulfonylurea may be used first, although the former may be avoided if renal function is suboptimal. Combination therapy with other classes, such as acarbose or a thiazolidinedione, is acceptable as long as patients are closely monitored. Likewise, oral agents may be used concomitantly with insulin.

Consultation with an endocrinologist may be appropriate, and referral to a diabetes centre with a dedicated multidisciplinary approach that includes a nurse practitioner, dietician, pharmacist, and social worker is preferred.

Summary

Pre-existing diabetes and NODM are major causes of post-transplant morbidity and mortality. Although the incidence of NODM remains to be defined, its adverse impact on graft and patient outcomes mandates a proactive approach to its diagnosis and prompt treatment. As RTRs survive longer and more patients with diabetes benefit from transplantation, these issues will acquire increasing public health importance. Identifying patients at high risk, modifying immunosuppression, and instituting intensive multidisciplinary care, together carry the potential to reduce the burden from this condition in this special population.

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Abstract of Interest

Hmg-CoA Reductase Inhibitors (Statins) Reduce the Incidence of Post-Renal Transplant Diabetes Mellitus (PTDM)

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BACKGROUND: HMG-CoA reductase inhibitors (statins) have anti-inflammatory effects, modify endothelial function, and improve peripheral insulin resistance. We hypothesized that statins influence the development of post-transplant diabetes mellitus (PTDM) in renal transplant recipients (RTR), who are a population at high risk for this condition.

METHODS: The records of all previously non-diabetic adult single-organ RTR in Toronto between 01/01/99 and 31/12/01 were reviewed with followup through 31/12/02. All RTR receiving a CNI (CsA or Tac), MMF, and prednisone as primary immunosuppression were included. PTDM was diagnosed based on current Canadian Diabetic Association criteria: FBG ≥ 7.0 mmol/l or 2-h PPG ≥ 11.0 mmol/l on ≥ 2 occasions. Statin use prior to PTDM development was recorded along with demographic and other potential predictor variables. Multivariate logistic regression analysis and Cox proportional hazards models utilizing PTDM as a time-dependent covariate were separately performed. Kaplan-Meier survival curves were compared by the log-rank test.

RESULTS: 297 RTR met entry criteria and were included in the analysis. PTDM incidence was 16% (N=49). PTDM and non-PTDM groups did not differ in demographic or other features at baseline. In univariate analysis, only statins ($p=0.0001$), ACE inhibitors ($p=0.02$), black race ($p=0.03$), acute rejection ($p=0.02$), and prednisone dose ($p<0.0001$) were associated with PTDM. By multivariate logistic regression, the use of statins ($p=0.003$; RR 0.28[0.12-0.65]), prednisone dose ($p<0.0001$; RR 2.47[1.78-3.45] per 5mg/d) and acute rejection ($p=0.03$; RR 2.86[1.11-7.35]) were significant. In the multivariate Cox model, statins ($p=0.003$, HR 0.32[0.15-0.69]), prednisone dose

($p=0.003$, HR 1.006[1.002-1.009]), and weight at transplant ($p=0.01$, HR 1.02[1.004-1.041] per 5kg) were significant. These effects were independent of lipid levels.

CONCLUSIONS: Statins may prevent PTDM development in RTR. Therapy with statins should be considered in all de-novo RTR in order to minimize the risk of PTDM. Prospective evaluation of interventions such as statin therapy to prevent DM in high risk populations is warranted.

A presentation at the Canadian Society of Transplantation Annual Scientific Meeting, Mont Tremblant, Quebec, February 25-29, 2004, and the American Transplant Congress, Boston, Massachusetts, May 15-19, 2004.

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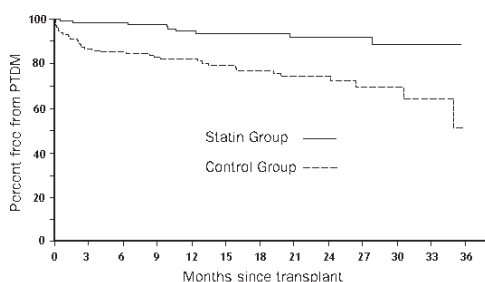
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