DIABETES IN THE RENAL TRANSPLANT PATIENT:
A PRIMER FOR NEPHROLOGY TRANSPLANT CLINICIANS

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ABSTRACT

Diabetes mellitus type 2 (DMT2) with onset after transplantation (new-onset diabetes after transplantation [NODAT]) is among the most significant threats to health following kidney transplantation. This article discusses the epidemiology, consequences, diagnosis, and management of NODAT in the renal transplant recipient. The incidence of new-onset diabetes after kidney transplantation ranges from approximately 2% to 25% with current immunosuppressive regimens, but rates as high as 46% were reported with earlier, more diabetogenic regimens. Consequences of NODAT include heightened risk of cardiovascular disease and cardiovascular death, microvascular complications, and reduced graft survival. The etiology of NODAT is not definitively known and is probably multifactorial, involving genetic, biological, and environmental factors. Many of the risk factors for NODAT are the same as those for DMT2 in the general population. Other risk factors for NODAT are specific to transplantation. For example, specific immunosuppressive drugs used to prevent graft rejection are major contributors to the development of diabetes. NODAT and its deleterious effects can be mitigated through judicious selection of immunosuppressive therapy, maintenance of a healthy body weight, regular physical activity, and pharmacologic and nonpharmacologic control of hypertension and dyslipidemia. Given the contribution of specific immunotherapies to development of NODAT, judicious selection of immunosuppressive therapy is one of the most important means of modifying risk of NODAT. Selection of immunosuppressive therapy for the recipient of a kidney transplant entails careful consideration of the benefits of effective immunosuppression and the diabetogenic risks of therapy in the context of patient-specific factors, including immunological, cardiovascular, and metabolic risk profiles. (Adv Stud Med. 2007;7(6):179-186)

INTRODUCTION

Improvements in immunosuppressive therapy have reduced the incidence of graft rejection and enhanced patient survival after kidney transplantation. Death with a functioning graft rather than graft rejection is now the most common cause of graft loss.1 However, the longevity of patients with kidney transplants is still reduced relative to that of the general population. Early mortality among renal transplant recipients is largely attributed to cardiovascular disease and diabetes mellitus type 2 (DMT2), which occur more frequently in renal transplant recipients than in the general population and are among the most significant threats to patients’ health after kidney transplantation.2,3 Further advances in long-term outcomes after kidney transplantation depend on effective prevention and control of cardiovascular and metabolic disease.

Highly prevalent in Western countries, DMT2 or its precursor, prediabetes, is often present before kidney transplantation.4 However, kidney transplantation is also frequently complicated by new-onset diabetes (NODAT) that is secondary to factors such as use of immunosuppressive therapy to prevent organ rejection.5 This article discusses the epidemiology, consequences, diagnosis, and management of NODAT in the renal transplant recipient. It is also important to stress that the risk of many of the complications of DMT2 are already increased in those with impaired fasting glucose

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relative to the general population. The overall incidence of transplant-associated hyperglycemia (NODAT and impaired fasting glucose) is extremely high, and the impact of impaired fasting glucose should not be forgotten when managing these patients.

DEFINITION

Diabetes is a metabolic disease in which defects in insulin action cause the body to process carbohydrates, lipids, and proteins in an abnormal manner. The 2 primary metabolic abnormalities in DMT2—impaired insulin secretion and insulin resistance (ie, deficient response of tissues to insulin)—cause defective metabolism of carbohydrates, lipids, and amino acids, and result in hyperglycemia, the cardinal sign of DMT2. The metabolic precursor of diabetes is impaired glucose tolerance, which is diagnosed in the presence of impaired fasting glucose and when postprandial blood glucose levels are elevated (ie, 140–199 mg/dL) but not high enough to meet criteria for diabetes (ie, >200 mg/dL).7

INCIDENCE

The incidence of NODAT in renal transplant recipients varies from study to study, depending on factors such as the study sample, the definition of diabetes, duration of follow-up, and the pattern of use of immunosuppressive therapy.1,2,7 The incidence of NODAT after kidney transplantation ranges from approximately 2% to 25% with current immunosuppressive regimens, but rates as high as 46% were reported with earlier, more diabetogenic regimens.3 A US Renal Data System study of 11 659 individuals who received their first kidney transplant in 1996 to 2000 was one of the most comprehensive recent assessments of the incidence of NODAT. It found that the cumulative incidences of NODAT were 9.1%, 16.0%, and 24.0% at 3, 12, and 36 months after transplant, respectively.8

CONSEQUENCES

Consequences of NODAT include a heightened risk of cardiovascular disease and cardiovascular death, microvascular complications, and reduced graft survival.

CARDIOVASCULAR CONSEQUENCES

Patients with DMT2 are at high risk of cardiovascular morbidity and mortality. Compared with individuals without diabetes, patients with diabetes are 3 to 5 times more likely to develop cardiovascular disease.9 Cardiovascular disease is the most common cause of death in diabetic adults. Eight of 10 deaths among those with diabetes are caused by cardiovascular disease.10-12 Patients with DMT2 are significantly more likely to experience adverse cardiovascular events, including death, than those without diabetes. In fact, patients with diabetes and no history of cardiovascular disease are at least as likely to experience fatal or nonfatal cardiac events as those without diabetes and a history of myocardial infarction.13 For example, in the East-West study conducted in Finland, the incidence of fatal or nonfatal myocardial infarction over a 7-year follow-up period was 19% among nondiabetic subjects with a prior myocardial infarction and 20% among diabetic subjects with no prior myocardial infarction.14 Diabetics with a prior myocardial infarction were at extremely high risk of a myocardial infarction: 45% experienced a fatal or nonfatal myocardial infarction during the 7-year followup period. Because diabetes confers a risk of cardiovascular death equivalent to that of established cardiovascular disease, the National Cholesterol Education Panel designates diabetes as a coronary heart disease risk equivalent.15 Coronary heart disease risk-equivalents carry a risk of major coronary events equivalent to that of established coronary heart disease.

These diabetes-associated cardiovascular risks, dramatic as they are, are magnified in recipients of kidney transplants relative to the general population. NODAT, like DMT2 in the general population, is associated with significant risk of cardiovascular disease and cardiovascular death. For example, the presence of diabetes increased the risk of ischemic heart disease by 178% for men and 440% for women among 1124 recipients of kidney transplants followed for 1 year compared with 53% for men and 82% for women in the Framingham Heart Study.16 In another study that followed 1347 recipients of first kidney transplants for 5 years, ischemic heart disease accounted for 53% of deaths with a functioning graft. Among 55 to 64 year olds with a first kidney transplant, the risk of death from ischemic heart disease versus that in the general population was 6.4 times higher in nondiabetic individuals and 20.8 times higher in diabetic individuals.
Microvascular Complications

Like DMT2 in the general population, NODAT is associated with microvascular complications, the most common of which include nephropathy, neuropathy, retinopathy, and infections. In a US Renal Data System study of 28,307 recipients of kidney transplants who had no evidence of pretransplant diabetes, 19% developed NODAT within 3 years of the transplant. Among those with NODAT, 58% had at least 1 diabetic complication, including renal complications (31.3%), neurological complications (16.2%), ketoacidosis (8.1%), and ophthalmic complications (8.3%).

Reduced Graft Survival

NODAT can reduce graft survival. In a US Renal Data System study of nearly 12,000 individuals who received their first kidney transplant in 1996 to 2000, the risk of graft failure was 63% higher in patients who developed NODAT than in patients who did not. Several mechanisms have been proposed to account for diabetes-associated reduction of graft survival. Diabetic nephropathy, diabetes-associated hypertension, and renal effects of changes in immunosuppressive regimens could contribute to impairment of graft function.

Causes and Risk Factors

The etiology of NODAT is not definitively known and is probably multifactorial, involving genetic, biologic, and environmental factors. Many of the risk factors for NODAT are the same as those for DMT2 in the general population. These risk factors are thought to reflect underlying causal factors. Risk factors for DMT2 in the general population include:

- **Obesity or overweight.** Individuals with a body mass index of at least 25 kg/m² are at risk of DMT2. The growing epidemic of obesity in the United States, where approximately 32% of individuals are obese (defined as a body mass index of at least 30 kg/m²), contributes to the increase in the prevalence of DMT2.
- **Sedentary lifestyle.** Lack of physical activity is an independent risk factor for DMT2.
- **Ethnicity.** The prevalence of diabetes among African Americans, Hispanic Americans, Asian Americans, and Native Americans is greater than that among whites. The onset of diabetes also tends to occur earlier among these groups. Epidemiologic data suggest roles of genetic susceptibility and a higher prevalence of risk factors such as visceral obesity as explanations for the higher prevalence of DMT2 among these ethnic groups. The racial groups at highest risk of diabetes are projected to comprise an increasingly larger proportion of the US population over the next 50 years. By 2050, approximately 50% of the US population will be composed of racial groups at high risk of DMT2.
- **Age greater than 45 years.** The incidence of DMT2 increases with age, and its peak onset occurs after the age of 50. Although DMT2 is most likely to occur in adults and the elderly, it is increasingly observed in children and adolescents—particularly among ethnic minorities among whom DMT2 has been characterized as an emerging epidemic.
- **Family history of diabetes.** Those with first-degree relatives with DMT2 are more likely to develop it than are those whose first-degree relatives do not have DMT2. Furthermore, the concordance for DMT2 is approximately 60% to 80% in monozygous twins and approximately 30% in dizygous twins, a finding that supports a genetic contribution to diabetes.
- **Impaired glucose tolerance.** Recent government figures suggest that up to 16 million Americans who currently do not meet diagnostic criteria for diabetes have impaired glucose tolerance (i.e., prediabetes, diagnosed in the presence of impaired fasting glucose and when postprandial blood glucose levels are elevated but not high enough to meet criteria for diabetes) and are at risk for developing DMT2.
- **Hypertension.** Patients with hypertension (140/90 mm Hg in adults) are more likely to have DMT2 than normotensive individuals.
- **Dyslipidemia.** Patients with dyslipidemia, especially those with low high-density lipoprotein (HDL) cholesterol (35 mg/dL in men and 45 mg/dL in women) and high triglyceride levels (200 mg/dL) are at increased risk of DMT2.
- **Waist circumference.** Waist circumference is a surrogate measure for visceral obesity. Men with waist circumference exceeding 40 inches or women with waist circumference exceeding 35 inches are at risk of DMT2. These criteria, devel-
Hepatitis C. Whereas the presence of hepatitis C infection causes a modest increase in the risk of DMT2 in the general population, the risk of NODAT is greatly increased after transplantation, particularly among hepatitis-C–positive patients who are immunosuppressed with tacrolimus.22,23

Other risk factors for NODAT are uncommon in the general population. For example, specific immunosuppressive drugs that are used to prevent graft rejection appear to be major contributors to the development of diabetes.3,24 The main immunosuppressive therapies used in renal transplant recipients—corticosteroids, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, the immunosuppressive antimetabolite azathioprine, and the inosine monophosphate dehydrogenase inhibitor mycophenolate mofetil—differ in their association with NODAT.1,2,4 Corticosteroids and calcineurin inhibitors (ie, tacrolimus, cyclosporine) are associated with NODAT, whereas azathioprine and mycophenolate mofetil are not. The effect of the mTOR inhibitors (eg, sirolimus, everolimus) is not yet well defined. The TOR pathway is important in glucose homeostasis. mTOR inhibitors probably affect glucose control, although this mechanism has not yet been well described. The importance of specific immunosuppressive therapies in influencing the development of NODAT is demonstrated by the finding that the type of immunosuppression accounted for 74% of the variability in the incidence of NODAT in a systematic review of 19 studies involving 3611 renal transplant recipients.25 Immunosuppression with tacrolimus, high-dose cyclosporine, and corticosteroids for organ rejection were risk factors for development of NODAT.

Among the calcineurin inhibitors, tacrolimus appears to be more diabetogenic than cyclosporine. In a meta-analysis of 16 randomized studies on the incidence of diabetes in recipients of kidney, liver, or heart transplants, NODAT was reported in 13.4% of patients.26 Among recipients of kidney transplants, the incidence of new-onset diabetes was significantly (P < .00001) higher with tacrolimus (9.8%) than cyclosporine (2.7%). A similar pattern of results was found for recipients of transplants of other organs. In the recently reported DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C[2] Monitoring Versus Tacrolimus) trial (n = 682), NODAT or impaired fasting glucose 6 months after renal transplantation occurred in 26.0% of patients treated with cyclosporine micromulsion compared with 33.6% of patients treated with tacrolimus (P = .046).27 The incidence of biopsy-proven acute rejection, graft loss, or death at 6 months did not differ between treatments (12.8% cyclosporine micromulsion, 9.8% tacrolimus, P = .211).

The association between corticosteroids and calcineurin inhibitors and NODAT is partly explained by the effects of these agents on glucose and insulin regulation. Corticosteroids decrease peripheral glucose utilization, increase hepatic glucose production, and inhibit insulin secretion.4,5 Calcineurin inhibitors reduce insulin secretion. The calcineurin inhibitor tacrolimus also inhibits insulin gene expression and impairs signaling by pancreatic β cells by preventing phosphorylation of cyclic adenosine monophosphate response element binding protein, an inducible activator of genes, including those mediating insulin signaling.6

Some of the risk factors for NODAT are modifiable. Risk can be mitigated through judicious selection of immunosuppressive therapy, maintenance of a healthy body weight, and pharmacologic and nonpharmacologic control of hypertension and dyslipidemia. Strategies to treat hepatitis C prior to transplantation could also reduce the risk of NODAT. Given the contribution of specific immunotherapies to development of NODAT, judicious selection of immunosuppressive therapy may be the most important modifiable risk factor.

MANAGEMENT

The consequences of NODAT can be mitigated by early detection and treatment of diabetes, in addition to judicious choice of immunosuppressive therapies.24 Table 1 summarizes recently published, internationally endorsed guidelines for the recognition and management of NODAT. General principles for the diagnosis and management of diabetes in the renal transplant recipient are discussed below.

DIAGNOSIS

Standardized criteria for the diagnosis of NODAT have not been developed. Most authorities recom-
mend using the American Diabetes Association (Table 2) or the World Health Organization standardized diagnostic criteria for DMT2 in diagnosing NODAT. The American Diabetes Association criteria for diagnosis of diabetes include symptoms of diabetes and a casual plasma glucose concentration of at least 200 mg/dL, a fasting plasma glucose concentration of at least 126 mg/dL, or a 2-hour plasma glucose concentration of at least 200 mg/dL during an oral glucose tolerance test (Table 2). The American Diabetes Association indicates that presence of any of the 3 criteria can suggest a diagnosis of diabetes and recommends that a positive finding with respect to one of the criteria be confirmed on a subsequent day by assessing for a second positive finding on any of the 3 criteria. The cut points for fasting plasma glucose and 2-hour postload glucose values on the oral glucose tolerance test were chosen on the basis of studies showing that the risk of microvascular complications of diabetes markedly increases above the designated levels.

The concentration of glycosylated hemoglobin (ie, hemoglobin A1c [HbA1c]) in the circulation is proportional to blood glucose concentrations and reflects glycemic state over the 8 to 12 weeks prior to sampling. HbA1c values are often used to measure effects of treatments for diabetes. However, they are not currently recommended for use in diagnosis, in part because of lack of nationwide standardization of the HbA1c test. In addition, the HbA1c is affected by anemia, which is often present in transplant patients.

**TREATMENT**

On the basis of data showing that improved glycemic control reduces serious complications of DMT2, management of established DMT2, including NODAT, is guided by the goal of improving glycemic control. Comprehensive diabetes management should

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<tr>
<th>Table 1. Guidelines for Recognition and Management of NODAT in Recipients of Organ Transplants</th>
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<tr>
<td><strong>Pretransplant Management</strong></td>
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<tr>
<td>• Screen for risk factors</td>
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<td>• Measure blood glucose</td>
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<tr>
<td>• Counsel patients on the importance of weight control, diet, and exercise</td>
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<tr>
<td>• Individualize immunosuppressive therapy</td>
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<tr>
<td><strong>Post-transplant Management</strong></td>
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<tr>
<td>Ongoing monitoring</td>
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<tr>
<td>Management of immunosuppressive therapy</td>
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<tr>
<td>Monitoring of patients with new-onset diabetes</td>
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<tr>
<td>Treating to target</td>
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<tr>
<td>Management of acute hyperglycemia</td>
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<tr>
<td>• Measure blood glucose and HbA1c*</td>
</tr>
<tr>
<td>• Consider steroid-free or steroid-sparing regimens</td>
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<tr>
<td>• Reduce exposure to calcineurin inhibitors</td>
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<tr>
<td>• Encourage self-monitoring of blood glucose</td>
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<tr>
<td>• Monitor glucose, lipids, and HbA1c* levels</td>
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<tr>
<td>• Assess for diabetic complications</td>
</tr>
<tr>
<td>• Follow guidelines outlined by the American Diabetes Association</td>
</tr>
<tr>
<td>• Adopt a treat-to-target approach (Table 3)</td>
</tr>
<tr>
<td>• Intervene immediately to avoid serious consequences for the patient and the graft</td>
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<tr>
<td>• Administer intensive insulin therapy in the hospital if required</td>
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<tr>
<td>• Treat dyslipidemia to target (Table 3)</td>
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<tr>
<td>• Treat hypertension to target (Table 3)</td>
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*HbA1c levels should be interpreted cautiously in patients with anemia or kidney impairment, which can interfere with the assay.

HbA1c = hemoglobin A1c; NODAT = new-onset diabetes after transplantation.


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<th>Table 2. American Diabetes Association Criteria for the Diagnosis of DMT2</th>
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<tr>
<td>Symptoms of diabetes plus casual plasma glucose concentration 200 mg/dL. Casual is defined as any time of day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.</td>
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<tr>
<td>OR</td>
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<td>Fasting plasma glucose 126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours.</td>
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<tr>
<td>2-hour postload glucose 200 mg/dL during an oral glucose tolerance test using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.</td>
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DMT2 = diabetes mellitus type 2.

also include diagnosis and management of conditions (e.g., obesity, hypertension, and dyslipidemia) that can contribute to and/or exacerbate DMT2, in addition to screening for and treatment of common complications, including retinopathy, cardiovascular disease, nephropathy, and neuropathy.20

The American Diabetes Association put forth specific goals for glycemic control in addition to blood pressure and blood lipids (Table 3).20 Guidelines for the management of NODAT recommend that patients be treated to these targets in order to reduce risk of complications of diabetes.22 More stringent goals for glycemic control (i.e., an HbA1c lower than 6%) may confer additional reductions in risk of complications.

Intervention strategies include lifestyle modification (e.g., diet and exercise) and pharmacotherapy. Aggressive implementation of a multifactorial treatment approach, including combination drug therapy, may be necessary.20,22,30 Diet and exercise are core components of management of DMT2. Weight loss in overweight or obese patients can improve insulin sensitivity and glucose utilization, and decrease requirements for insulin therapy or oral hypoglycemics. Weight loss also may decrease blood pressure and triglyceride levels. Exercise can facilitate weight loss and increase insulin sensitivity by lowering blood glucose and HbA1c levels. It can also improve lipid profiles by decreasing triglycerides and total cholesterol and increasing HDL cholesterol.

Although diet and exercise are key components of diabetes management, they alone are almost never wholly effective in controlling DMT2 but require supplementation with pharmacotherapy. The pharmacotherapies for DMT2 target the mechanisms underlying insulin resistance and deficient insulin secretion, the 2 primary metabolic defects in DMT2 (Figure).31 Administered as monotherapy, each of these classes of medication—with the exception of the α-glucosidase inhibitors, which are less effective than the other agents—confers a 1% to 2% reduction in HbA1c levels in controlled clinical comparisons with diet or placebo.31 Furthermore, the head-to-head trials that have been conducted show comparable effects between medication classes on blood glucose.31 The use of these medications in patients with NODAT has not been systematically studied; no particular agent appears to be more appropriate for the post-transplant patient than others based on data available to date.

Metformin is an effective treatment that can be used in patients with good renal function. It can cause lactic acidosis in patients with renal failure, sepsis, or cardiovascular compromise.31

Besides improving glycemic control, glucose-modulating interventions can be effective in reducing blood pressure and improving dyslipidemia. However,
when blood pressure and lipid goals are not achieved with glucose-moderating interventions alone, additional pharmacotherapy may be warranted. Medication classes often used to treat hypertension in patients with diabetes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, diuretics, β blockers, and calcium channel blockers. The American Diabetes Association recommends that all patients with diabetes and hypertension be treated with an ACE or an angiotensin receptor blocker.20

When pharmacotherapy is required to meet lipid targets among patients with a low-density lipoprotein (LDL) exceeding 130 mg/dL, the American Diabetes Association recommends the use of a statin.20 Lowering LDL to less than 100 mg/dL is the first priority of lipid-modulating therapy. To increase HDL and reduce triglycerides, nicotinic acid, fibrates, and niacin may be added. Issues particularly relevant for renal transplant recipients include potential drug interaction between calcineurin inhibitors and statins, both of which are metabolized by cytochrome P450 3A, and potential nephrotoxicity of fibrates except gemfibrozil.21

**IMMUNOSUPPRESSIVE THERAPY**

Selection of immunosuppressive therapy for the recipient of a kidney transplant entails careful consideration of the benefits of effective immunosuppression and the diabetogenic risks of therapy in the context of patient-specific factors, including immunological, cardiovascular, and metabolic risk profiles. Minimal use of corticosteroids and early tapering of corticosteroid doses should be considered in patients at high risk of or diagnosed with NODAT. Avoidance of calcineurin inhibitors or, in the presence of persistent hyperglycemia, conversion from calcineurin inhibitors to other immunosuppressive therapy, such as mTOR inhibitors or mycophenolate mofetil, should also be considered.

Because tacrolimus may be more diabetogenic than cyclosporine, conversion from tacrolimus to cyclosporine or an alternative therapy should be considered in patients with persistent hyperglycemia. Although the impact of conversion from a calcineurin inhibitor to alternative therapy on the incidence and course of NODAT has not been assessed to date, beneficial effects on renal function have been documented in several studies. Conversion from tacrolimus to cyclosporine may increase the risk of hypertension and hyperlipidemia. The potential for sirolimus-associated hyperlipidemia and measures for managing it (eg, use of statins) should be considered in choosing the immunosuppressive regimen.

In considering conversion of immunosuppressive therapy, the risk of organ rejection should be weighed against potential benefits. The Heart Spare the Nephron Study, which was designed to evaluate the efficacy and safety of replacement of a calcineurin inhibitor with an mTOR inhibitor in heart transplant patients receiving a regimen of a calcineurin inhibitor, mycophenolate mofetil, and corticosteroids, was recently prematurely stopped because of a higher-than-expected incidence of acute rejection. Although these results in heart transplant patients cannot be generalized to renal transplant patients, the finding illustrates the importance of weighing risks and benefits when considering changes to the immunosuppressive regimen.

**CONCLUSIONS**

NODAT causes significant morbidity and mortality in recipients of kidney transplants. Evidence suggests that early detection and aggressive treatment can prevent diabetes or mitigate its consequences in the renal transplant recipients. Judicious selection of immunosuppressive therapy tailored to the cardiovascular, metabolic, and immunological risk profiles of the individual patient is particularly important in this regard.

**REFERENCES**


