REVIEW

New-onset diabetes mellitus after kidney transplantation: Current status and future directions

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Abstract

A diagnosis of new-onset diabetes after transplantation (NODAT) carries with it a threat to the renal allograft, as well as the same short- and long-term implications of type 2 diabetes seen in the general population. NODAT usually occurs early after transplantation, and is usually diagnosed according to general population guidelines. Non-modifiable risk factors for NODAT include advancing age, African American, Hispanic, or South Asian ethnicity, genetic background, a positive family history for diabetes mellitus, polycystic kidney disease, and previously diagnosed glucose intolerance. Modifiable risk factors for NODAT include obesity and the metabolic syndrome, hepatitis C virus and cytomegalovirus infection, corticosteroids, calcineurin inhibitor drugs (especially tacrolimus), and sirolimus. NODAT affects graft and patient survival, and increases the incidence of post-transplant cardiovascular disease. The incidence and impact of NODAT can be minimized through pre- and post-transplant screening to identify patients at higher risk, including by oral glucose tolerance tests, as well as multi-disciplinary care, lifestyle modification, and the use of modified immunosuppressive regimens coupled with glucose-lowering therapies including oral hypoglycemic agents and insulin. Since NODAT is a major cause of post-transplant morbidity and mortality, measures to reduce its incidence and impact have the potential to greatly improve overall transplant success.

Key words: Cyclosporine; Graft; Kidney; New-onset diabetes; Tacrolimus; Transplantation

Core tip: New-onset diabetes after kidney transplantation (NODAT) is detrimental to patient and graft survival. Early diagnosis through the identification of modifiable and non-modifiable risk factors for NODAT and appropriate screening, accompanied by good glycemic control that involves a multidisciplinary care approach will help result in good short- and long-term kidney transplant outcomes.

INTRODUCTION

Kidney transplantation is widely considered to be the therapy of choice for patients with end-stage renal disease (ESRD) because of its ability to provide the maximum amount of replacement of renal function and a consequent improvement in patient morbidity and mortality. Among the various complications experienced by kidney transplant recipients (KTR), new-onset diabetes after transplantation (NODAT) is a well-known condition by which an organ transplant recipient such as a KTR develops diabetes mellitus (DM) at some point after the transplant procedure. The purpose of this review is to discuss the epidemiology and management of this common and important post-transplant disorder. A special emphasis will be placed on studies performed during the past ten years, with the intent of providing management recommendations for both diabetes and transplant professionals.

A diagnosis of NODAT carries with it a threat to the renal allograft, as well as the same short- and long-term implications of type 2 DM, but these occur at an accelerated pace[1]. DM can both cause and expedite the course of cardiovascular disease (CVD) as well as the failure of multiple organ systems[2]. According to the World Health Organization (WHO), the number of patients worldwide with DM has doubled from 170 million to 340 million over the past ten years. In addition, the WHO predicts that DM will be the seventh leading cause of death by 2030. This increase in incidence of DM has extended across many population groups, including perhaps transplant recipients.

Over the past decade, concomitantly with DM, there has also been a corresponding increase in the number of patients seeking kidney transplants. According to the 2010 United States Renal Data System Annual Data Report, the annual number of kidney transplants in that country increased from 13425 to 17350 over the decade between 1998 and 2008[3]. Thus, there is also a larger KTR population at increased risk for NODAT. Although type 2 DM is an important cause of ESRD and consequently an important contributor to clinical consequences in incident KTR cohorts, we focus here on NODAT, as an entity distinct from pre-existing DM in a patient receiving a kidney transplant.

INCIDENCE AND PREVALENCE OF NODAT

The prevalence of NODAT after kidney transplantation has increased[4], and varies between 2% and 53% based on several estimates[5]. One reason for the wide variation in reported prevalence may be due to the challenges faced in making the diagnosis. Until about a decade ago, there was no consensus definition for NODAT. Previously, it was defined by fasting or random blood glucose levels of varying thresholds, or perhaps quite naively, by the need for insulin or oral hypoglycemic agents in the post-transplant period[6]. This issue was addressed by the development of the 2003 Consensus Guidelines, developed by the American Diabetes Association (ADA) and the WHO[7]. According to these guidelines, NODAT is present if the patient has symptoms of DM, casual plasma glucose $\geq$ 11.1 mmol/L, or 8-h fasting plasma glucose $\geq$ 7.0 mmol/L. In 2010, the definition for DM was revised by the ADA to include the 2-h oral glucose tolerance test (OGTT), with a 2-h value of $\geq$ 11.1 mmol/L being indicative of DM. The general principle behind standardized NODAT incidence reporting is that the diagnostic criteria should reflect what is used in the general population. Hopefully, these developments will allow for more consistent reporting of NODAT in the future, leading in turn to more precise estimates of incidence rates.

It is well established that NODAT usually occurs early after kidney transplantation. One long-term study[8] conducted between 1976 and 2004 in 1580 Egyptian KTR demonstrated a diagnosis of NODAT in 18.2% patients overall, in whom 52.4% were diagnosed by 6 mo and 11.5% between 6 and 12 mo. A French study of 527 KTR indicated a median time-to-onset of 1.6 mo, with an incidence of 7% over 2 years[9]. Incidence estimates in the United States are 9.1% at 3 mo, 16% at 12 mo, and 24% at 36 mo[10]. The incidence may be increasing even in children[11]. Most studies reporting NODAT prevalence do not include OGTT data, as a result of which significant underestimation of incidence may occur. Variation in studies with regards to length of follow-up, intensity of routine screening, and degree of use of standardized definitions will all have an impact on incidence estimates. Furthermore, glycemic control improves in some patients with increasing time post-transplant, as a result of immunosuppressive medication dose reduction and other interventions. This in turn affects prevalence estimates and interpretation of incidence rates. Addition of HbA1c testing may also modify reported incidence rates. However, HbA1c testing has not been routinely employed at most transplant centres.

RISK FACTORS FOR NODAT

The risk factors specific to NODAT have been well-delineated. These can be broadly classified into non-modifiable and modifiable risk factors. These are summarized in Table 1.

NON-MODIFIABLE RISK FACTORS FOR NODAT

Non-modifiable risk factors include advancing age, black race, genetic background, a positive family history for DM, and previously diagnosed glucose intolerance[12]. Polycystic kidney disease is also believed to be a risk factor. All of these risk factors can usually be identified

Table 1 Risk factors for new-onset diabetes after transplantation

Non-modifiable	Modifiable
Advanced age	Obesity
African American, Hispanic, or South Asian descent	Sedentary lifestyle
Genetic, *e.g.*, HLA B27	Metabolic syndrome
Adult polycystic kidney disease	Viral infections, *e.g.*, HCV, cytomegalovirus
Previous glucose intolerance, *e.g.*, during pregnancy, steroid therapy for renal or non-renal disease	Corticosteroids
Male donor	Calcineurin-inhibitors (tacrolimus > cyclosporine)
Deceased donor	Sirolimus
	Acute rejection

HCV: Hepatitis C virus; HLA: Human leukocyte antigen.

before transplantation.

Since the ESRD population continues to age, it is possible that the incidence of NODAT will increase as a result of more elderly patients being transplanted for their ESRD. Age is considered to be the strongest risk factor for NODAT[13]. It was long ago shown that patients above the age of 45 may be at higher risk for NODAT[14]. A later study estimated that risk at about 2.9-fold[15]. The incidence of NODAT may increase by as much as 50% for every 10-year increase in age[16]. Age over 60 has been associated with a risk of 2.6-fold[10]. However, age *per se* is not a precluding factor to kidney transplantation[17] and the risk for NODAT does not typically dissuade transplant centres from performing transplants in older patients.

Besides African-American or Hispanic descent[12], KTR of South Asian origin may also be at higher risk for NODAT[18]. The relative risk for NODAT has been estimated at 1.68 for blacks and 1.35 for Hispanics compared to Caucasians[10]. Using the 2003 consensus criteria, blacks are considered to be at a two-fold risk for NODAT[19]. The increased risk for NODAT, at least in blacks, is believed to be at least partly due to variation in the pharmacokinetics of various immunosuppressive agents[1]. Variability in dosing requirements based on ethnicity has been demonstrated recently for tacrolimus, with increased amounts of this diabetogenic agent needed in East Asians[20]. It is unclear at this time, however, if the diabetogenic effects of immunosuppressive medication are influenced by ethnicity, although this has been speculated[7].

Genetic predisposition to NODAT includes traditional associations with the alleles human leukocyte antigen A28, A30, B27, and Bw42. A number of genetic associations with NODAT have been identified in the last decade. For example, there has been a reported association with the R325W polymorphism in the SLC30A8 zinc transporter gene of pancreatic islets, with the R/r inheritance being associated with higher risk[21]. Another study from the same group suggested the association of *TCF7L2* gene variants with NODAT[22]. This association with TCF7L2 has also been demonstrated by another group[23]. Other associations of specific gene variants with NODAT include KCNQ1[24], NFATc4[25], adiponectin 276G/T[26], and mitochondrial haplotype H[27]. While all of these associations are interesting, it remains to be seen if such findings can be replicated in different populations, and whether they can be demonstrated to be independent risk factors for NODAT in prospectively conducted studies. Furthermore, the expense and inconvenience of such assessments greatly limits the ability to study these and other gene candidates further.

In the past decade, NODAT has also been associated with autosomal dominant polycystic kidney disease (ADPKD)[28,29], as well as autosomal recessive polycystic kidney disease[30]. ADPKD in particular is a common disease and cause of ESRD, particularly in Caucasians, and so it remains to be definitively proven as a risk factor for NODAT since both ADPKD and NODAT are common in KTR. A plausible mechanism for the association also needs to be developed.

Finally, previously diagnosed glucose intolerance is a risk factor for NODAT[13]. Glucose intolerance may have been diagnosed at the time of pregnancy, or when corticosteroids were used as part of the therapy for the primary renal disease or a related or unrelated systemic disease. In such cases, even though DM may have resolved with cessation of steroid therapy, the risk for DM may persist lifelong. To our knowledge, these risks have not been evaluated prospectively. Also, donor factors for NODAT considered "non-modifiable" include male gender and deceased, as opposed to living donor kidneys. However, these risk factors are unlikely to ever be evaluated prospectively, and so will not be discussed further.

MODIFIABLE RISK FACTORS FOR NODAT

There are many more risk factors for NODAT that may be considered modifiable, at least on a theoretical basis. The most significant risk factors are as follows.

Obesity has detrimental effects to transplantation for a variety of reasons. Obesity has been estimated to increase the risk for NODAT, with a relative risk of 1.73[13]. The risk for NODAT increases linearly for every 1 kg above 45 kg[13]. While obesity in the context of transplantation is traditionally understood as body mass index > 30 kg/m^2, body fat percentage may also be a useful marker[31]. It remains undetermined, however, whether it is pre-transplant weight that increases the risk for NODAT, or whether it is the weight gain that occurs soon after transplantation that is the cause. At least one study indicates that is the former[32]. Nonetheless, longer-term studies may be needed to demonstrate the association of weight gain with NODAT[13]. Adiponectin is a hormone that is reduced with increasing adiposity. Increased adipose tissue is also associated with inflammation. NODAT has been associated with reduced

adiponectin and increased C-reactive protein levels[33], indicating that these are also possible mechanisms for the association seen.

The metabolic syndrome is often associated with obesity. When a definition for metabolic syndrome such as the National Cholesterol Education Program Adult Treatment Panel III is used, which does not contain diabetes as a mandatory component, the presence of metabolic syndrome has been associated with an increased risk for NODAT. In the Patient Outcomes in Renal Transplantation study[34], metabolic syndrome was independently associated with NODAT (HR = 3.46, 95%CI: 2.40-4.98, *P* < 0.0001).

Hepatitis C virus (HCV) infection has been associated with DM in the general population, particularly over the age of 40[35]. Just like DM, HCV also causes ESRD by causing glomerular disease, and HCV can be acquired through blood contamination in hemodialysis units. As a result, it is not uncommon for HCV-infected patients to be considered for kidney transplantation when there is no evidence for hepatic dysfunction and viral titres are sufficiently low or undetectable. The one-year incidence of NODAT was found to be 25.6% in those who were HCV-positive, compared to 14.4% in those who were negative[10]. Another study found an adjusted Odds ratio for NODAT approaching 4.0 in those with HCV[36]. The risk for NODAT with HCV may be exacerbated by the use of tacrolimus[37]. Cytomegalovirus (CMV) infection has also been considered as a risk factor for NODAT, with the mechanism being impaired insulin release[38]. Unlike HCV however, CMV is much more easily treated in the post-transplant setting and so receives considerably less attention as a risk factor.

Corticosteroids remain a mainstay of post-transplant immunosuppression and are a part of most medication regimens. The risk for NODAT with steroids relates both to the dose used and the duration of therapy[13]. Steroids induce gluconeogenesis and glycolysis, increasing both fasting and post-prandial glucose levels. Glycogenesis is decreased. Insulin resistance, to which KTR may be predisposed, is an important effect of steroid therapy. They also impair pancreatic beta-cell function[39]. While a maintenance dose of 5 mg/d of prednisone is typically used for KTR, higher doses (such as 1 mg/kg per day) are used in the early post-transplant phase. Higher doses are also used as bolus therapy when acute rejection of the transplant occurs. There is a dose dependent relationship between steroid dose and glucose levels[40].

Tacrolimus and cyclosporine are widely used calcineurin-inhibitor (CNI) drugs in KTR. Most patients receive one or the other drug as part of their immunosuppressive drug regimen. Between these two, tacrolimus is considered to be more diabetogenic by about 50%[10,41]. Unlike in the case of steroids, this effect is not believed to be dose-dependent[16,42], although this is controversial[43]. Tacrolimus is being increasingly preferred as the CNI of choice at most transplant centres

due to its demonstrated superior efficacy and safety[44], despite the risk for diabetes. However, it is possible to use much lower doses presently[44]. Deficiency of calcineurin leads to decreased insulin production. CNI inhibit the uptake of glucose molecules by cells due to a reduction in the number of glucose transporter type 4 (GLUT-4) receptor molecules on the cell membrane surface of adipocytes[45]. GLUT-4 is an insulin-regulated protein present primarily in adipose tissue and striated muscle, enabling the translocation of glucose into the cell cytoplasm[46]. Thus, reduction in GLUT-4 leads to hyperglycemia. Tacrolimus also reduces glucokinase activity in pancreatic islets, thereby suppressing glucose-induced insulin release[47]. Although both impaired insulin release and increased insulin resistance are both believed to be mechanisms for CNI-induced NODAT, the former may be more important. Islet cell damage in the form of cytoplasmic swelling, vacuolization, and altered insulin staining can be demonstrated as a result of CNI therapy[48]. CNI also cause reduced insulin gene expression[49].

Sirolimus is another immunosuppressive agent used in transplantation that has been contextualized to NODAT. The association of sirolimus with NODAT has been believed to be due to its combination with CNI, and so conversion from a CNI to sirolimus as the main immunosuppression has been perceived as beneficial[50]. However, some studies seem to indicate that sirolimus is a risk factor for NODAT. These include both large database studies[51] and smaller single-centre reviews[52]. The effect may be mediated by hypertriglyceridemia[53]. Sirolimus may also inhibit pancreatic beta cell proliferation. At best, sirolimus is neutral with respect to NODAT risk[13].

The potential pathogenic mechanisms for drug-induced NODAT are summarized in Table 2.

CLINICAL SIGNIFICANCE OF NODAT

RTR who develop NODAT are most likely to be at the same risk for developing the short- and long-term complications of diabetes as people with type 2 diabetes. However, there have been few prospective, long-term, or interventional studies with adequate statistical power to support this statement. It is clear, however, from smaller studies that NODAT has an adverse effect on important transplant- and patient-related outcomes.

An older study has demonstrated that after 12 years of post-transplant follow-up, graft survival in patients with NODAT was only 48% compared to 70% in those who did not develop NODAT, with NODAT predicting a relative risk of graft loss of 3.72[54]. In the shorter term, graft survival was shown to be reduced by 17% after 3 years and 34% after 4 years in those with DM compared to those without DM[55]. In one prospective study, more than 1400 KTR underwent an OGTT at 10 wk post-transplant and were followed for a median of 6.7 years. Impaired glucose tolerance was found to be associated

Table 2 Potential pathogenic mechanisms for drug-induced new-onset diabetes mellitus after transplantation

Immunosuppressive drug	Mechanism for new-onset diabetes after transplantation
Corticosteroids	Increased gluconeogenesis
	Increased insulin resistance
	Reduced glycogenesis
	Decreased insulin release
	Impaired pancreatic beta cell function
Calcineurin-inhibitors (cyclosporine, tacrolimus)	Reduced glucose uptake
	Decreased insulin release
	Reduced insulin gene expression
	Direct pancreatic beta cell toxicity
Sirolimus	Hypertriglyceridemia
	? Decreased pancreatic beta cell proliferation

?: Requires further investigation.

with a 40% greater mortality risk[56]. This increased risk was not seen with impaired fasting glucose (IFG). In a prospective, single-centre study of 201 consecutive KTR in Norway, the 8-year major adverse cardiac event rate was 7% in those without DM, 21% in those with DM before transplantation, and 20% in those with NODAT[57]. Perhaps due to low statistical power, NODAT was not associated with mortality in this study. In another single centre cohort of over 1800 KTR, NODAT was associated with a hazard ratio of 1.80 for mortality[58]. The main cause of mortality is CVD[58].

An important distinction to be made is if NODAT leads to patient mortality independent of transplant graft function. In one study[59], an association was detected between NODAT and death with a functioning graft, but there was no impact on graft survival when censored for death. It is easier to demonstrate associations when NODAT is combined with pre-existing DM[60]. In order to identify the unique contribution of NODAT to mortality, independent of graft function, longer follow-up is required.

NODAT also imposes a significant cost to health care systems. In the United States, NODAT was estimated to cost more than $12000 in the first post-transplant year, and over $19000 in the year after this[41]. This cost is most likely related to the treatment for, and morbidity associated with DM.

Regardless of the implications of NODAT for cardio-vascular risk, graft function, or mortality, a diagnosis of NODAT carries great significance for the individual patient. Transplant patients typically require three immunosuppressive medications, to which prophylactic antibiotics, antihypertensive agents, and others are often added. Patients with NODAT are prescribed oral hypoglycemic agents and sometimes insulin in addition to all of these. They are also subject to new dietary restrictions, which will often be superimposed on those mandated by a chronic kidney disease state (such as potassium restriction). Hospitalization may occur for both hyperglycemia and hypoglycemia[61]. All of these have an important impact on quality of life. Studies assessing this aspect of NODAT implications are few. NODAT has been associated in older studies with

peripheral neuropathy and diabetic nephropathy[54], as well as more infections[62], including severe infections[63].

PREVENTION AND MANAGEMENT OF NODAT

Prevention of NODAT

Some common preventative strategies for NODAT are summarized in Table 3. Preventing NODAT has the potential to prevent many of the short- and long-term complications of NODAT. Screening is an important part of any preventative strategy. Screening for NODAT risk prior to transplantation, as well as the risk for cardiac events, will allow for better informed consent and also help to guide post-transplant management. One recommendation is to obtain a fasting glucose level in all transplant candidates, with a subsequent OGTT performed if IFG is detected[64]. A pre-transplant OGTT may be justified if the fasting blood glucose (FBG) is as low as 5.1 mmol/L[65]. Even if the OGTT is normal, a pre-transplant random BG > 6.0 mmol/L is associated with a NODAT risk of over 25%, and > 7.2 mmol/L with a risk exceeding 50%[66]. Use of OGTT may be justifiable in all transplant candidates if the population is at particularly high risk, such as a multi-ethnic population. More sophisticated testing such as HOMA-IR assessment is not feasible routinely. HbA1c testing has not been evaluated as a pre-transplant screening strategy. If a transplant candidate is determined to be at high risk for NODAT, this should be discussed with the candidate before the transplant, and if appropriate, their proposed post-transplant immunosuppressive strategy discussed as well.

Screening for NODAT has also been employed in the post-transplant setting. Self-testing of blood glucose in the afternoon during the early post-transplant phase has been associated with an increased rate of detection of NODAT[67]. An OGTT performed at 10 wk post-transplant may help to predict longer-term hyperglycemia[68]. One difficulty with OGTT in large post-transplant clinics is that it may interfere with CNI blood level measurements, which are strictly timed. It is reasonable to measure fasting glucose at least monthly, and random blood glucose at least twice weekly for the first few months after transplantation. The HbA1c can also be checked. Since the published incidence and prevalence rates published in the literature are too variable to be helpful to individual transplant centres, it behooves every transplant centre to properly estimate its own incidence and prevalence rates, particularly in the early post-transplant period. Making an early diagnosis of NODAT is important because preventative measures can enhance the KTR's chances for a better quality of life and also prolong their graft survival[12].

As with those at-risk for DM in other populations, lifestyle modification is likely to have a favorable impact on NODAT incidence. Recommendations for weight loss in obese patients prior to transplantation may be beneficial for preventing NODAT, but remains difficult

Table 3 Management strategies for new-onset diabetes after transplantation

Prevention strategies	Management strategies
Identification of risk factors (Table 1) with pre-transplant counseling	Regular blood glucose monitoring with appropriate follow-up
Pre- and post-transplant screening: random blood glucose, fasting blood glucose, 2-h oral glucose tolerance test with appropriate follow-up	Multi-disciplinary care
Lifestyle modification: weight control, diet, exercise (subject to dialysis-imposed restrictions)	Lifestyle modification: weight control, diet, exercise
Rapid corticosteroid reduction or avoidance	Rapid corticosteroid reduction
Selective calcineurin-inhibitor use (*e.g.*, cyclosporine instead of tacrolimus)	Conversion of cyclosporine to tacrolimus
? Newer immunosuppressive agents (*e.g.*, alemtuzumab, belatacept)	Oral hypoglycemic agents: metformin, sulfonylureas, meglitinides, dipeptidyl peptidase-4 antagonists (alone and/or in combination)
? Magnesium oxide	Insulin
? Statins	Monitoring for complications

?: Requires further investigation.

to enforce due to the predisposition for malnutrition in patients on dialysis. Nonetheless, safe and closely supervised dietary and exercise recommendations for dialysis patients should be encouraged, particularly in those identified to be at higher risk for NODAT. Prompt attention from allied health professionals such as nurse practitioners and dieticians may help prevent NODAT from being established when hyperglycemia is detected.

The role of pharmacotherapy in the prevention of NODAT has also been investigated. Since early post-transplant hypomagnesemia is common, magnesium oxide supplementation has been investigated and has been associated with a reduction in FBG[69]. The use of statins in the post-transplant period has been associated with a reduced incidence of NODAT[70]. However, rosuvastatin has not been associated with improved insulin sensitivity in non-diabetic KTR[71], and so this pleiotropic effect of statins remains to be established[72]. Although angiotensin-converting enzyme inhibitors have also been associated with reduced NODAT incidence[70], their beneficial effect has not been demonstrated prospectively. Similarly, metformin has not been tested as a preventative strategy.

Since immunosuppressive medication remains the most readily available tool at the disposal of transplant clinicians to reduce the incidence of NODAT, much attention has been given to the reduction in exposure to existing immunosuppressive drugs such as corticosteroids and tacrolimus. Such reduction is often facilitated through the testing of newer pharmacological therapies. In a large, randomized controlled trial of corticosteroid withdrawal at 7 d post-transplant *vs* no withdrawal, a trend was noted towards better glycemic control in the withdrawal arm[73]. However, there was no difference in NODAT rates[73]. Despite this, fewer patients in the corticosteroid withdrawal arm required insulin for NODAT at 5 years[73]. On the other hand, a large retrospective study involving more than 25000 KTR reported significant benefits of steroid avoidance at initial hospital discharge when compared to a steroid-containing regimen with respect to NODAT at three years[74]. Corticosteroid withdrawal has also been shown to be beneficial when combined with tacrolimus reduction[75]. Other studies have shown that complete corticosteroid withdrawal has no additional benefit beyond only dose reduction[40].

Although tacrolimus has a 50% greater association with NODAT than cyclosporine[10], it is the preferred CNI in many transplant programs for other reasons such as graft function in large clinical trials[44]. Reduced exposure to tacrolimus has also been associated with a similar incidence of NODAT to cyclosporine monitored using the 2-h instead of trough level[76]. In the randomized DIRECT study[77], which also used 2-h cyclosporine monitoring, a marginal increase in the composite safety endpoint of NODAT and IFG (33.6% *vs* 26.0%, $P = 0.046$) was noted with tacrolimus. Sometimes cyclosporine is switched to tacrolimus late after transplantation for reasons such as the development of other side effects, or rejection. In such instances, the risk of impaired glucose metabolism does not appear to be increased[78]. In addition, either tacrolimus or cyclosporine may be switched to sirolimus in order to reduce the burden of CNI nephrotoxicity. However, conversion to sirolimus has been associated with worsening insulin sensitivity[79]. The use of alemtuzumab, which is an anti-lymphocyte induction agent, has been associated with a reduced risk for NODAT[80]. Belatacept, which is a recently introduced selective costimulation blocker in kidney transplantation, has been associated with a reduced incidence of NODAT compared to cyclosporine when studied as a prespecified endpoint in two Phase III studies[81]. Both alemtuzumab and belatacept are induction therapies and so cannot be used for this purpose if a higher risk for NODAT is detected post-transplant.

Management of NODAT

Management strategies for NODAT are summarized in Table 3. Even if attempts to prevent NODAT are meticulous, it is likely that NODAT will occur in at least a proportion of KTR. The goals for management at this juncture include adequate glycemic control, perhaps with complete resolution of hyperglycemia without pharmacotherapy, and minimizing the short- and long-term complications of hyperglycemia. At our centre, non-fasting blood tests including glucose measurements

are obtained twice weekly for the first three months and weekly for the next three months. Fasting blood tests including glucose are obtained at least monthly. Our centre also employs an intensive multidisciplinary approach in the post-transplant clinic setting that includes a nurse practitioner with specialized expertise in diabetes prevention and management. This health care professional selectively reviews all clinic patients identified as having NODAT or being at high risk for NODAT. In addition, KTR have access to a dietician and pharmacist at all times in the clinic. Reading material about NODAT is also readily available. While such resource-intensive measures are probably helpful to individual patients, their overall effectiveness at a population level remains to be demonstrated. At other centres, adoption of a healthy diet and exercise program coupled with weight control strategies has demonstrated improvement in glycemic control over 6 mo[82]. One challenge in this regard will be multi-ethnicity of KTR[83] and possible language barriers. Collaboration between nephrologists and endocrinologists will help in the delivery of optimal care.

When antihypertensive medication is necessary for blood pressure control, it is reasonable to avoid or minimize the use of beta-blockers and thiazide diuretics in the absence of a compelling indication in those deemed at risk for NODAT. While clinical trials of antihypertensive agents in KTR are especially rare, there have also been no prospective studies of antihypertensive medications in KTR with NODAT as a pre-specified endpoint.

It is tempting for clinicians to alter transplant-related immunosuppression once NODAT has developed, with the view of optimizing glycemic control and perhaps avoiding the use of diabetes-specific medication. Reducing corticosteroid exposure carries an enhanced risk of transplant rejection[84]. Switching from tacrolimus to cyclosporine once hyperglycemia or NODAT has developed is controversial. Cyclosporine possesses a side effect profile somewhat different from tacrolimus that includes hypertrichosis and gingival hyperplasia. Nonetheless, this conversion has been attempted as rescue therapy from NODAT in small studies, with demonstration that glycemic control can be improved[85-87]. However, acute rejection remains a risk[88]. Specific features related to NODAT in patients that can predict a successful conversion have not yet been identified.

If it is clear that lifestyle modification alone will be insufficient to control hyperglycemia, then pharmacotherapy targeting glucose metabolism should be initiated. In the very early post-transplant phase, when corticosteroids are being rapidly tapered, additional pharmacotherapy may not be required if the hyperglycemia is mild. The choice between insulin and oral hypoglycemic agents depends on the severity, timing, and expected duration of hyperglycemia[49]. Insulin therapy is safe[50] particularly when graft function is not yet established or is unstable. Since corticosteroids are typically administered in the morning in KTR, a combination of intermediate and short-acting insulin administered several times during the day and corresponding to mealtimes may be required. In less urgent instances, oral hypoglycemic agents can be commenced without resorting to insulin firsthand.

The choice of oral hypoglycemic agent is dictated by the level of renal function. No agent is specifically contraindicated in KTR, and there are no significant drug interactions with CNI or other immunosuppressive drugs. Pharmaceutical approaches generally mirror those utilized in the general population, with no studies specific to KTR available. In addition, the target HbA1c for KTR has not been defined[49]. Metformin improves insulin sensitivity, which is often affected in NODAT. The safety of metformin in KTR with sufficient renal function has been formally demonstrated[88]. Since the estimated GFR in KTR with well-functioning grafts often exceeds 50 mL/min per 1.73 m^2, metformin can be safely used for most patients. A theoretical disadvantage to using metformin in KTR would be gastrointestinal upset, to which KTR are already prone by virtue of immunosuppressive medications such as mycophenolate mofetil. However, metformin may counter the post-transplant weight gain associated with corticosteroid administration, but this has not been demonstrated. Keeping these in mind, metformin is often employed as a first-line agent in KTR with NODAT.

Sulfonylureas, which enhance insulin secretion, are also widely used in KTR. Their use is again dictated by level of renal function, and unlike metformin, they may exacerbate post-transplant weight gain. Newer sulfonylureas like glipizide and gliclazide may be used in KTR, with appropriate monitoring for hypoglycemia. Amongst the thiazolidinediones, which are selective agonists of the peroxisomal proliferator-activated receptor gamma, rosiglitazone has been shown to improve glucose tolerance, insulin sensitivity, and even endothelial function in a small group of KTR[89]. Its short-term efficacy has also been shown by other groups[90]. Thiazolidinediones should again be used with extreme caution if graft function is severely impaired. Congestive heart failure is a significant concern, and many KTR already have impaired cardiac function. Furthermore, cyclosporine may promote a sodium-retentive state. As a result, thiazolidinediones are usually not used.

Amongst the meglitinides, which are short-acting drugs that induce insulin secretion, repaglinide has been shown to be safe in KTR[91]. Repaglinide can also be used in severe renal graft dysfunction. Dipeptidyl peptidase-4 (DPP-4) antagonists have been employed in KTR. These drugs inhibit DPP-4, which is responsible for the rapid degradation of numerous substrates including the glucagon-like peptide 1, whose role is to increase pancreatic insulin secretion. Among the DPP-4 antagonists, sitagliptin has been shown to be both safe and efficacious in KTR[92,93]. A theoretical risk in KTR is an increased risk of infections, to which they may already be prone by virtue of being in an immunosuppressed state.

It is reasonable to employ rationally selected

combinations of two or three of the above drugs before proceeding to insulin therapy. However, the initiation of insulin should not be delayed unnecessarily, since prolonged hyperglycemia may result in hospitalization from intravascular volume depletion and serious comorbidities such as infections. Opportunistic infections of many kinds typically occur in the first 6 mo post-transplant, which corresponds to the phase when NODAT usually occurs.

FUTURE DIRECTIONS

Renal transplant survival has significantly improved over the last 50 years. Death with graft function, often as a result of CVD, has become a major cause of graft loss. As a result, increasing attention is being given to cardiovascular risk factors such as DM, within which NODAT is a significant component. Intensive screening for NODAT should be the norm in all transplant centres. Efforts to combat NODAT have to be balanced against the risks for graft rejection. Large clinical trials of newer immunosuppressive agents in kidney transplantation are few, but the inclusion of NODAT as a prespecified endpoint will help to better understand not only the most important contributing risks for NODAT, but also identify those interventions that are most likely to result in a lower NODAT incidence. Correspondingly, clinical trials that address treatment strategies for diabetes post-transplant have received very little attention. This is indeed unfortunate given the magnitude of NODAT prevalence and its financial implications for society, not to mention the profound impact of NODAT on transplant recipients. Until such trials are performed, multidisciplinary care focused on intensive glucose control in keeping with general population guidelines, along with management of other cardiovascular risk factors should remain the standard.

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