Can New-Onset Diabetes After Kidney Transplant Be Prevented?

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Because the negative consequences of new-onset diabetes mellitus after transplantation (NODAT) diminish the significant gains of kidney transplantation, it is imperative to develop clinical interventions to reduce the incidence of NODAT. In this review, we discuss whether intensive lifestyle interventions that delay or prevent type 2 diabetes mellitus may decrease the incidence of NODAT. We examine the literature pertaining to incidence and timing of onset of NODAT, as well as the risk factors and pathophysiology that NODAT shares with type 2 diabetes mellitus, namely pathways related to increased insulin resistance and decreased insulin secretion. Our central hypothesis is that NODAT results from the same metabolic risk factors that underlie type 2 diabetes mellitus. These risk factors are altered and enhanced by transplantation, "tipping" some transplant recipients with seemingly normal glucose homeostasis before transplant toward the development of NODAT. We describe the diabetogenic properties of transplant immunosuppressive drugs. We describe novel methods of prevention that are being explored, including resting the pancreatic β-cells by administration of basal insulin during the period immediately after transplant. On the basis of the current evidence, we propose that intensive lifestyle modification, adapted for individuals with chronic kidney disease or end-stage renal disease, as well as resting pancreatic β-cells during the immediate postoperative period, may lower the incidence of NODAT.

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New-onset diabetes after transplant (NODAT) is a common complication of kidney transplantation. Prior studies show that approximately 15–30% of nondiabetic kidney transplant recipients develop NODAT in the first year after transplant (1–3). Many more develop impaired glucose regulation but do not quite meet diagnostic criteria for diabetes.

The frequent occurrences of impaired glucose regulation and new-onset diabetes after transplantation have been well described. Furthermore, the incidence, risk factors, impact, and treatment of NODAT also have been reported (1,3–8). Missing from the literature is a detailed review of NODAT that emphasizes potential clinical strategies for its prevention. Our review describes the pathophysiology of NODAT and incorporates the lessons learned from the prevention of type 2 diabetes mellitus in understanding and implementing prevention strategies for NODAT.

CLINICAL AND ECONOMIC SIGNIFICANCE OF NODAT

—Kidney transplantation is the best therapy for end-stage renal disease (ESRD) (9), but subsequent development of impaired glucose regulation or NODAT undermines the many benefits of kidney transplantation by lowering allograft and patient survival and impairing quality of life (6,7). In a U.S. Renal Data System (USRDS) study of 11,659 patients who received a transplant between 1996 and 2000, NODAT was associated with a more than 60% increase in incidence of graft failure (hazard rate ratio 1.63 [95% CI 1.46–1.84]) and an almost 90% increase in mortality rate (1.87 [1.60–2.18]) (2). Another analysis of USRDS data demonstrated frequent occurrence of diabetes complications, including ketoacidosis, hyperosmolarity, ophthalmic complications, neurologic complications, and hypoglycemic shock, in patients with NODAT (4). NODAT also increases the annual cost of care from $15,000 to $36,500 (3).

The number of transplant recipients developing NODAT is rising as the rate of ESRD and kidney transplantation increases. The 2010 USRDS Annual Data Report described a 23% increase (from 13,425 to17,350) in the number of kidney transplants over the decade between 1998 and 2008 (10). With higher numbers of transplants, more recipients are at risk for NODAT. It is difficult to ascertain if the true incidence rate of NODAT is increasing. One study has suggested that the incidence rate is indeed rising, and provides two potential explanations: *1*) The bioavailability of calcineurin inhibitors (CNIs) is much improved, resulting in higher blood levels and therefore greater exposure to their diabetogenic properties and 2) there have been significant changes in recipient characteristics over time, especially in body weight at time of transplant (11). The national secular trend toward overweight and obesity extends to patients with ESRD who are seeking kidney transplantation, resulting in higher body weight before transplant and thereby increasing the risk of NODAT(12). In fact, in the U.S., the prevalence of obesity (BMI $\geq$30 kg/m^2) among transplant recipients at the time of kidney transplantation doubled between 1987 and 2001 (13). Thus, a higher number of obese patients receiving transplants, now and in the future, may contribute to growth in the incidence rate of NODAT.

IT IS IMPORTANT TO DECREASE THE INCIDENCE OF NODAT

—Compelling reasons to develop clinical intervention strategies that decrease the incidence of NODAT include *1*) to avoid complications of NODAT in each individual transplant recipient; *2*) to protect the social investment (cost of dialysis and transplantation) already made in the transplant recipient; *3*) to optimize the distribution of a scarce resource so that kidney allografts have good outcomes and recipients do not rejoin the list of those waiting

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for a kidney. The pathophysiology of NODAT may point to interventions that may help to address this important problem.

PATHOPHYSIOLOGY OF NODAT

Timing

There is a five- to sixfold higher incidence of new-onset of diabetes mellitus among transplant recipients during the first year after transplantation than among patients who remain on the transplant waiting list, with a decline after the first year to an annual incidence of 4–6% (3) (Fig. 1). One retrospective observational study of Medicare beneficiaries estimated that the onset of NODAT occurred in a majority of patients within the first 3–6 months after transplant (5). Why NODAT develops quickly, usually within 1 year after transplant, among patients with seemingly normal glucose metabolism before transplantation is not well understood. One hypothesis is that NODAT and type 2 diabetes mellitus share a common pathophysiology. If so, then NODAT results from risk factors similar to those for type 2 diabetes mellitus that are enhanced by transplantation among patients with seemingly normal glucose homeostasis before transplant.

Pathogenesis

Figure 2 describes the pathogenesis of NODAT. Both traditional type 2 diabetes mellitus risk factors (older age, obesity, minority race/ethnicity, family history of type 2 diabetes mellitus, hepatitis C seropositivity) and risk factors unique to transplant recipients (immunosuppressants and cytomegalovirus infection) are associated with NODAT (2,11,16). Immunosuppressive drugs, including glucocorticoids, CNIs tacrolimus and cyclosporine), and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) are also diabetogenic (17–21). The diabetogenic effect of glucocorticoids results primarily from insulin resistance, followed by enhanced gluconeogenesis in the liver as well as decreased glucose uptake and glycogen synthesis in skeletal muscle cells. The diabetogenic effects of CNIs are attributed to both increased insulin resistance and impaired insulin secretion (18,19). CNIs also inhibit the activation of nuclear factor of activated *t*-cells and the transducer of regulated CREBP 2 as well as the phosphoinositide 3-kinase/Akt pathway; through these mechanisms CNIs diminish pancreatic β-cell survival in murine models (19). Thus, data from mouse models, albeit sparse, suggest that calcineurin signaling may indirectly affect the insulin sensitivity of skeletal muscle. Robust studies of the effects of calcineurin inhibition on β-cell survival, insulin resistance, or both merit further investigation in human subjects. mTOR inhibitors initially were believed to be devoid of diabetogenic effects (20); however, single-center and large registry studies later found sirolimus to be associated with a higher risk for NODAT, independent of effects of CNIs (17,21). Suggested pathogenic mechanisms of sirolimus-induced hyperglycemia include impaired insulin-mediated suppression of hepatic glucose production, deposition of ectopic triglycerides leading to insulin resistance, and direct pancreatic β-cell toxicity.

Similarities in the pathogenesis of type 2 diabetes mellitus and NODAT

Abnormalities in both insulin sensitivity and insulin secretion are central to the development of type 2 diabetes mellitus. The balance between insulin sensitivity and insulin secretion necessary to maintain normal glucose metabolism has been well described (22,23). As occurs in type 2 diabetes mellitus, both an increase in peripheral insulin resistance and an impairment in insulin response or secretion have been implicated in tipping patients toward the development of NODAT. Results of several previous studies suggest that insulin resistance contributes to the development of diabetes after kidney transplant (24). Just as obesity and chronic inflammation lead to insulin resistance and subsequent development of type 2 diabetes mellitus (25), it has been suggested that inflammation and obesity before transplant are associated with NODAT. Low levels of adiponectin, high concentrations of C-reactive protein and triglycerides, and high BMI before transplant predicted NODAT, which is consistent with this hypothesis (26).

PREDICTION OF TYPE 2 DIABETES MELLITUS AND NODAT

—An elevated level of glucose in the blood, whether examined in the fasting state or during an oral glucose tolerance test (OGTT), is among the best predictors of type 2 diabetes mellitus in population studies (27). Using OGTTs, insulin and glucose levels were obtained from participants in the Diabetes Prevention Program (DPP) and used to estimate insulin sensitivity (1/fasting insulin and the insulin sensitivity index) and insulin secretion (corrected insulin response and ratio of 30-min change in insulin to 30-min change in glucose). Improvements in insulin sensitivity and insulin secretion that occurred as a response to intervention were associated with lower diabetes risk, supporting the hypothesis that effectiveness of intensive lifestyle was due to improved insulin sensitivity concomitant with preservation of pancreatic β-cell function (28).

Although useful in population studies, neither the OGTT nor the homeostasis model assessment of insulin resistance, derived from concentrations of fasting glucose and insulin, may adequately mirror the altered carbohydrate metabolism of individuals with chronic kidney disease (CKD) or ESRD. Concentrations of endogenous insulin are elevated in patients with CKD because of decreased renal clearance of endogenous insulin (29). Patients with CKD and ESRD are more resistant to insulin than those with normal

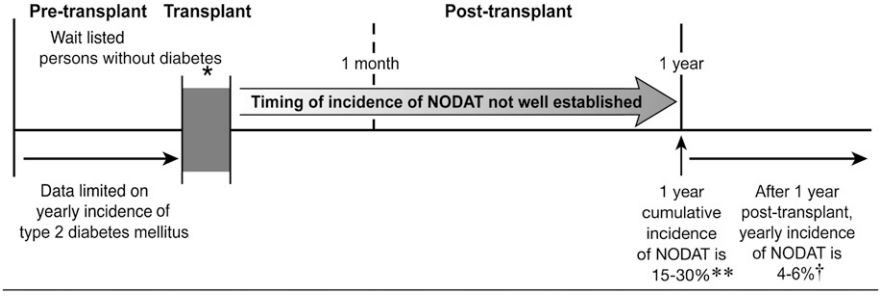

Figure 1—*Incidence of new-onset diabetes mellitus before and after transplant. *Sixty-six percent of patients without diabetes before transplantation developed inpatient hyperglycemia and required insulin at hospital discharge. Inpatient hyperglycemia was associated with a fourfold increase in the development of NODAT (14,15). **Statistics from refs. 1 and 2. †Statistic from ref. 3.*

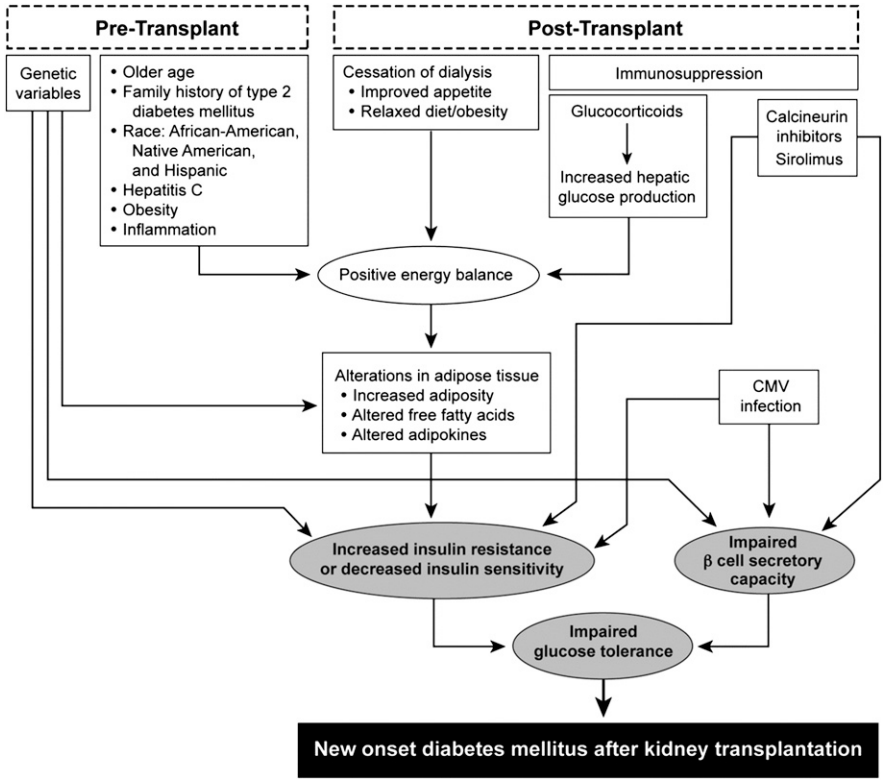

Figure 2—*Proposed mechanisms in the pathogenesis of NODAT. CMV, cytomegalovirus.*

renal function, as assessed with a hyperinsulinemic euglycemic clamp (30). Although clamp studies have been performed at all stages of kidney disease and in patients with stable renal function after transplantation (30), they have not been evaluated as predictors of NODAT. The use of homeostasis model assessment of insulin resistance to predict NODAT is modestly supported in one study (31). Despite the logistics of the test, the hyperinsulinemic euglycemic clamp may prove to be a better tool for the prediction of NODAT, as suggested by some investigators (32).

Prediction of NODAT before kidney transplant

Assessment of risk of NODAT ideally should occur before kidney transplantation so that intervention might begin as soon as possible. Despite the limitations mentioned above, impaired glucose tolerance and other components of the metabolic syndrome before transplant are risk factors for NODAT (12,33). Among a cohort of patients without diabetes before kidney transplant, we described a pretransplant risk score for NODAT using seven simple pretransplant clinical and laboratory measurements in kidney transplant recipients at a single center. The seven variables included older age, planned corticosteroid therapy after transplant, prescription for gout medicine, higher BMI, higher fasting glucose, higher triglycerides, and family history of type 2 diabetes mellitus. The results suggest that some of the important type 2 diabetes mellitus risk factors also contribute to the development of NODAT (12). Two risk scores for predicting type 2 diabetes mellitus (San Antonio Diabetes Prediction Model and the Framingham Offspring Study-Diabetes Mellitus algorithm) also predicted NODAT; the areas under the receiver operating characteristic curves for these two risk scores were 0.807 and 0.756, respectively (34).

In many genome-wide association studies, genetic variations modestly increase the risk of type 2 diabetes mellitus (35). Studies of genetic variations (single nucleotide polymorphisms) and NODAT have not been conclusive (36,37), although a recent study found that the G allele at position *−174* of the *IL-6* gene promoter predicted NODAT among overweight subjects (38). Another study reported associations of significant variations of interleukin (IL)-7R, IL-17E, IL-17R, and IL-17RB, which recently were reported to be associated with type 1 diabetes mellitus, suggesting that inflammation of islet β-cells might play a crucial role in the pathogenesis of NODAT in renal transplantation recipients (39).

LIFESTYLE INTERVENTIONS TO PREVENT DIABETES

Lifestyle modification prevents type 2 diabetes mellitus

Lifestyle interventions promoting reduced fat/reduced energy diets, daily moderate-intensity physical activity, and modest weight loss reduce incidence of type 2 diabetes mellitus. In the largest such study, the DPP, a lifestyle weight-reduction intervention reduced diabetes incidence by 58% compared with a group receiving only standard advice about diet and exercise (40). In the Finnish Diabetes Prevention Study, a similar lifestyle intervention had almost identical effects, reducing the incidence rate of diabetes by 58% (41). In smaller studies of Chinese, Japanese, and Asian Indian populations, lifestyle intervention was efficacious in preventing or delaying type 2 diabetes mellitus in high-risk individuals (42–44) (Table 1).

Although studies of the general population show that intensive modification of diet and physical activity can prevent or delay progression of prediabetes to overt type 2 diabetes mellitus, the question of whether NODAT can be prevented using a similar strategy has not, to our knowledge, been tested.

Can lifestyle modification be adapted for prevention of NODAT?

Several compelling lines of evidence support the idea that lifestyle intervention, specifically tailored to patients with CKD or ESRD and delivered before and immediately after transplantation, might lower the incidence of NODAT. Type 2 diabetes mellitus and NODAT share similar risk factors, especially obesity. The prevalence of obesity (BMI $\geq$30 kg/m^2) at the time of transplantation among transplant recipients in the U.S. has doubled between 1987 and 2001 (13). Because higher BMI before transplant correlates with insulin resistance after transplantation, obesity treatment seems to be reasonable target for intervention. For the purpose of decreasing the incidence of NODAT, reduction of fat mass might best begin before transplantation in patients with CKD, including dialysis patients. Obesity prevention may also benefit patients who already have received a transplant because

Table 1—*Impact of dietary and physical activity modifications on risk of development of type 2 diabetes mellitus in five randomized clinical trials*

Study	Country	Study population inclusion criteria	Interventions	Results	Reference
Diabetes Prevention Program (DPP)	U.S.	Nondiabetic overweight or obese adults with elevated fasting and postload plasma glucose	Lifestyle modification (≥7% weight loss and ≥150 min of physical activity per week) or metformin 850 mg b.i.d. or placebo	58% Reduction in diabetes incidence with lifestyle modification compared with placebo group 31% Reduction in diabetes incidence in the metformin group compared with the placebo group	Knowler et al. (40)
Finnish Diabetes Prevention Study	Finland	Middle aged (40–64 years), BMI >25 kg/m^2 IGT (WHO criteria)	Intensive lifestyle intervention (individualized dietary counseling by a study nutritionist, weight reduction >5% from baseline, exercise >4 h/week) or standard, nonpersonalized lifestyle advice (control group)	58% Reduction in diabetes incidence with lifestyle modification compared with standard advice	Tuomilehto et al. (41)
The Da Qing Impaired Glucose Tolerance and Diabetes Study	China	IGT	Control or one of three active treatment groups: diet only, exercise only, diet + exercise	6-Year cumulative incidence of T2DM* Control: 67.7% (95% CI 59.8–75.2) Diet only: 43.8% (95% CI 35.5–52.3) Exercise only: 41.1% (95% CI 33.4–49.4) Diet + Exercise: 46.0% (95% CI 37.3–54.7)	Pan et al. (42)
Indian Diabetes Prevention Programme	India	IGT	Randomized to four groups: Group 1: control Group 2: advice on lifestyle modification Group 3: treated with metformin Group 4: treated with both metformin and lifestyle modification	3-Year cumulative incidence rates of diabetes were 55.0%, 39.3%, 40.5%, and 39.5% in groups 1–4, respectively. Relative reduction of risk of diabetes was 28.5% in group 2 (95% CI 20.5–37.3; P = 0.018), 26.4% in group 3 (95% CI 19.1–35.1; P = 0.029) and 28.2% in group 4 (95% CI 20.3–37.0; P = 0.022), compared with the control group	Ramachandran et al. (43)
Zensharen Study for Prevention of Lifestyle Diseases	Japan	Overweight adults with impaired fasting glucose	Randomized to two groups: Intervention group received individual instructions and follow-up support for lifestyle modification from the medical staff nine times Control group received similar individual instructions four times at 12-month intervals during the same period	44% Reduction in diabetes incidence with intensive lifestyle modification compared with a less intensive intervention group. Greater reductions in persons at higher risk.	Saito et al. (44)

*The relative decrease in the rate of development of diabetes in the active treatment groups was similar when subjects were stratified as lean or overweight, defined as BMI <25 kg/m^2 or ≥25 kg/m^2, respectively. IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; WHO, World Health Organization

there is an observed weight gain of 10% during the first year after transplant (45). NODAT most frequently occurs in the first year after transplantation; therefore, excess adiposity before transplant might well affect the risk of NODAT. Thus, a lifestyle intervention aimed at lowering fat mass may be appropriate for the prevention of NODAT. The timing of a weight loss intervention remains uncertain. Earlier studies documented a survival benefit associated with higher BMI in dialysis patients (46,47); however, BMI may represent higher muscle mass or it may represent higher fat mass. Recent studies suggest that it is higher muscle mass, rather than higher fat mass, that predicts longer survival in dialysis patients (48,49). Furthermore, in a longitudinal study of 121,762 patients receiving hemodialysis, declining serum creatinine (a surrogate for muscle mass) over time was a stronger predictor of mortality than was weight loss, also suggesting that the protective effect of high BMI is a result of muscle mass, not fat mass (49). Thus, an intervention aimed at increasing muscle mass while decreasing fat mass before transplantation may decrease the incidence of NODAT and some complications, including wound infections and development of delayed graft function (50), and may confer improved allograft and patient survival (51); however, clinical trials are needed to test this hypothesis.

Patients with CKD self-report low levels of physical activity (52), and in-center hemodialysis, three times per week for 3–4 h per treatment, strongly promotes inactivity. Patients receiving chronic hemodialysis have lower physical activity on dialysis days than nondialysis days, and a majority of the reduced activity is explained by less movement recorded during dialysis treatment (53). Other factors, such as anemia, hypervolemia, and uremic cachexia, may contribute to decreased physical activity. A lifestyle intervention similar to the DPP may safely reverse the inactivity of patients before transplant.

Because current antirejection therapies, including glucocorticoids, CNIs, and mTOR inhibitors, are well-established risk factors for NODAT and yet are not easily substituted, the potential effectiveness of lifestyle intervention assumes even greater importance; however, to our knowledge, the feasibility or efficacy of a lifestyle intervention to lower the incidence of NODAT has not been described.

DRUG THERAPY TO PREVENT NODAT

Drug therapy before transplant

Metformin (40) and pioglitazone (54) are effective in the prevention of type 2 diabetes mellitus in patients without renal failure. Because of their adverse effects (lactic acidosis and volume retention), their use in CKD and ESRD is restricted. Acarbose (55) and rosiglitazone (56) also reduce the incidence of type 2 diabetes mellitus, but they are not widely used in the U.S. and their effects in renal failure are not well known.

Hepatitis C has been identified in epidemiologic studies as a risk factor for both type 2 diabetes mellitus and NODAT. One small study of 14 subjects with hepatitis C who were treated with α-interferon before transplant showed a lower incidence of NODAT compared with 40 subjects who were not treated. There was no mention of the virologic response achieved in those who were treated (57). In another small cohort of 16 renal transplant recipients who received interferon and had a sustained virologic response, none developed NODAT during a mean follow-up of 22.5 months (8). Thus, it is plausible that successful treatment of hepatitis C before transplant can potentially reduce risk of NODAT.

Drug therapy after transplant

Previous studies have reported a high incidence of de novo hyperglycemia immediately after transplant (14,15). The pancreatic β-cell is exposed to several stressors immediately after kidney transplant surgery, including the surgical procedure itself, high-dose corticosteroids, and initiation of CNIs. Thus, resting the β-cell with basal insulin and optimizing β-cell protection with tighter control to near-normoglycemic treatment goals could further reduce the number of patients with future impaired glucose tolerance and NODAT. A recent study randomized nondiabetic patients to two groups in the immediate postoperative period. The first was the basal insulin group (treatment group), in whom basal insulin treatment was initiated with a morning dose of 6, 8, or 10 IU isophane insulin for previous evening blood glucose measurements of 140–180, 180–240, or 240 mg/dL, respectively. The normoglycemic goal was 110–120 mg/dL. In addition, short-acting insulin was used for corrections of hyperglycemia during the postoperative period, followed by appropriate increase in isophane insulin. The control or standard arm received short-acting insulin, oral antidiabetic therapy for hyperglycemia, or both. Treatment was administered in those with blood glucose ≥180 mg/dL. The treatment group had lower odds of NODAT (OR 0.27 [95% CI 0.10–0.72]) than the control group, and HbA1C was, on average, 0.38% lower in the treatment group than the control group (58).

Belatacept, a selective inhibitor of T-cell activation, is a parenteral immunosuppressant that replaces CNIs. Studies suggest that transplant recipients who receive belatacept have a better metabolic profile and a lower incidence of NODAT compared with those who receive CNIs (59).

After transplantation, metformin or pioglitazone may be prescribed for treatment of pre-existing type 2 diabetes mellitus or NODAT in patients with good allograft function (60). No study has investigated the role of either of these oral agents in the prevention of NODAT.

CONCLUSIONS—Kidney transplantation, an expensive therapeutic modality, is the best therapy for ESRD, but NODAT affects allograft and patient survival. With the rise in obesity among patients waiting for a kidney transplant and an anticipated increase in the number of patients with NODAT, safe and effective interventions to reduce the incidence of NODAT are critically needed. Although lifestyle intervention may have rare adverse effects, the evidence supporting successful prevention of type 2 diabetes mellitus strongly suggests that similar interventions should be tried in the kidney transplant population. Furthermore, clinical trials of interventions to prevent NODAT are needed to determine the best timing for such an intervention and the long-term effects on graft and patient survival. Lifestyle modifications in combination with less diabetogenic immunosuppressants can conceivably decrease incidence of NODAT. If the incidence of NODAT can be reduced, patients, providers, private insurers, and federal programs such as Medicare and Medicaid may all stand to benefit. If successful, lifestyle intervention might ultimately improve quality of life, morbidity, and mortality for transplant recipients and lengthen the life span of the transplanted kidney, and the cost of caring for patients with kidney transplants might also be reduced.

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