REVIEW

New-onset diabetes after transplantation: focus on treatment strategies

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Practice Points

- Screening for diabetes, cardiovascular risk factors and metabolic syndrome should begin prior to transplantation.
- The diagnosis of new-onset diabetes after transplantation is made per American Diabetes Association (ADA) criteria, with the exclusion of the A1c during the first 10 weeks post-transplant.
- Lifestyle education, including dietary choices and physical activity, is a key step and likely requires access to certified diabetes educators.
- Pharmacologic treatment requires a stepwise approach, often starting with oral agents in patients with fasting blood glucose <250 mg/dl.
- Patients with more severe hyperglycemia (fasting blood glucose >250 mg/dl) require initial insulin therapy.
- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are shown to confer cardiovascular benefits in post-transplant patients, but their use should be considered within the context of potential drug interactions, renal failure, hyperkalemia and anemia.
- Statins, fibrates and aspirin have a role in primary and secondary prevention of cardiovascular events, and may also be initiated after consideration of potential drug interactions.

SUMMARY New-onset diabetes after transplantation is an increasingly common complication after solid organ or bone marrow transplantation. New-onset diabetes after transplantation is a multifactorial condition involving both host and donor risk factors. Diabetes mellitus decreases graft and, thus, patient survival, with an excess mortality attributed primarily to cardiovascular disease. Like Type 2 diabetes mellitus, treatment involves a stepwise approach. Lifestyle modification plays a key role in therapy. Glycemic control may improve if glucocorticoids and calcineurin inhibitors can be replaced by medications with less diabetogenic potential. Beyond glycemic control, antihypertensives, lipid treatment and aspirin are key components of therapy. However, these agents must be carefully chosen to avoid interactions with antirejection medications.

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New-onset diabetes mellitus after transplantation (NODAT) or post-transplant diabetes is a common complication after solid organ or bone marrow transplantation. In 2003, an international panel of experts published guidelines for the detection and treatment of NODAT [1]. In 2005 the guidelines were extended and management options for kidney, liver and heart transplant patients were included [2]. However, the management of NODAT has been a clinical challenge due to a paucity of clinical trials in this population.

New-onset diabetes mellitus after transplantation is associated with increased risk of cardiovascular disease and infectious complications. In addition, studies have shown that diabetics have both decreased graft and patient survival after transplantation compared with nondiabetics. The excess mortality may be attributable in part to a higher incidence of infectious disease and graft failures, but is primarily related to cardiovascular disease, the leading cause of mortality in post-transplant patients [3–6].

Diagnosis of NODAT

Most experts recommend using the American Diabetes Association (ADA) or WHO criteria for diagnosis of NODAT **(Table 1)** [7]. However, in the early post-transplant period HbA1c level may not be a reliable criteria, particularly in individuals who received blood transfusions at the time of transplantation. Thus, in general, it is not recommended to check the HbA1c level until 10 weeks post-transplant [8]. In addition, alterations in glycosylated hemoglobin occur in uremic patients due to the increased formation of carbamylated hemoglobin [9,10]. Nevertheless, the NODAT guidelines do recommend using the HbA1c assay for monitoring established NODAT but urge caution in interpreting the assay in the context of anemia and renal impairment. Recent literature suggests that an oral glucose tolerance test may be a better way to diagnose NODAT [11,12].

Incidence

The incidence of NODAT is reported to range from 2 to 50% in solid organ transplants [5,13–17] and 17–60% in bone marrow transplants [18,19], but the incidence appears to be declining in recent years, possibly due to fewer rejections and less steroid use. The variable incidence reported is attributable to the use of many different criteria for diagnosis and the use of different regimens of immunosuppressive agents [5]. The time to onset is usually within 1 year, but may vary from 1 month to 5 years. NODAT resolves in a third to a half of patients, but appears to be permanent in others [4,14].

Relationship of transplant medications with NODAT

Agents that are commonly used for immunosuppression after solid organ transplantation include glucocorticoids, calcineurin inhibitors, azathioprine, mycophenolate mofetil and mammalian target of rapamycin inhibitors such as sirolimus. The agents most associated with diabetes mellitus are glucocorticoids and calcineurin inhibitors.

■ Glucocorticoids

Glucocorticoids are the most common cause of drug-induced diabetes mellitus. They induce hyperglycemia through multiple mechanisms: inducing hepatic gluconeogenesis, decreasing peripheral insulin sensitivity and inhibiting pancreatic insulin secretion. The dose of steroid administration and duration of treatment is proportional to the incidence and severity of diabetes. Steroid sparing or steroid withdrawal

Table 1. Criteria for the diagnosis of diabetes (American Diabetes Association guidelines update 2011).

1.	HbA1c ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay
2.	FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h
3.	2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
4.	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dl (11.1 mmol/l)

DCCT: Diabetes Control and Complications Trial; FPG: Fasting plasma glucose; NGSP: National Glycohemoglobin Standardization Program; OGTT: Oral glucose tolerance test.
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protocols have been shown to reduce insulin resistance and improve glucose metabolism in renal transplant recipients [20,21].

Calcineurin inhibitors

Calcineurin inhibitors cyclosporine and tacrolimus act against the T-cell activator protein, calcineurin, inhibiting T-cell activation and cytokine gene expression. Both agents are associated with hyperglycemia, but tacrolimus possesses a greater diabetogenic effect than cyclosporine [22–24]. The mechanism of NODAT with calcineurin inhibitors is thought to be due to impaired insulin secretion. Hjelmesaeth *et al.* showed a decrease in insulin and C-peptide secretion in hemodialysis patients after cyclosporine administration, using insulin clamp studies [25]. *In vitro* studies have shown that tacrolimus impairs insulin gene expression in cultured β cells in a dose-dependent manner. The addition of corticosteroids to calcineurin inhibitors has been shown to potentiate the hyperglycemic effect [26,27].

Other agents

Azathioprine and mycophenolate have no effects on glucose metabolism. The effects of sirolimus on glucose metabolism are controversial. Its beneficial effect on glucose metabolism in some studies could explain its successful use in islet cell transplantation. Conversely, concern exists regarding possible worsened insulin resistance [28]. *In vitro* effects of sirolimus on islet cells have shown deleterious effects [29]. *In vivo* studies of rapamycin on rodent and human islets result in reduced insulin secretion and impaired β-cell function at doses higher than used in clinical settings [30]. There is evidence that sirolimus has no deleterious effects on human islet insulin secretion at levels used for immunosuppression in humans. Studies in mini-pigs treated with sirolimus demonstrated improved basal- and glucose-stimulated insulin [31]. In a small cohort of renal transplant recipients, sirolimus caused worsening of glucose intolerance and insulin resistance [32]. Johnston *et al.* used the data from United States Renal Data System and concluded that sirolimus is independently associated with NODAT [33]. A newer agent, the polyclonal antibody basiliximab, has been associated with impaired glucose homeostasis after kidney transplantation [34]. Other polyclonal antibodies (i.e., daclizumab, muromonab) and everolimus have no known diabetogenic properties [28].

Box 1. Risk factors for the development of new-onset diabetes mellitus after transplantation.

- Nonmodifiable risk factors in recipient:
  - African–American or Hispanic race
  - Age >40 years
  - Family history of diabetes
  - Impaired glucose tolerance
  - History of acute rejection
  - History of polycystic kidney disease
- Donor-related risk factors:
  - Male donor
  - Cadaveric donor
  - HLA mismatches
- Modifiable risk factors in recipient:
  - Obesity
  - Hepatitis C
  - Cytomegalovirus
  - Immunosuppressive medication regimen

Risk factors for development of NODAT

New-onset diabetes mellitus after transplantation is a multifactorial condition **(Box 1)**. Risk factors include African–American or Hispanic race, age >40 years, male donor, HLA mismatches, cadaveric donor, polycystic kidney disease, family history of diabetes, abnormal glucose tolerance prior to transplant and acute rejection history. The potentially modifiable risk factors are overweight (BMI >25), hepatitis C, cytomegalovirus infection, and the choice of immunosuppressive medication and dose [4,5,14,16,35,36]. Successful antiviral treatment of hepatitis C in liver transplant recipients appears to be associated with improved glucose control and decreased incidence of diabetes [37]. Results from studies that analyzed the association between HLA phenotypes and NODAT are contradictory. A few studies have not found a relationship between the degree of HLA mismatch and risk of NODAT [38]. Kasiske *et al.* [4] and Madhav *et al.* [39] showed the existence of this association. Kasiske *et al.* reported recipients with six HLA mismatches to be at significantly greater risk for developing NODAT than were those with zero HLA mismatches [4]. Madhav *et al.* observed HLA-B13 to be associated with the development of NODAT [39].

Screening

International consensus guidelines recommend monitoring fasting blood glucose weekly for the first 4 weeks, at 3, 6 and 12 months and annually thereafter. If impaired fasting glucose is detected, an oral glucose tolerance test is

recommended to further check for the development of diabetes [2]. Several studies have demonstrated that high pretransplantation insulin levels [40], elevated random blood glucose [41] and impaired fasting glucose [42] can predict future development of NODAT. Griffith *et al.* concluded that pretransplantation C-peptide level >3.6 ng/ml and peak steroid dose >1 mg/kg/day can predict NODAT [43]. C-peptide elevation was positively correlated with increasing age, pretransplant BMI and Homeostasis Model of Assessment – Insulin Resistance (HOMA–IR) score (fasting insulin mU/l × fasting glucosemmol/l). These methods have been suggested for screening patients prior to transplantation to determine NODAT risk and to guide selection of immunosuppressant therapy.

Treatment options: stepwise approach

The management of NODAT should follow a stepwise approach similar to the management of Type 2 diabetes [44]. Options include nonpharmacologic lifestyle interventions, modification of immunosuppressive therapy, pharmacologic therapy, management of cardiovascular risk factors and screening for diabetic complications. The initial treatment selection is based on the fasting blood sugar (FBS) level. HbA1c level is often not a reliable indicator in the first 3 months after transplantation, considering that many patients receive blood transfusion during the surgery or in the postoperative period. The use of HbA1c beyond 10 weeks after transplant is a reasonable stratification tool to guide further treatment, and a 'treat to goal' approach is applicable in NODAT. HbA1c should be monitored carefully and therapy intensified every 2–3 months until a goal HbA1c of less than 7 is achieved. When choosing additional agents it is recommended to combine agents with different mechanisms of action and different targets of action.

■ Nonpharmacologic interventions

All patients regardless of their FBS level should receive counseling on lifestyle interventions, which include weight control, decreased caloric intake, consistent carbohydrate diet and exercise. Weight gain, often related to the immunosuppressive therapy and prolonged immobility in the peritransplant period, is thought to be one of the main factors in NODAT development. Lifestyle interventions to reduce weight and increase insulin sensitivity are a very important step in the management of diabetes. Treatment of obesity in the post-transplant period was extensively reviewed by Potluri and Hou, who recommend pharmacologic and surgical approaches in appropriate patients [45]. Education on self-monitoring of blood glucose and teaching on hypoglycemia recognition, prevention and treatment are other critically important points in the management of diabetes. Including certified diabetes educators in the NODAT management team is highly recommended.

■ Modification of immunosuppressive agents

Modification of immunosuppression can be a very important step in management of NODAT. The major diabetogenic agents in transplant protocols are steroids and calcineurin inhibitors. Use of steroid sparing regimens has been shown to significantly improve a patient's glucose tolerance during the first year after transplantation. Decreasing the dose of steroids towards a more physiologic dose (5 mg/day of prednisone) resulted in improved insulin sensitivity [20]. Luan *et al.* retrospectively evaluated the effects of a steroid-free maintenance regimen on kidney graft recipients and concluded that withdrawal of steroids is not associated with worse allograft and recipient outcomes [46]. Woodle *et al.* compared early steroid cessation to long-term steroid use for 5 years. NODAT incidence was similar in both groups; however, fewer corticosteroid withdrawal patients required insulin therapy at 5 years. Steroid withdrawal provided similar long-term renal allograft survival and function with improvements in cardiovascular risk factors (i.e., triglycerides, NODAT requiring insulin and/or weight gain) [47]. Conversely, Hricik *et al.* reported that withdrawal of steroids led to a negative impact on long-term graft function and survival in renal African–American patients [48].

Tacrolimus is associated with a greater diabetogenic effect than cyclosporine. Renal transplant data suggest that switching from tacrolimus to cyclosporine may be beneficial in patients with diabetes [49]. Ghisdal *et al.* retrospectively evaluated kidney transplant recipients with NODAT [50]. In this study 34 out of 54 patients were converted from tacrolimus to cyclosporine. After 12 months of follow-up, graft function remained stable, and only one acute rejection episode was directly associated with the change in calcineurin inhibitor. The remission rate of NODAT reached 42% in this study. The largest

study, comparing tacrolimus and cyclosporine is the DIRECT trial [51]. The incidence of NODAT or impaired fasting glucose at 6 months post-transplant was significantly lower with cyclosporine than with tacrolimus without a significant difference in short-term outcomes. Only one patient in the cyclosporine group required a combination of insulin and oral treatment versus ten patients in the tacrolimus group.

However, the risk of NODAT should be balanced with the risk of graft failure. Kasiske *et al.* reported that despite the association between tacrolimus and NODAT, and the association between NODAT and reduced graft survival, tacrolimus was nevertheless associated with improved graft survival when NODAT risk was weighted against the increased risk of acute graft rejection due to discontinuation of this agent [4]. Matas *et al.* studied the long-term risk of acute rejection based on immunosuppressive protocol and compared it to NODAT risks. They concluded that graft survival was worse with acute rejection compared with NODAT [52].

Specific diabetes medications

Although there is a paucity of evidence to support specific glycemic goals in patients with NODAT, it seems reasonable to follow glycemic guidelines such as outlined for Type 2 diabetes patients. Subjects with NODAT are not protected from diabetes complications, and may in fact be more susceptible to diabetes complications [53] in part due to concomitant medical diseases. A major concern with NODAT patients is the risk of adverse interactions between immunosuppressant agents and other agents indicated for glycemic control. **Tables 2 & 3** outline potential drug interactions [101]. **Table 4** summarizes published studies investigating therapeutics in NODAT, and **Table 5** outlines ongoing studies.

Table 2. Potential drug interactions between immunosuppressants and glucose-lowering agents.

Hypoglycemic agents	Antirejection drugs				
	Azathioprine	Cyclosporine	Mycophenolate mofetil	Sirolimus	Tacrolimus
Acarbose	No	No	No	Yes[††]	No
Chlorpropamide	No	Yes[‡]	No	Yes[††]	No
Exenatide	No	No	No	No	No
Sulfonylureas	No	Yes[‡]	No	Yes[††]	No
Insulin[†]	No	No	No	Yes[††]	No
Liraglutide	No	No	No	No	No
Metformin	No	No	No	No	No
Miglitol	No	No	No	Yes[††]	No
Nateglinide	No	Yes[§]	No	Yes[††]	No
Pioglitazone	No	No	No	Yes[††]	No
Repaglinide	No	Yes[§]	No	Yes[††]	No
Rosiglitazone	No	No	Yes[#]	Yes[††]	No
Saxagliptin	No	Yes[§¶]	No	Yes[††]	Yes[¶]
Sitagliptin	No	Yes[¶]	No	Yes[††]	Yes[¶]
Tolazamide	No	Yes[‡]	No	Yes[††]	No
Tolbutamide	No	Yes[‡]	No	Yes[††]	No

[†]Insulin category includes aspart, detemir, glargine, glulisine, lispro, neutral protamine Hagedorn and regular insulin.
[‡]Cyclosporine may diminish the therapeutic effect of sulfonylureas, and sulfonylureas may increase the serum concentration of cyclosporine.
[§]Cyclosporine is a CYP3A4 inhibitor and may decrease the metabolism of CYP3A4 substrates (nateglinide, repaglinide, saxagliptin). Monitor for increased effects of the CYP substrate if cyclosporine is initiated or dose increased, and decreased effects of the CYP substrate if cyclosporine is discontinued or dose decreased.
[¶]Cyclosporine and tacrolimus are p-glycoprotein inhibitors, which may enhance the distribution of the p-glycoprotein substrates, saxagliptin and sitagliptin, to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., the brain, T lymphocytes, testes).
[#]Rosiglitazone may increase the serum concentration of the active metabolite mycophenolic acid. Closely monitor red blood cell counts, hemoglobin, hematocrit and mycophenolic acid serum levels with rosiglitazone initiation or dose increase and concomitant mycophenolate mofetil therapy.
[††]Sirolimus may cause hypoglycemia; monitor for additive hypoglycemic effects when used concomitantly with these diabetes medications.
Data taken from [101].

Table 3. Potential drug interactions between immunosuppressants and other commonly used agents in new-onset diabetes mellitus after transplantation.

Agents	Azathioprine	Corticosteroids	Cyclosporine	Mycophenolate mofetil	Sirolimus	Tacrolimus
Aspirin	No	No	No	No	No	No
ACE inhibitors	Yes[†]	No	Yes[¶]	No	Yes[†††]	No
Aliskiren	No	No	Yes[#]	No	No	No
β-blocker (carvedilol)	No	No	Yes[††]	No	No	No
CCBs (dihydropyridine)	No	No	Yes[‡‡]	No	No	Yes[‡‡‡]
CCBs (nondihydropyridine)	No	Yes[‡]	Yes[‡‡]	No	No	Yes[§§§]
Diuretics	No	Yes[§]	Yes[¶]	No	No	Yes[¶¶¶]
Ezetimibe	No	No	Yes[§§]	No	No	No
Fibrates	No	No	Yes[¶¶]	No	No	No
Statins	No	No	Yes[##]	No	No	Yes[###]

[†]Monitor for increased toxic effects (e.g., neutropenia) of azathioprine with initiation or dose increase of an ACE inhibitor.

[‡]Nondihydropyridine CCBs may decrease the metabolism of corticosteroids. Monitor for toxic effects of corticosteroids if coadministered with diltiazem or verapamil.

[§]Corticosteroids may enhance the hypokalemic effect of thiazide and loop diuretics. Consider addition of potassium-sparing diuretic or potassium supplementation with concomitant treatment.

[¶]Monitor for increased signs and symptoms of nephrotoxicity during coadministration of cyclosporine and ACE inhibitors. Maintenance of adequate hydration and caution with diuretic use may reduce risk of adverse effects.

[#]Cyclosporine may increase the serum concentration of aliskiren. Concomitant use of these agents is not recommended.

[††]Carvedilol may increase the serum concentration of cyclosporine.

[‡‡]Cyclosporine may decrease the metabolism of dihydropyridine and nondihydropyridine CCBs. Nicardipine may likewise inhibit the metabolism of cyclosporine. Monitor for decreases in blood pressure during concomitant therapy with cyclosporine and CCBs. For patients receiving nicardipine, closely monitor serum cyclosporine concentrations. Reductions in cyclosporine dosage may be necessary.

[§§]Cyclosporine may increase the serum concentration of ezetimibe, and ezetimibe may likewise increase the serum concentration of cyclosporine. Monitor for increased toxicity of cyclosporine and ezetimibe if coadministered, especially in patients with renal impairment. In such circumstances, consider dose adjustment of ezetimibe.

[¶¶]Cyclosporine may enhance the nephrotoxic effect of fibrates. Furthermore, fibrates may decrease the serum concentration of cyclosporine. Careful consideration should occur regarding the risks and benefits before using this combination. Additional monitoring of renal function and cyclosporine concentrations is likely required, and adjustment of cyclosporine dosage may be necessary.

[##]Cyclosporine may increase the serum concentration of statins. Monitor for toxic effects (e.g., increased serum creatine phosphokinase, myopathy, rhabdomyolysis) of statins if cyclosporine is being used or the dose is increased. Limit rosuvastatin to 5 mg/day and simvastatin to 10 mg/day. Fluvastatin does not appear to be affected by cyclosporine.

[†††]Sirolimus may enhance the toxic effects of ACE inhibitors. Caution patients regarding the increased risk of angioedema, and urge them to immediately report any signs or symptoms of this condition.

[‡‡‡]Dihydropyridine CCBs may increase the serum concentration of tacrolimus.

[§§§]Nondihydropyridine CCBs may decrease the metabolism of tacrolimus.

[¶¶¶]Potassium-sparing diuretics may enhance the hyperkalemic effect of tacrolimus. Avoid concomitant use of these agents.

[###]Tacrolimus may increase the serum concentration of statins. However, data suggest a limited effect. No management action is required with this combination.

ACE: Angiotensin-converting enzyme; CCB: Calcium channel blocker.

Data taken from [101].

■ Metformin

Metformin is an insulin sensitizer and is the preferred initial agent in nontransplant Type 2 diabetes patients. In NODAT patients metformin is often not considered due to fear of lactic acidosis from impaired renal function after surgery or nephrotoxic side effects of calcineurin inhibitors. Metformin is also contraindicated in liver and heart failure patients. Therefore, its use is limited in NODAT patients. However, Kurian *et al.* performed a retrospective chart review of 54 patients with NODAT after renal transplant, of which 21 received metformin and 33 received a thiazolidinedione, with 16–72 months follow-up [54]. The authors concluded that metformin is safe in post-transplant patients, but monotherapy may not be sufficient in the transplant population. The most recent Cochrane review found no increased risk of lactic acidosis with metformin compared with other antihyperglycemic agents when contraindications were taken into account [55]. Herrington *et al.* extensively reviewed the topic of metformin dosing in renal disease and suggested the following approach [56]. For mild renal impairment (stage 1–2 chronic kidney disease [CKD]; glomerular filtration rate [GFR] 60–90 ml/min), continue metformin use. In moderate renal impairment (stage 3 CKD; GFR 30–60 ml/min), metformin may be continued with caution. For those with GFR between 90 and 60 ml/min and in the elderly (over 70 years old), the starting and maximum dose of metformin may be cut in half. Once GFR falls below 60 ml/min, metformin dosing should be halved again, but can probably be used safely. As GFR falls from 60 towards 30 ml/min the balance of risk and benefit should be closely weighed, and metformin continued only if no suitable alternative is found. For patients with a GFR below 60 ml/min, renal function should be monitored regularly.

■ Sulfonylureas

Observational studies suggest that sulfonylurea monotherapy is not able to control hyperglycemia in post-transplant patients [57,58]. Tuerk *et al.* in 2008 reported a retrospective study of 75 patients with NODAT, and compared 47 patients receiving gliquidone monotherapy to 28 patients receiving rosiglitazone monotherapy. Both groups achieved similar and statistically significant improvements in glycemic control with HbA1cs below 7 [59]. Thus, sulfonylureas appeared to be a safe option for NODAT therapy, although a few patients required dose decreases due to hypoglycemia. This is the only study published to assess the use of sulfonylureas in NODAT. When prescribing sulfonylureas one should beware of the increased risk of hypoglycemia, especially common in transplant patients with renal and hepatic insufficiency.

■ Glinides

Glinides are short-acting insulin-secretagogues, which act directly on the pancreatic β cell to stimulate rapid insulin secretion dependent on ambient glucose. They can be used in chronic renal failure and are therefore a potential treatment option for NODAT. Turk *et al.* reported a comparison of patients treated with repaglinide or rosiglitazone [60]. Glucose lowering efficacy was similar with 61 and 74% achieving a decrease in HbA1c of 1.3 and 1.2% in the repaglinide versus rosiglitazone group, respectively. Furthermore, no clinically important interactions with cyclosporine or tacrolimus were reported and no drug level changes noted. Voytovich *et al.* published a study of 14 patients with NODAT or impaired glucose, who received nateglinide for 2 weeks. The study concluded that nateglinide

Table 4. Published studies investigating new-onset diabetes mellitus after transplantation therapies.

Author (year)	Design	Results	Ref.
Baldwin *et al.* (2004)	Seven patients with NODAT and 11 patients with pre-existing diabetes. Rosiglitazone–glyburide, rosiglitazone–repaglinide and rosiglitazone alone regimens were studied in NODAT group	A1c improvement from 8.6 ± 1.5% to 6.7 ± 0.5% ($p = 0.035$). No significant effect on tacrolimus or cyclosporine level	[57]
Luther *et al.* (2004)	Ten patients with diabetes after transplantation (four patients with NODAT) were studied. Serum creatinine, HbA1c, total daily insulin dose, tacrolimus dose, tacrolimus level and prednisone dose were followed for 242 days and compared with the corresponding values measured before the initiation of pioglitazone	Decrease in HbA1c from 8.36 to 7.08 and decrease in total daily insulin dose were achieved. No statistically significant change in creatinine, tacrolimus dose and level, or prednisone level was seen	[67]
Villanueva *et al.* (2005)	40 patients with NODAT were followed for 3–12 months. They were started initially on NPH/regular insulin, then rosiglitazone was added	91% of patients discontinued insulin while titrating up rosiglitazone. 39% used rosiglitazone alone, the rest required addition of sulfonylurea. All patients achieved a normal HbA1c	[58]
Turk *et al.* (2006)	23 patients treated with repaglinide were compared with control group of 19 patients on rosiglitazone. Follow-up time: 6 months. All patients had new-onset diabetes after renal transplant	14 of 23 patients were successfully treated (mean A1c decreased from 7.6 to 5.8) in repaglinide group, and 14 of 19 in rosiglitazone group achieved similar success	[60]
Kurian *et al.* (2008)	54 patients with post-transplant diabetes, 21 in metformin group and 33 in TZD group, were followed for 16–72 months	Both metformin and TZD are safe in post-transplant diabetes	[54]
Tuerk *et al.* (2008)	Retrospective study of 57 patients with NODAT, gliquidone monotherapy (29 patients) was compared with rosiglitazone (28 patients)	Both groups were followed for 6 months and achieved similar statistically significant improvement in glycemic control	[59]
Voytovich *et al.* (2005)	Ten glucose-intolerant renal transplant recipients were treated with rosiglitazone for 4 weeks. Endothelial function, insulin sensitivity and glucose levels were studied	4 weeks' treatment with rosiglitazone was associated with increased insulin sensitivity, lowered fasting and 2 h plasma glucose and improved endothelial function in renal transplant recipients. No adverse events were reported	[66]
Voytovich *et al.* (2007)	Study of 14 patients with NODAT or impaired glucose, who received nateglinide for 2 weeks	Insulin secretion and 2 h glucose response were improved in patients treated with nateglinide. No adverse events were reported	[61]

NODAT: New-onset diabetes mellitus after transplantation; NPH: Neutral protamine Hagedorn; TZD: Thiazolidinedione.

Table 5. Studies ongoing into new-onset diabetes mellitus therapies.

Study	Setting	Focus	Ref.
Effectiveness of Pramlintide on Control of Post-transplant Diabetes Mellitus	University of Colorado, Denver, USA; August 2009–2011	Pramlintide is added to oral agents or insulin therapy in post-transplant diabetes mellitus. HbA1c is measured at 3 and 6 months. Continuous glucose monitoring and improvement in blood sugars are secondary outcome measures	[102]
The Effect of Sitagliptin Treatment on Glucose Metabolism and Endothelial Function in Renal Transplant Recipients	Oslo University School of Pharmacy, Norway; August 2008–March 2010	Primary goals are to study the effect of sitagliptin on insulin secretion in renal transplant recipients. Secondary objectives are to study the effect on insulin sensitivity, fasting blood glucose, endothelial function, cyclosporine and tacrolimus blood concentrations. 14 patients receive sitagliptin versus placebo for 4 weeks	[103]
Treat-to-Target Trial of Basal Insulin in Post-transplant Hyperglycemia (TIP)	Medical University of Vienna, Department of Internal Medicine III Vienna, Austria; January 2009–December 2010	Prospective, randomized safety and efficacy study of long-acting insulin (Insulatard®) versus conventional medications (based on ward physician decision). 50 patients, 25 in each arm, will be followed for 180 days after renal transplant. Primary end point is the difference in HbA1c between the two study arms. Hypoglycemic episodes and other complications will be studied to assess safety	[104]
Vildagliptin in New Onset Diabetes After Transplantation	Medical University of Vienna, Austria; September 2009–October 2010	32 patients, primary outcome measures are to assess whether monotherapy with vildagliptin improves glycemic control in kidney transplanted patients with newly diagnosed NODAT as judged by OGTT after 3 months of treatment compared with placebo. HbA1c, FBS and safety will be assessed as well	[105]

FBS: Fasting blood sugar; NODAT: New-onset diabetes mellitus after transplantation; OGTT: Oral glucose tolerance test.

was a safe option and resulted in improved postprandial hyperglycemia. Both insulin secretion and 2-h glucose response were improved in patients treated with nateglinide [61].

■ Thiazolidinediones

Thiazolidinediones stimulate peroxisome proliferator activated receptor-γ and act as insulin sensitizers. The first agent, troglitazone, was withdrawn from usage due to associated liver toxicity. Although newer agents, rosiglitazone and pioglitazone, do not appear to share the hepatotoxic potential of troglitazone, there is a concern for cardiovascular disease risk with these agents, particularly rosiglitazone. The well-documented side effect of fluid retention doubles the risk of heart failure and is associated with up-regulation of epithelial sodium channels (ENAc). Furosemide, despite its higher natriuretic potential was found to be less effective than spironolactone (an indirect inhibitor of ENAc) or amiloride (a direct ENAc inhibitor) in treating edema due to thiazolidinediones [62]. Rennings *et al.* challenged the previous findings and showed that rosiglitazone did not change furosemide response [63]. Additional concerns for these agents include congestive heart failure and increased risk of fractures, especially in postmenopausal women [64,65]. Nevertheless, thiazolidinediones are described in the literature as a good option for NODAT and can be used as adjunctive therapy to other oral agents or insulin.

Rosiglitazone was initially the preferred thiazolidinedione in NODAT as it is not metabolized through the cytochrome P450 CYP3A4 system and has potentially lower risk of interactions with immunosuppressant agents. Baldwin *et al.* studied seven patients with NODAT who received rosiglitazone with glyburide, rosiglitazone with repaglinide or rosiglitazone alone. This group had successful diabetes control with an average HbA1c of 6.7%. No adverse interactions with tacrolimus or cyclosporine or effects on the level of immunosuppressant agents were seen [57]. Villanueva *et al.* reported 40 patients with NODAT who were followed for 3–12 months. They were initially started on insulin neutral protamine Hagedorn (NPH)/regular, and 91% were able to transition off insulin to rosiglitazone alone (39%) or rosiglitazone plus sulfonylurea (62.5%). Thirteen percent of the patients developed edema, but none of the patients discontinued rosiglitazone because of the side effects [58]. Voytovich *et al.* studied endothelial function, insulin sensitivity and glucose levels in patients treated with rosiglitazone for 4 weeks. The results of the study showed improved mean glucose level, improved insulin sensitivity and endothelial function; however, the study was small (ten subjects), and patients served as their own controls, thus results must be interpreted with caution [66]. NODAT studies with pioglitazone have reported similar hypoglycemic effects

and lack of interactions with immunosuppressant agents. For example, Luther *et al.* reported that the addition of pioglitazone to insulin or sulfonylurea improved HbA1c level, and had no adverse effects or interactions with tacrolimus. Renal function remained stable [67]. There is no cardiovascular data regarding use of these antiglycemic agents post-transplantation. Therefore, agents with potential cardiovascular risk such as rosiglitazone should be used with caution.

■ Incretins

The incretins are a newer class of therapy available for diabetic patients. This class includes the glucagon-like peptide-1 (GLP-1) agonists, exenatide and liraglutide, and the dipeptidyl peptidase IV (DPP-IV) inhibitors sitagliptin and saxagliptin. Exenatide and liraglutide are GLP-1 agonists, which are administered by injection and act to lower postprandial blood glucose levels. These drugs lower HbA1c by 0.5–1%, are not associated with hypoglycemia, and have the additional benefit of 5–10 lbs potential weight loss at 6 months [68]. The GLP-1 agonists seem attractive as therapeutic agents in NODAT, but no sufficient data on the efficacy and safety of these agents in NODAT patients are available. Common side effects include nausea, diarrhea and nasopharyngitis [69,70]. Pancreatitis has been reported as a rare occurrence [71,72].

The DPP-IV inhibitors sitagliptin and saxagliptin work by delaying degradation of endogenous GLP-1. They decrease HbA1c levels by 0.6% to 0.9%, are weight neutral, relatively well tolerated, do not cause hypoglycemia and are safe in renal impairment. They can be used as monotherapy or in addition to metformin, thiazolidinediones or insulin. Triple medication combination is particularly effective in Type 2 diabetes patients [73]. Experimental data report potential protective effects of DPP-IV inhibitors on islet function after exogenous stress stimuli including immunosuppressants. Similar to the GLP-1 agonists, there is a lack of data regarding these agents in NODAT, but studies are pending **(Table 5)**.

■ Insulin

Few studies have specifically assessed the safety and efficacy of insulin compared with other therapies for NODAT. In contrast to several hypoglycemics, insulin appears to have no significant interactions with antirejection drugs [101]. In the perioperative period, intensive glucose control with insulin has been retrospectively linked with improved outcomes [74]. Prospective data has shown improved outcomes in liver patients treated perioperatively with intravenous insulin to achieve strict glycemic control [75]. In the outpatient setting, patients not at goal on two oral agents will generally require the addition of or transition to insulin therapy. A basal dose of NPH, levemir or glargine may be added to the oral hypoglycemic regimen.

At our institution insulin is initiated for severe hyperglycemia, characterized by fasting plasma glucose >250 mg/dl. We also use insulin when HbA1c values remain >8% after 3 months on two oral hypoglycemics [76]. The choice of premix versus basal plus bolus dosing will depend on the lifestyle and preferences of the patient. Individuals with consistent eating patterns may benefit from the convenience and consistency of pre-mix insulin. Patients with variable meal patterns will be able to achieve tighter glycemic control on basal plus bolus therapy. Finances also factor into the choice between regular and NPH insulin versus newer analogs. Treating the needs and preferences of the individual is key to successful insulin therapy.

■ Our approach & recommendations

We recommend for all patients undergoing transplantation to be screened for hyperglycemia in both the pre- and post-transplant period **(Figure 1)**. The use of screening protocols and early endocrinology referral is important for best outcomes. Ideally, all patients undergoing transplantation evaluation, but particularly those individuals at high risk for NODAT, should meet with a certified diabetes educator to discuss lifestyle changes such as meal choices and physical activity. The choice of immunomodulating agents should be made based on risk of NODAT as well as other factors, and steroid sparing regimens are preferred for high-risk individuals. Screening for diabetes complications should be performed at time of diagnosis and again by 3–5 years of onset, according to ADA guidelines.

Our initial treatment approach is based on FBS and HbA1c level (HbA1c only used >10 weeks post-transplantation). We advocate a stepwise approach with a change in management (advancing to the next step) every 2–3 months if glucose control is not achieved **(Figure 2)**. All patients are counseled on nonpharmacologic

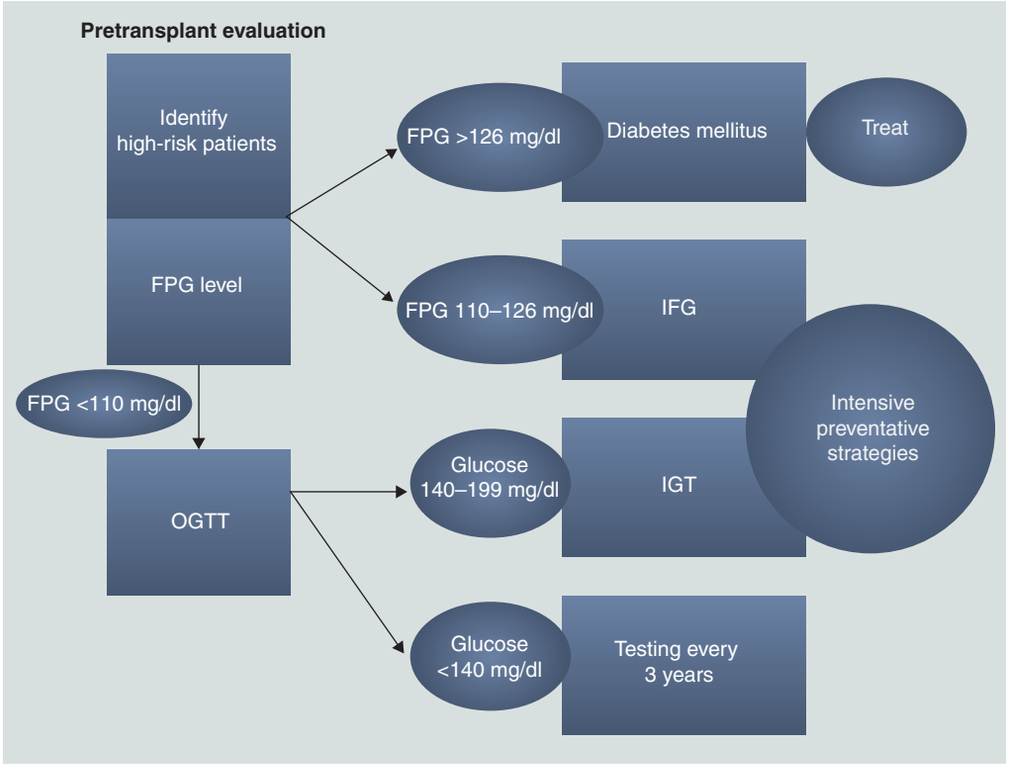

Figure 1. Evaluation of patients undergoing consideration for transplant.
FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; OGTT: Oral glucose tolerance test.

lifestyle interventions, including diet, exercise and weight loss. Modification of immunosuppression is an important consideration for all patients, regardless of their glycemic control. For patients with FBS <150 mg/dl and random blood sugar <180 mg/dl, monotherapy with glinides, incretins, thiazolidinediones or metformin is an appropriate first choice. If HbA1c <7% is not achieved within 3 months we recommend adding either a second oral agent with different mechanism of action or insulin. If HbA1c <7% is still not achieved with two oral agents we recommend insulin therapy.

For patients with FBS of 150–250 mg/dl and random blood sugar <300 mg/dl, we consider dual therapy with oral agents or the use of insulin as the first step. If oral agents are used and HbA1c is not at goal within 3–4 months we rapidly add insulin or transition to insulin therapy. In patients with FBS >250 mg/dl or random blood sugar >300 mg/dl, insulin therapy should be initiated first. If steroids and calcineurin inhibitors are tapered, glycemic control may improve and some patients can be transitioned off insulin to oral agents. Discontinuation of insulin and changing to oral therapy is more likely in NODAT patients than in individuals with Type 2 diabetes.

The majority of medications used to treat hyperglycemia are affected by renal function, as reviewed by O'Mara [77]. We recommend that first-generation sulfonylureas and α-glucosidase inhibitors be avoided or used in reduced doses in patients with CKD. Metformin may be used with mild CKD stage 1–2 (GFR 60–90 ml/min) at a 50% reduced dose. Thiazolidinediones do not require dose adjustments for kidney disease but may cause fluid retention. We concur with guidelines from the National Kidney Foundation that for moderate to severe CKD, insulin, glipizide, the DPP-IV inhibitors (i.e., saxagliptin, sitagliptin), repaglinide, pioglitazone and rosiglitazone may be used [78]. However, renal failure increases the risk of hypoglycemia due to decreased clearance of insulin and some oral hypoglycemic agents and impaired renal gluconeogenesis. Thus, heightened monitoring for hypoglycemia in the setting of moderate to severe CKD is warranted.

Beyond glucose control: role of other medications in NODAT

Cardiovascular disease is the leading cause of death in transplant recipients, and NODAT patients appear to be at even greater risk than patients without diabetes. There is a wealth of evidence that dyslipidemia and hypertension are major risk factors for the development of cardiovascular disease, thus attention to control of lipids and blood pressure in NODAT patients is important.

■ Statins

Dyslipidemia is common after transplantation and has been attributed to immunosuppressive agents, especially sirolimus [79]. Statin therapy has been associated with multiple benefits in the post-transplant population, including survival benefit and reduced development of NODAT [80]. Statin use may be beneficial for all transplant recipients with NODAT [2,81,82]. The Assessment of Lescol in Renal Transplantation (ALERT) study showed fluvastatin to be safe and effective in lowering LDL by 32% in renal transplant patients followed for 5 years. However, cardiovascular benefit was limited as fluvastatin did not generally reduce the rate of coronary intervention procedures or mortality [83]. In a retrospective study of 1574 adult renal transplant recipients, patients treated with statins had a 24% better survival than those who did not receive the drugs [82]. Concern in using statins arises from the potential for drug interactions with immunosuppressants (Table 3). However, Aliabadi *et al.*

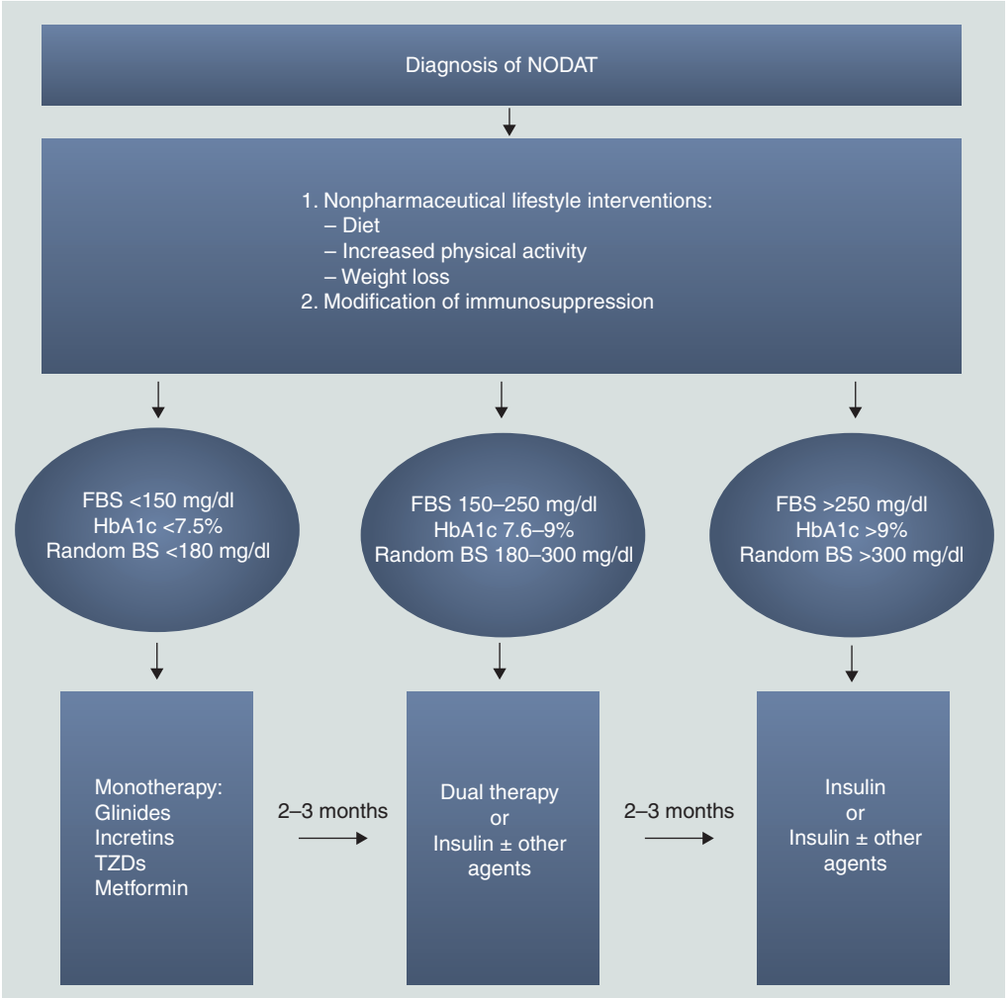

Figure 2. Stepwise management approach.
BS: Blood sugar; FBS: Fasting blood sugar; NODAT: New-onset diabetes mellitus after transplantation; TZDs: Thiazolidinediones.

reported atorvastatin and pravastatin use in cardiac transplant patients switched from cyclosporine to sirolimus. Blood lipid levels after the switch were not associated with statin type, and overall safety was acceptable. Hepatotoxicity rate was 4% and only temporary [84].

■ Fibrates

All fibrates except gemfibrozil have potential nephrotoxicity, and fenofibrate has been shown to reduce cyclosporine levels in heart transplant recipients [85]. These agents should be used with caution in the post-transplant population, especially in renal insufficiency. As it remains controversial whether hypertriglyceridemia is an independent risk factor for cardiovascular disease, and the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) study suggested that most diabetic subjects do not have any additional benefit when a fibrate is added to a statin [86], the primary focus of lipid-lowering therapies should remain a statin. However, for patients with significant elevations of triglycerides who are at risk for pancreatitis fibrates should be used, albeit cautiously and with close monitoring of immunosuppressant levels, liver function tests and symptoms.

■ Antihypertensives

A blood pressure target of 130/80 mmHg or below is recommended for patients with NODAT. Therapy may be initiated with an angiotensin-converting enzyme (ACE) inhibitor with further agent(s) added to reduce blood pressure to the target level. No antihypertensive medications are currently contraindicated in transplant patients. ACE inhibitor therapy in post-renal transplant patients on cyclosporine and tacrolimus improved blood pressure control. Additional benefit was seen in regression of left ventricular hypertrophy in patients on cyclosporine. This effect was independent of blood pressure reduction and was attributed to interactions between ACE inhibitors and cyclosporine [87]. However, ACE inhibitors have been associated with severe acute tubular necrosis in renal transplant patients on cyclosporine. In these cases, renal failure occurred in the absence of renal artery stenosis or acute rejection [88]. A systematic review involving 1549 patients assessed the effect of ACE-inhibitor or angiotensin receptor blocker (ARB) use after kidney transplant. ACE-inhibitor or ARB use was associated with a significant decrease in GFR (-5.8 ml/min), a lower hematocrit (-3.5%) and decrease in proteinuria (-0.47 g/d), but no change in serum potassium level. There were insufficient data to determine the effect on patient or transplant survival [89]. The 2005 guidelines for NODAT management advise caution regarding the use of ACE inhibitors and other antihypertensive agents in the first 6 months post-transplantation, especially in patients with high doses of calcineurin inhibitors or renal artery stenosis [2]. The renal transplant literature specifically recommends against ACE inhibitor or ARB therapy until 3–6 months have elapsed from transplant to avoid hyperkalemia, acute kidney injury and anemia [90].

■ Aspirin

Although outcome data are lacking, aspirin use should also be considered to reduce the risk of cardiovascular events in NODAT patients. Aspirin appears safe for this population as it is not known to interact with any of the major antirejection drugs [101]. Furthermore, low-dose aspirin has been shown to significantly reduce the risk of renal-vein thrombosis in renal-transplant recipients [91].

Conclusion

New-onset diabetes mellitus after transplantation is a serious complication after solid organ or bone marrow transplantation that requires prompt treatment to improve graft and patient survival. Screening should begin prior to transplantation and continue through the transplantation process. Onset of diabetes mellitus is often delayed 1–2 years after transplantation, mandating testing at weekly, progressing to monthly intervals during the first year post-transplantation and annually thereafter. Lifestyle modification, involving obesity management, is crucial for preventing and treating cardiovascular disease in this high-risk population. Adjusting immunosuppressive regimens to taper glucocorticoids and tacrolimus may significantly improve glycemic control. As for Type 2 diabetes, therapy should follow a stepwise approach, with oral agents generally followed by insulin. However, little clinical data is available to suggest whether oral agents are safer than or as effective as insulin in this population. In addition to hypoglycemic medications, NODAT patients benefit from aggressive treatment of hypertension and lipids. Special attention should be given to potential drug interactions in the setting of immunosuppressive regimens.

Future perspective

Many gaps and uncertainties exist in the management of NODAT. Ongoing clinical trials investigating newer therapies will add to our knowledge regarding NODAT management (Table 5). Two clinical trials in Norway and Austria are investigating the effects of DPP-IV inhibitors monotherapy in comparison to placebo. More studies on GLP-1 agonists are needed, as these agents may have added benefits of weight loss and postprandial glycemic control, which seems to be one of the pathogenic mechanisms in NODAT. Theoretically, incretin-based agents could be a great choice for monotherapy or adjunctive therapy in NODAT, and we are looking forward to randomized trial data to support the use of this class of agents. Glinides are another class of therapy under study. A few trials are underway, studying the effectiveness of nateglinide and pramlintide as combination therapy with oral agents or insulin. More studies to compare insulin, insulin–oral combinations and oral combination therapies are needed to answer clinical questions of how to approach patients with NODAT. The difference in immunosuppressive therapy protocols in patients with different types of transplants may need close attention and individual approach. We anticipate that emerging knowledge on the management of NODAT will lead to improved patient and graft survival, thus diminishing the current concern raised by the development of diabetes in transplant recipients.

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