

## New Onset Diabetes Mellitus After Solid Organ Transplantation

Phuong-Thu T. Pham, MD<sup>a</sup>,  
Phuong-Chi T. Pham, MD<sup>a,b</sup>,  
Gerald S. Lipshutz, MD, MS, FACS<sup>c</sup>,  
Alan H. Wilkinson, MD, FRCP<sup>a,\*</sup>

<sup>a</sup>*Kidney and Pancreas Transplantation, Department of Medicine, University of California, Los Angeles, David Geffen School of Medicine, Peter Morton Building, 200 UCLA Medical Plaza, Suite 365, Los Angeles, CA 90095-1693, USA*

<sup>b</sup>*Olive View-UCLA Medical Center, 14445 Olive View Drive, Nephrology Division, 2B-182, Sylmar, CA 93142, USA*

<sup>c</sup>*Departments of Surgery and Urology, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA 90095, USA*

New onset diabetes mellitus after transplantation (NODAT) is a well-known complication following solid organ transplantation and has been reported to occur in 4% to 25% of renal transplant recipients, 2.5% to 25% of liver transplant recipients, and 2% to 53% of all solid organ transplants [1–3]. The variation in the reported incidence may be due in part to the lack of a universal agreement on the definition of NODAT, the duration of follow-up, and the presence of modifiable and non-modifiable risks factors. Over the last decade, hepatitis C virus (HCV) infection has increasingly been recognized as a risk factor for NODAT. In HCV-infected liver recipients, the prevalence of post-transplant diabetes ranges between 40% and 60% [3–5]. Similar to the findings in non-transplant settings, diabetes mellitus developing after transplantation has been shown to be associated with an increased risk of cardiovascular disease and infectious complications. Furthermore, reduced patient survival and accelerated graft loss have been reported [6]. This article presents an overview of the literature on the current diagnostic criteria for NODAT and discusses suggested risk factors for the development of NODAT, its potential pathogenic mechanisms, and its impact on post-transplant outcomes after solid organ transplantation.

---

\* Corresponding author.

E-mail address: [awilkinson@mednet.ucla.edu](mailto:awilkinson@mednet.ucla.edu) (A.H. Wilkinson).

Suggested guidelines for early identification and management of NODAT are also discussed.

### **Definition and diagnosis of new onset diabetes mellitus after transplantation**

Over the years, the precise incidence of NODAT has been difficult to determine due to the lack of a standard definition of the condition. Historically, post-transplant diabetes has variably been defined as a random glucose level greater than 200 mg/dL or a fasting glucose level greater than 140 mg/dL or the need for insulin therapy in the post-transplant period. In 2003, the International Expert Panel consisting of experts from the transplant and diabetes field set forth International Consensus Guidelines for the diagnosis and management of NODAT [1,7]. It is recommended that the definition and diagnosis of NODAT should be based on the definition of diabetes mellitus and impaired glucose tolerance (IGT) as described by the World Health Organization (WHO) [7]. Diabetes mellitus is defined as a fasting plasma glucose (FPG) level of  $\geq 126$  mg/dL (7.0 mmol/L) or a plasma glucose level of  $\geq 200$  mg/dL (11.1 mmol/L) 2 hours after a 75-g oral glucose challenge (oral glucose tolerance test) confirmed by repeat testing on a different day. FPG values between 110 and 125 mg/dL (6.1–6.9 mmol/L) are defined as impaired fasting glucose (IFG), and 2-hour plasma glucose values between 140 and 199 mg/dL (7.8–11.1 mmol/L) are defined as IGT. The diabetes guidelines acknowledge that both IFG and IGT are important predictive factors for the progression to overt diabetes and are well-established risk factors for microvascular and cardiovascular disease [8]. The current WHO and American Diabetes Association (ADA) guidelines for the diagnosis of pre-diabetic states (IFG and IGT) and diabetes mellitus are provided in Box 1 [1].

### **Risk factors for new onset diabetes mellitus after transplantation**

Although the risk factors for developing diabetes after transplantation may vary among studies, commonly reported predisposing factors include African American and Hispanic ethnicity, obesity defined as a body mass index  $\geq 30$  kg/m<sup>2</sup>, age older than 40 years, a family history of diabetes among first-degree relatives, IGT before transplantation or the presence of other components of the metabolic syndrome (eg, hypertriglyceridemia, low high-density lipoprotein [HDL] defined as HDL  $< 40$  g/dL in men and  $< 50$  g/dL in women, hypertension, and hyperuricemia), recipients of deceased donor kidneys, HCV infection, and immunosuppressive therapy including corticosteroids and the calcineurin inhibitors tacrolimus and, to a lesser extent, cyclosporine [9]. The antimetabolites azathioprine and mycophenolate mofetil have not been shown to be diabetogenic. In fact, the concomitant use of mycophenolate mofetil has been suggested to

**Box 1. World Health Organization and American Diabetes Association criteria for the diagnosis of diabetes mellitus**

*Criteria for the diagnosis of diabetes mellitus<sup>a</sup>*

Symptoms<sup>b</sup> of diabetes mellitus plus casual<sup>c</sup> plasma glucose concentrations  $\geq 200$  mg/dL (11.1 mM)

or

FPG  $\geq 126$  mg/dL (7.0 mM), where fasting is defined as no caloric intake for at least 8 hours

or

2-hour plasma glucose  $\geq 200$  mg/dL (11.1 mM) during an oral glucose tolerance test<sup>d</sup>

*Criteria for normal FPG and IFG or IGT*

FPG

FPG  $< 110$  mg/dL (6.1 mM) = normal fasting glucose

FPG  $\geq 110$  mg/dL (6.1 mM) and  $< 126$  mg/dL (7.0 mM) = IFG

or

Oral glucose tolerance test

2-hour plasma glucose  $< 140$  mg/dL (7.8 mM) = normal glucose tolerance

2-hour plasma glucose  $\geq 140$  mg/dL (7.8 mM) and  $< 200$  mg/dL (11.1 mM) = IGT

<sup>a</sup> A confirmatory laboratory test based on measurements of venous plasma glucose must be done on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.

<sup>b</sup> Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

<sup>c</sup> Casual is defined as any time of day without regard to time since last meal.

<sup>d</sup> The oral glucose tolerance test should be performed as described by the WHO using a glucose load containing an equivalent of 75 g of anhydrous glucose dissolved in water.

*Adapted from Davidson J, Wilkinson AH, Dantal J, et al. New-onset diabetes after transplantation: 2003 international consensus guidelines. Transplantation 2003;77:SS3-24; with permission.*

mitigate the diabetogenic effect of tacrolimus [6]. It is conceivable that the use of azathioprine or mycophenolate mofetil will allow clinicians to use lower doses of other diabetogenic immunosuppressive medications.

Although early clinical trials suggested that sirolimus was devoid of diabetogenic effect, subsequent studies in animal models and in recipients of renal transplants suggest that sirolimus is associated with reduced insulin sensitivity and a defect in the compensatory  $\beta$ -cell response [10,11]. Studies in diabetic mice transplanted with islet cells suggest that sirolimus is associated with reduced islet engraftment and impaired  $\beta$ -cell function in

transplants. In one single-center study, cyclosporine and sirolimus combination therapy was associated with a higher incidence of NODAT when compared with cyclosporine immunosuppression alone [12].

Other potential risk factors for the development of NODAT include the presence of certain HLA antigens such as A30, B27, and B42, increasing HLA mismatches, acute rejection history, cytomegalovirus (CMV) infection, male gender as recipient, and male gender as donor [9]. More recently, polycystic kidney disease has also been suggested to confer an increased risk for diabetes after renal transplantation [13–15]. Suggested risk factors for NODAT are summarized in Fig. 1.

The following sections provide an overview of the literature on post-transplant diabetes mellitus associated with immunosuppressive agents (corticosteroids, cyclosporine, and tacrolimus) and HCV and CMV infection. Suggested potential pathogenic mechanisms associated with individual risk factors are also discussed.

#### *Corticosteroid-associated new onset diabetes*

Starlz first described the now well-established contributory role of corticosteroids in NODAT in 1964 in renal transplant recipients [16]. The diabetogenic effect of corticosteroids has been suggested to be dose dependent. In a prospective study of 173 consecutive kidney transplant recipients, overt NODAT and glucose intolerance as assessed by an oral glucose tolerance test developed in 18% and 31%, respectively, at 10 weeks after transplantation. A significant relationship between the prednisolone dose and glucose

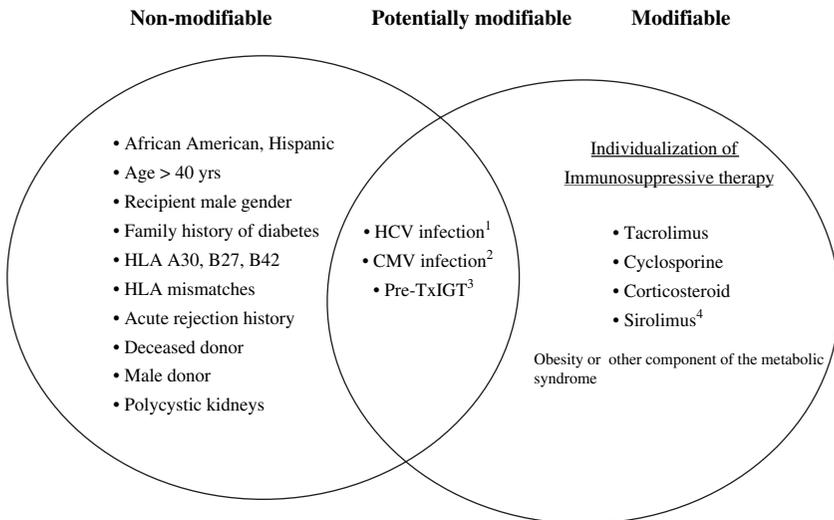


Fig. 1. Risk factors for NODAT. Pre-Tx; pre-transplant, <sup>1</sup>Consider pre-transplant treatment of HCV (see text). <sup>2</sup>Aggressive post-transplant CMV prophylaxis. <sup>3</sup>Counseling on lifestyle modifications (see text). <sup>4</sup>Further studies are needed.

intolerance was demonstrated by univariate and multivariate linear regression analyses. A 0.01 mg/kg/d increase in prednisolone dose was associated with a 5% risk of developing NODAT [17]. Hjelmeseath and colleagues [18] first demonstrated that a dose reduction in oral prednisolone to 5 mg daily significantly improved glucose tolerance during the first year after transplantation. Multiple linear regression analysis revealed that each 1-mg reduction of the prednisolone dose led to an estimated decline in 2-hour blood glucose of 0.12 mmol/L. In a small study involving 57 stable renal transplant recipients, Midtvedt and colleagues [19] found that a prednisolone dose reduction from a mean of 16 mg daily (range, 10 to 30 mg) to 9 mg (range, 5 to 12.5 mg) resulted in an average increase in the insulin sensitivity index of 24%. Complete withdrawal of 5 mg/d of prednisolone did not influence insulin sensitivity significantly. Whether complete withdrawal of chronic low-dose corticosteroid therapy (prednisolone, 5 mg daily) improves glucose metabolism remains to be studied. The dose-dependent diabetogenic effect of corticosteroid was also observed in recipients of nonrenal organ transplants. In a retrospective review involving 88 heart transplant recipients, Depczynski and colleagues [20] found that patients in whom NODAT developed received higher mean doses of prednisolone at 3 months when compared with those who remained free of diabetes at a mean follow-up of 27 months (0.21  $\pm$  0.03 mg/kg/d versus 0.19  $\pm$  0.03 mg/kg/d,  $P < .01$ ).

Experimental animal models have shown that corticosteroids affect glucose metabolism by increasing hepatic glucose production and reducing peripheral insulin sensitivity [21]. Both insulin resistance and relative insulin deficiency have been suggested to have a role in the development of steroid-induced NODAT. Steroid sparing or steroid withdrawal protocols in the early post-transplant period have been shown to reduce insulin resistance and improve glucose metabolism in renal transplant recipients [22]. The precise mechanisms of steroid-induced insulin resistance are not well understood and may be multifactorial. Decreased insulin receptor number and affinity, impaired glucose uptake in skeletal muscles, impaired suppression of endogenous insulin production, activation of the glucose-free fatty acid cycle, and reduced glycogen synthesis have all been implicated [16,23].

#### *Calcineurin inhibitor-associated new onset diabetes: cyclosporine versus tacrolimus*

Although clinical trials comparing the incidence of NODAT in patients treated with cyclosporine versus tacrolimus have yielded mixed results, tacrolimus has more consistently been shown to have a greater diabetogenic effect. Data obtained from the United States Renal Data System revealed that by 2 years post transplant, the incidence of NODAT was approximately 70% greater among patients treated with tacrolimus versus cyclosporine (30% versus 18%, respectively) [24]. The incremental increase in the incidence of

NODAT at 1 year was 15.4% for tacrolimus-treated patients and 9.4% for cyclosporine-treated patients. The corresponding incremental increases in the incidence of NODAT at 2 years were 17.7% and 8.4%, respectively.

The incidence of NODAT after liver transplantation has also been found to be higher in tacrolimus-treated versus cyclosporine-treated patients at 1 year post transplant. In a large randomized trial involving more than 500 liver transplant recipients, NODAT occurred in 26.6% versus 16.1% of patients receiving tacrolimus and cyclosporine immunosuppressive therapy, respectively [25].

Currently, there are limited data on the incidence of NODAT after heart transplants. In small single-center studies, a trend toward a higher incidence of NODAT has been observed in recipients of heart transplants receiving tacrolimus versus cyclosporine-based immunosuppression [26]. In a study involving 85 heart transplant patients, NODAT was observed in 14% and 12% of tacrolimus- and cyclosporine-treated patients, respectively [26]. In a meta-analysis to evaluate the reported incidence of NODAT after solid organ transplantation, Heisel and colleagues [27] found a higher incidence of insulin-dependent diabetes mellitus (IDDM) in tacrolimus versus cyclosporine-treated patients across renal and nonrenal transplant groups including liver, heart, and lung transplants. In renal transplant recipients, IDDM occurred in 9.8% of tacrolimus versus 2.7% of cyclosporine-treated patients ( $P < .00001$ ). Similar trends were observed among recipients of nonrenal organ transplants (11.1% versus 6.2%, respectively [ $P < .003$ ]).

Nonetheless, not all studies show that tacrolimus is more diabetogenic than cyclosporine [28]. It has been suggested that the inconsistent results obtained among studies are due, in part, to the difference in the definitions of NODAT and the difference in calcineurin inhibitor dose and drug levels [28,29]. In a single-center study consisting of 139 patients without known pre-transplant glucose abnormalities, Maes and colleagues [29] showed that a high tacrolimus trough level, particularly a level of greater than 15 ng/mL in the first month after transplant, was a significant risk factor for persistent IFG or diabetes mellitus beyond the first year after transplantation. In a single-center study consisting of 45 orthotopic liver transplant recipients treated with either cyclosporine ( $n = 9$ ) or high- ( $n = 15$ ) versus low-dose tacrolimus ( $n = 13$ ), the incidence of NODAT was 11%, 40%, and 23%, respectively [30]. Of interest, a potential interaction between HCV status and the use of tacrolimus immunosuppression has been suggested. In a retrospective study of more than 400 kidney transplant recipients with no known pre-transplant diabetes, Bloom and colleagues [31] showed that among the HCV-positive cohort, NODAT occurred more often in the tacrolimus versus the cyclosporine-treated groups (57.8% versus 7.7%,  $P < .0001$ ). In contrast, among the HCV-negative cohort, the rate of NODAT was similar between the two calcineurin inhibitor groups (10% for tacrolimus versus 9.4% for cyclosporine, respectively,  $P = .521$ ).

Impaired insulin secretion has been suggested to contribute to the development of calcineurin inhibitor-associated NODAT [21]. Experimental studies have shown that calcineurin inhibitors impair the function of cultured  $\beta$  cells by impairing insulin gene expression [21,32]. In recipients of pancreas transplants, the calcineurin inhibitors cyclosporine and tacrolimus have been shown to cause reversible toxicity to islet cells. In a study of 26 pancreas allograft biopsies from 20 simultaneous kidney-pancreas transplant recipients, a significant correlation was seen between the presence of islet cell damage and serum levels of tacrolimus and cyclosporine, as well as with the tacrolimus peak level [33]. Cytoplasmic swelling and vacuolization and a marked decrease or absence of dense core secretory granules in  $\beta$  cells were demonstrated on electron microscopy. The islet cell damage was more frequent and severe in the tacrolimus group (10 of 13) when compared with the cyclosporine group (5 of 13). Serial biopsies from two patients with hyperglycemia and evidence of islet cell damage receiving tacrolimus immunosuppression demonstrated reversibility of the damage on discontinuation of tacrolimus.

#### *Hepatitis C virus-associated new onset diabetes*

The association between HCV infection and IFG or the development of frank type 2 diabetes mellitus in the non-transplant population has long been suggested. Potential mechanisms of the diabetogenic effect of HCV infection include insulin resistance, decreased hepatic glucose uptake and glycogenesis, and a direct cytopathic effect of the virus on pancreatic  $\beta$  cells [34]. Over the last decade, the link between HCV and the development of NODAT has also been increasingly recognized in solid organ transplant recipients. Nevertheless, the pathogenesis of HCV-associated NODAT remains poorly understood. Clinical studies in recipients of orthotopic liver transplants have implicated insulin resistance associated with active HCV infection as a predominant pathogenic mechanism. Independent investigators have shown a temporal relationship between recurrent allograft hepatitis and increasing viral loads and the development of NODAT [3,35]. Furthermore, patients who responded to antiviral therapy were observed to have improvement in glycemic control [3,35,36]. In a small cohort of 17 non-diabetic HCV-positive and 33 non-diabetic HCV-negative orthotopic liver transplant recipients, Baid and colleagues [3] showed that the presence of HCV infection was independently associated with a 62% increase in insulin resistance ( $P = .0005$ ). It was suggested that the virus had a direct effect on insulin resistance, because no difference in  $\beta$ -cell function or hepatic insulin extraction between the HCV-positive and HCV-negative groups was observed.

In a small study consisting of 16 renal transplant candidates with a sustained virologic response to interferon treatment given in the pre-transplant period, none developed NODAT at a mean follow-up of 22.5 months

(range, 2 to 88 months) [37]. It is conceivable that successful pre-transplant treatment of hepatitis C could potentially reduce the incidence of NODAT after kidney transplantation.

### *Cytomegalovirus-associated new onset diabetes*

The link between CMV infection and the development of NODAT was first reported in 1985 in a renal transplant recipient [38]. Limited studies suggest that both asymptomatic CMV infection and CMV disease are independent risk factors for the development of NODAT [39]. In a study consisting of 160 consecutive non-diabetic renal transplant recipients who were prospectively monitored for CMV infection during the first 3 months after transplantation, Hjelmesaeth and colleagues [39] found that asymptomatic CMV infection was associated with a fourfold increased risk of new onset diabetes (adjusted relative risk, 4.00;  $P = .025$ ). Patients with active CMV infection had a significantly lower median insulin release when compared with their CMV-negative counterparts, suggesting that impaired pancreatic  $\beta$ -cell insulin release may be involved in the pathogenic mechanism of CMV-associated NODAT. It is speculated that CMV-induced release of proinflammatory cytokines may lead to apoptosis and functional disturbances of pancreatic  $\beta$  cells [40].

### **Impact of new onset diabetes mellitus after transplantation on patient and allograft outcomes**

Clinical studies evaluating the impact of NODAT on patient and allograft outcomes after solid organ transplantation have yielded variable results. Nonetheless, ample literature suggests that kidney transplant recipients in whom NODAT develops are at a two- to three-fold increased risk of fatal and nonfatal cardiovascular disease events when compared with non-diabetic patients [41,42]. In one single-center study, the 8-year (range, 7–9 years) cumulative incidence of major cardiac events defined as cardiac death or nonfatal acute myocardial infarction was 7% in recipients without diabetes ( $n = 138$ ) versus 20% in those with NODAT ( $n = 35$ ) [42]. The development of NODAT has also been shown to be associated with an adverse impact on patient survival and an increased risk of graft rejection and graft loss, as well as an increased incidence of infectious complications. In a study consisting of 173 renal transplant recipients, the 1-year patient survival rates for those with versus without NODAT were 83% and 98%, respectively ( $P < .01$ ) [43]. In a single-center study consisting of 40 renal transplant recipients with NODAT and 30 non-diabetic control patients, the 12-year graft survival rate in diabetic and nondiabetic patients was 48% and 70%, respectively ( $P = .04$ ) [44]. Data from the United Renal Data System consisting of over 11,000 Medicare beneficiaries who received primary kidney transplants between 1996 and 2000 demonstrated that in

a comparison of patients with “no diabetes,” NODAT was associated with a 63% increased risk of graft failure ( $P < .0001$ ), a 46% increased risk of death-censored graft failure ( $P < .0001$ ), and an 87% increased risk of mortality ( $P < .0001$ ) [6].

Similar to the setting of renal transplantation, the development of NODAT after liver transplantation has been reported to be associated with increased morbidity and mortality. Baid and colleagues [3] showed that the development of NODAT after liver transplantation was an independent risk factor for mortality (hazard ratio, 3.67;  $P < .0001$ ). In a subset of HCV-positive patients, the cumulative mortality in those with NODAT was significantly higher than in those without NODAT (56% in HCV-positive, NODAT-positive versus 14% in HCV-positive, NODAT-negative;  $P = .001$ ). In a retrospective study consisting of 46 orthotopic liver transplant recipients with NODAT and 92 age- and sex-matched case-control orthotopic liver transplant recipients who did not have pre- or post-transplant diabetes mellitus, John and colleagues [45] found that in a comparison with the case-control group, the development of NODAT was associated with significant cardiovascular and infectious complications. The incidences of cardiac and major and minor infections in the NODAT group compared with the case-control group were as follows: cardiac complications, 48% versus 24% ( $P = .05$ ); major infections, 41% versus 25% ( $P = .07$ ); and minor infections, 28% versus 5% ( $P = .01$ ). In addition, acute rejection episodes were seen more commonly in the NODAT group (50% versus 30%,  $P = .03$ ).

Currently, there is a paucity of data on the impact of NODAT on post-transplant outcomes after heart transplantation. Experimental animal models and small single-center studies suggest that NODAT may have a pivotal role in the development of cardiac allograft vasculopathy in heart transplant patients, limiting long-term survival in this population [46]. In a study of 66 heart transplant recipients without overt diabetes, hyperglycemia defined as a glucose level greater than 8.9 mmol/L 2 hours after a 75-g oral glucose challenge significantly predicted the development of coronary artery stenosis and death during the subsequent 5 years of follow-up. The probability of freedom from coronary artery disease 5 years after transplantation in patients with hyperglycemia versus those without hyperglycemia was  $70 \pm 10\%$  and  $91 \pm 11\%$ , respectively ( $P \leq .01$ ). The corresponding probability of freedom from coronary artery disease death or retransplantation at 5 years was  $90 \pm 7\%$  versus 100% [47]. It is conceivable that the presence of NODAT confers an increased risk of cardiovascular disease and overall morbidity and mortality across all type of solid organ transplantation.

### **Detection and management of diabetes mellitus in recipients of solid organ transplants**

Early detection and management of cardiovascular disease risk factors in general and of diabetes mellitus in particular should be an integral part of

the management of transplant recipients. The following discussion focuses on the diagnosis and management of diabetes mellitus in the pre- and post-transplant period.

### *Pre-transplant baseline evaluation*

The 2004 updated International Consensus Guidelines on New-onset Diabetes after Transplantation suggest that a pre-transplant baseline evaluation should include a complete medical and family history, including documentation of glucose history [7]. FPG should be tested at regular intervals, and a 2-hour oral glucose tolerance test should be performed in those with normal FPG. The use of an oral glucose tolerance test is recommended for screening purposes because it is more predictive of increased cardiovascular disease risk and mortality than FPG testing, particularly in individuals with IGT. Furthermore, it has been suggested that oral glucose tolerance test diagnostic criteria may be more sensitive in identifying patients with IGT than those set for FPG [1]. Patients with evidence of IGT or an abnormal oral glucose tolerance test before transplantation should be counseled on lifestyle modifications including weight control, diet, and exercise. Pre-transplant treatment of HCV-infected renal transplant candidates should be considered. Selection of an immunosuppressive regimen should be tailored to each individual patient, weighing the risk of diabetes after transplantation against the risk of acute rejection. A suggested pre-transplant baseline evaluation of potential transplant candidates is shown in Fig. 2.

### *Management of established new onset diabetes mellitus after transplantation*

The management of NODAT should follow the conventional approach for patients with type 2 diabetes mellitus as recommended by many clinical guidelines established by well-recognized organizations including the ADA. A global guideline for the management of type 2 diabetes mellitus is available through the International Federation Global Guideline Web site at <http://www.d4pro.com/diabetesguidelines/index.htm>. Further intervention may include an adjustment or modification in immunosuppressive medications and pharmacologic therapy to achieve a target hemoglobin A<sub>1C</sub> level of less than 6.5%. Corticosteroid dose reduction has been shown to significantly improve glucose tolerance during the first year after transplantation [6]; however, any dose reduction should be weighed against the risk of acute rejection. A steroid sparing regimen or steroid avoidance protocol should be tailored to each individual patient. Tacrolimus to cyclosporine conversion therapy in patients who fail to achieve target glycemic control or in those with difficult to control diabetes has yielded variable results.

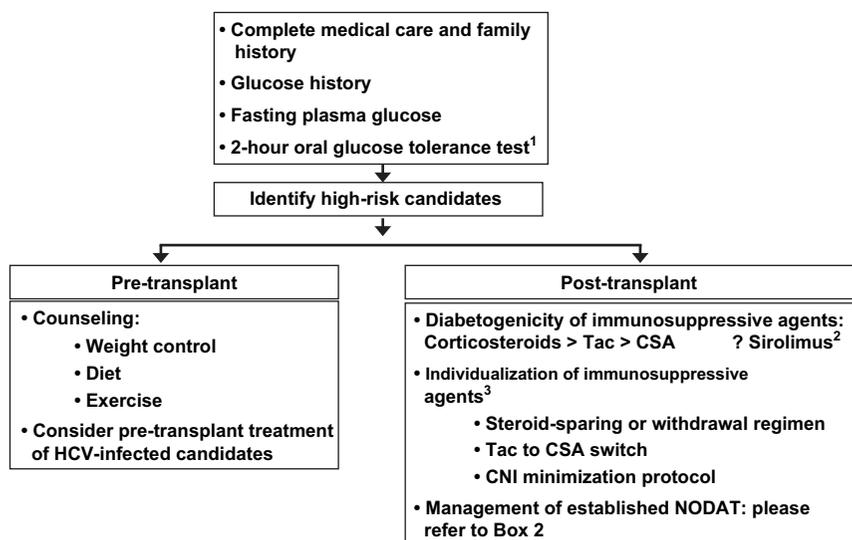


Fig. 2. Pre-transplant baseline evaluation. CSA, cyclosporine; CNI, calcineurin inhibitor; Tac, tacrolimus. <sup>1</sup>Please see text. <sup>2</sup>Further studies are needed. <sup>3</sup>Modification of immunosuppressive regimen should be done at the discretion of the transplant physician.

When lifestyle modification fails to achieve adequate glycemic control, medical intervention is recommended. Orally administered agents can be used alone or in combination with other oral agents or insulin. Although oral hypoglycemic agents may be effective in many patients with corticosteroid or cyclosporine or tacrolimus-induced NODAT, insulin therapy may be necessary in as many as 40% of patients [48], particularly in the early post-transplant period.

The choice of pharmacologic therapy is based on the potential advantages and disadvantages associated with the different classes of oral agents. Although metformin (a biguanide derivative) is the preferred agent for overweight patients, its use should be avoided in patients with impaired allograft function owing to the possibility of lactic acidosis. Care should also be taken when the sulfonylurea derivatives are prescribed to patients with impaired allograft function or to elderly patients due to the increased risk of hypoglycemia. In general, it is best to start with a low dose and to titrate upward every 1 to 2 weeks. The “non-sulfonylureas” meglitinides are insulin secretagogues with a mechanism of action similar to that of the sulfonylureas. Nonetheless, they have a more rapid onset and shorter duration of action and seemingly lower risks of hypoglycemia and weight gain [48,49]. These agents are best suited for patients whose food intake is erratic, for elderly patients, and for patients with impaired graft function. They are best taken before meals; the dose may be omitted if a meal is skipped.

The thiazolidinedione derivatives are insulin sensitizers that may allow for a reduction in insulin requirement. Potential adverse effects of these agents include weight gain, peripheral edema, anemia, pulmonary edema, and congestive heart failure. The incidence of peripheral edema is increased when thiazolidinedione derivatives are used in combination with insulin [49]. More recently, during the A Diabetic Outcome Progression Trial (ADOPT) conducted to compare glycemic control in patients on rosiglitazone, metformin, or glyburide, a higher incidence of fractures in the upper arm, hand, and foot was noted among female patients treated with rosiglitazone [50,51]. Subsequently, pioglitazone was also recognized to be associated with a similar increased risk of fracture in women but not in men, although further studies are needed [51]. The risk of fractures associated with use of the thiazolidinedione derivatives in the transplant setting is currently not known. Nonetheless, thiazolidinedione derivatives should be used with caution, particularly in female transplant recipients who are also receiving steroid immunosuppressive therapy.

Drug-to-drug interactions should also be carefully considered. The meglitinide derivatives repaglinide and, to a lesser extent, nateglinide are metabolized through the cytochrome P-450 isozyme CYP 3A4; therefore, glucose levels should be monitored closely when the patient also receives a strong inhibitor (eg, cyclosporine, gemfibrozil, or the azole antifungal) or inducer (eg, rifampin, carbamazepine, phenytoin, or St. John's wort) of the CYP 3A4 system [48]. The use of gemfibrozil, a CYP 3A4 inhibitor, and repaglinide combination therapy has been shown to dramatically increase the action of the latter, resulting in prolonged hypoglycemia. Coadministration of cyclosporine and repaglinide has also been shown to enhance the blood glucose lowering effect of repaglinide and increase the risk of hypoglycemia [52]. In contrast, rifampin, a strong inducer of CYP 3A4, considerably decreases the plasma concentration of repaglinide and also reduces its effects [53]. Although tacrolimus is also metabolized via the CYP 3A4 system and should be susceptible to many drug interactions similar to those of cyclosporine, these interactions are not as well documented.

Monitoring of patients with post-transplant diabetes mellitus should include measuring the hemoglobin A<sub>1C</sub> level every 3 months and screening for diabetic complications, including tests for microalbuminuria, regular ophthalmologic examinations, and regular foot care. The hemoglobin A<sub>1C</sub> level cannot be accurately interpreted within the first 3 months post transplantation due to various factors, including a history of blood transfusion in the early post-transplant period and the presence of anemia or impaired allograft function. The former may render the test invalid until new hemoglobin is formed and the latter (anemia and kidney impairment) can directly interfere with the A<sub>1C</sub> assay. More recently, an artifactual reduction in the A<sub>1C</sub> level has been reported in islet cell transplant recipients taking dapsons for *Pneumocystis carinii* (*P jiroveci*) prophylaxis. The cause is not yet known, but a reduction in red blood cell lifespan with or without hemolysis has been implicated [54].

**Box 2. Management of new onset diabetes mellitus after transplantation***Dietary modification*

Dietitian referral

For diabetic dyslipidemia: a diet low in saturated fats and cholesterol and high in complex carbohydrates and fiber is recommended

*Lifestyle modifications*

Exercise

Weight reduction or avoidance of excessive weight gain

Smoking cessation

*Adjustment or modification in immunosuppressive medications<sup>a</sup>*

Rapid steroid taper, steroid sparing or steroid avoidance protocols

Tacrolimus to cyclosporine conversion therapy

*Pharmacologic therapy*

Acute marked hyperglycemia (may require inpatient management): intensive insulin therapy (consider insulin drip when glucose  $\geq 400$  mg/dL)

Chronic hyperglycemia (treat to target HbA<sub>1C</sub> < 6.5%): oral glucose lowering agent monotherapy or combination therapy<sup>b</sup> with or without insulin therapy; consider diabetologist referral if HbA<sub>1C</sub> remains  $\geq 9.0\%$

*Monitoring of patients with NODAT*

Hemoglobin A<sub>1C</sub> every 3 months

Screening for microalbuminuria

Regular ophthalmologic examination

Regular foot care

Annual fasting lipid profile

Aggressive treatment of dyslipidemia and hypertension

<sup>a</sup> Clinicians must be familiar with the patient's immune history before manipulating their immunosuppressive therapy (see text).

<sup>b</sup> The choice of a particular agent should be based on the characteristics of each individual patient (see text).

*Adapted from* Pham PT, Pham PC, Danovitch GM. Cardiovascular disease posttransplant. *Seminars Nephrol* 2007;27(4):430-44; with permission.



## Summary

NODAT is a serious complication that can adversely impact patient and allograft outcomes. Identification of the high-risk patient and implementation of measures to reduce the incidence of IGT or overt diabetes should be an integral part of the pre- as well as post-transplant management of transplant recipients. The pre-transplant screening process should include obtaining an FPG at regular intervals, and a 2-hour oral glucose tolerance test should be performed in those with normal FPG. Emphasis should be placed on dietary modification, regular aerobic exercise, weight reduction, and tobacco avoidance. Selection of an immunosuppressive regimen should be individualized, and the risk of developing diabetes after transplantation should be weighed against the risk of rejection. In patients with established NODAT, management should include lifestyle changes and pharmacologic therapy to achieve a target hemoglobin A<sub>1C</sub> level of less than 6.5%. Adjustment or modification in immunosuppressive medications should be performed at the discretion of the transplant physician. Similar to the non-transplant setting, the management of diabetes mellitus after transplantation requires a multidisciplinary approach in which every potential complicating factor must be closely monitored and treated.

## References

- [1] Davidson J, Wilkinson AH, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003;7:SS3–24.
- [2] Montori VM, Velosa JA, Basu, et al. Post-transplantation diabetes: a systematic review of the literature. *Diabetes Care* 2002;25:583–92.
- [3] Baid S, Cosimi AB, Farrell ML, et al. Post-transplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation* 2001;72:1066–72.
- [4] Knobler H, Stagnaro-Green A, Wallenstein S, et al. Higher incidence of diabetes in liver transplant recipients with hepatitis C. *J Clin Gastroenterol* 1998;26:30–3.
- [5] Bigam D, Pennington J, Carpentier A, et al. Hepatitis-C related cirrhosis: a predictor of diabetes after orthotopic liver transplantation. *Gastroenterology* 2000;32:87–90.
- [6] Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003;3(2):178–85.
- [7] Wilkinson AH, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005;19:291–8.
- [8] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2002;25:S5.
- [9] Pham PT, Danovitch GM, Pham PC. The medical management of the renal transplant recipient. In: Johnson RJ, Feehally J, editors. *Comprehensive clinical nephrology*. 3rd edition. Philadelphia: Mosby; 2007. p. 1085–101.
- [10] Teutonico A, Schena PF, Di Paolo S. Glucose metabolism in renal transplant recipients: effect of calcineurin inhibitor withdrawal and conversion to sirolimus. *J Am Soc Nephrol* 2005;16:3128–35.
- [11] Zhang N, Su D, Qu S, et al. Sirolimus is associated with reduced islet engraftment and impaired beta-cell function in transplants. *Diabetes* 2006;55:2429–36.

- [12] Romagnoli J, Citterio F, Nanni E, et al. Incidence of posttransplant diabetes mellitus in kidney transplant recipients immunosuppressed with sirolimus in combination with cyclosporine. *Transplant Proc* 2006;38:1034–6.
- [13] Hamer RA, Chow CL, Ong ACM, et al. Polycystic kidney disease is a risk factor for new-onset diabetes after transplantation. *Transplantation* 2007;83(1):36–40.
- [14] Ducloux D, Motte G, Vautrin P, et al. Polycystic kidney disease as a risk factor for post transplant diabetes mellitus. *Nephrol Dial Transplant* 1999;14:244–6.
- [15] de Mattos AM, Olyaei AJ, Prather JC, et al. Autosomal dominant polycystic kidney disease as a risk factor for post-transplant diabetes mellitus following renal transplantation. *Kidney Int* 2005;67:714–20.
- [16] Jindal RM, Revanur VK, Jardine AG. Immunosuppression and diabetogenicity. In: Hakim N, Stratta R, Gray D, editors. *Pancreas and islet transplantation*. 1st edition. New York: Oxford University Press; 2002. p. 247–75.
- [17] Hjelmsaeth J, Hartmann A, Kofstad J, et al. Tapering off prednisolone and cyclosporine the first year after renal transplantation: the effect on glucose tolerance. *Nephrol Dial Transplant* 2001;16:829–35.
- [18] Hjelmsaeth J, Hartmann A, Kofstad J, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 1997;64(7): 979–83.
- [19] Midtvedt K, Hjelmsaeth J, Hartmann A, et al. Insulin resistance after renal transplantation: the effect of steroid dose reduction and withdrawal. *J Am Soc Nephrol* 2004;15(12): 3233–9.
- [20] Depczynski B, Daly B, Campbell LV, et al. Predicting occurrence of diabetes mellitus in recipients of heart transplants. *Diabet Med* 2000;17:15–9.
- [21] Crutchlow MF, Bloom RD. Transplant-associated hyperglycemia: a new look at an old problem. *Clin J Am Soc Nephrol* 2007;2:343–55.
- [22] Van Hooff JP, Christiaans MHL, van Duijhoven EM. Evaluating mechanisms of post-transplant diabetes mellitus. *Nephrol Dial Transplant* 2004;19(Suppl 6):vi8–12.
- [23] Venkatesan N, Davidson MB, Hutchinson A. Possible role of the glucose-fatty acid cycle in dexamethasone-induced insulin antagonism in rats. *Metabolism* 1987;36:883–91.
- [24] Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among US wait-listed and transplanted renal allograft recipients. *Am J Transplant* 2003;3(5):590–8.
- [25] European FK 506 Multicentre Study Group. Randomised trial comparing tacrolimus to cyclosporine in prevention of liver allograft rejection. *Lancet* 1994;344:423–8.
- [26] Taylor DO, Barr ML, Radovancevic B, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. *J Heart Lung Transplant* 1999;18:336–45.
- [27] Heisel O, Heisel R, Balshaw R, et al. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004;4(4): 583–95.
- [28] Meiser BM, Uberfuhr P, Fuchs A, et al. Single-center randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of acute myocardial rejection. *J Heart Lung Transplant* 1998;17:782–8.
- [29] Maes BD, Kuypers D, Messiaen T, et al. Post-transplant diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. *Transplantation* 2001; 72(10):1655–61.
- [30] Cai TH, Esterl RM, Nichols F, et al. Improved immunosuppression with combination tacrolimus (FK506) and mycophenolic acid in orthotopic liver transplantation. *Transplant Proc* 1998;30:1413–4.
- [31] Bloom RD, Rao V, Weng F, et al. Association of hepatitis C with post-transplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol* 2002;13:1374–80.

- [32] Redmon JB, Olson LK, Armstrong MB, et al. Effects of tacrolimus (FK506) on human insulin gene expression, insulin mRNA levels, and insulin secretion in HIT-T15 cells. *J Clin Invest* 1996;98:2786–93.
- [33] Drachenberg CB, Klassen DK, Weir MR, et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. *Transplantation* 1999;68(3):396–402.
- [34] Bloom RD, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. *Am J Transplant* 2006;6:2232–7.
- [35] Delgado-Borrego A, Casson D, Schoenfeld D, et al. Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation* 2004;77:703–10.
- [36] Simo R, Lecube A, Genesca J, et al. Sustained virological response correlates with reduction in the incidence of glucose abnormalities in patients with chronic hepatitis C virus infection. *Diabetes Care* 2006;29:2462–6.
- [37] Kamar N, Toupance O, Buchler M, et al. Evidence that clearance of hepatitis C virus RNA after  $\alpha$ -interferon therapy in dialysis patients is sustained after renal transplantation. *J Am Soc Nephrol* 2003;14:2092–8.
- [38] Lehr H, Jao S, Waltzer WC, et al. Cytomegalovirus-induced diabetes mellitus in a renal transplant recipient. *Transplant Proc* 1985;17:2152–4.
- [39] Hjelmesaeth J, Sagedal S, Hartmann A, et al. Asymptomatic cytomegalovirus infection is associated with increased risk for new-onset diabetes and impaired insulin release after renal transplantation. *Diabetologia* 2004;47(9):1550–6.
- [40] Hjelmesaeth J, Muller F, Jenssen T, et al. Is there a link between cytomegalovirus infection and new-onset post-transplant diabetes mellitus? Potential mechanisms of virus induced  $\beta$ -cell damage. *Nephrol Dial Transplant* 2005;20:2311–5.
- [41] Ojo AO. Cardiovascular complications after renal transplantation and their prevention. *Transplantation* 2006;82:603–11.
- [42] Hjelmesaeth J, Hartmann A, Leivestad T, et al. The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006;69(3):588–95.
- [43] Boudreaux JP, McHugh L, Canafax DM, et al. The impact of cyclosporine and combination immunosuppression on the incidence of post transplant diabetes in renal allograft recipients. *Transplantation* 1987;44(3):376–87.
- [44] Miles AM, Sumrani N, Horowitz R, et al. Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? *Transplantation* 1998;65(3):380–4.
- [45] John PR, Thuluvath PJ. Outcomes of patients with new-onset diabetes mellitus after liver transplantation compared with those without diabetes mellitus. *Liver Transpl* 2002;8(8):708–13.
- [46] Marchetti P. New-onset diabetes after transplantation. *J Heart Lung Transplant* 2004;23(5S):S194–201.
- [47] Valantine H, Rickenbaker P, Kemna M, et al. Metabolic abnormalities characteristic of dys-metabolic syndrome predict the development of transplant coronary artery disease. *Circulation* 2001;103:2144–52.
- [48] Jindal RM, Hjelmesaeth J. Impact and management of post-transplant diabetes mellitus. *Transplantation* 2000;70(Suppl 11):SS58–63.
- [49] Cheng AYY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. *CMAJ* 2005;172(2):213–26.
- [50] Kahn SE, Haffner SM, Heise MA. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy for the ADOPT study. *N Engl J Med* 2006;355:2427–43.
- [51] Hampton T. Diabetes drugs tied to fractures in women. *JAMA* 2007;297:1645–7.
- [52] Hatorp V, Hansen KT, Thomsen MS. Influence of drugs interacting with CYP3A4 on the pharmacokinetics, pharmacodynamics and safety of the prandial glucose regulator repaglinide. *J Clin Pharmacol* 2003;43(6):649–60.

- [53] Niemi M, Backman JT, Neuvonen PJ, et al. Rifampin decreases the plasma concentrations and effects of repaglinide. *Clin Pharmacol Ther* 2000;68(5):495–500.
- [54] Tartiana F, Faradji RN, Monroy K, et al. Dapsone-induced artifactual A1C reduction in islet transplant recipients. *Transplantation* 2007;83(6):824.
- [55] Pham PT, Pham PC, Danovitch GM. Post-transplant cardiovascular disease. *Seminars in Nephrol* 2007;27(4):430–44.