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New Onset Diabetes After Solid Organ Transplantation

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1. Introduction

New onset diabetes mellitus after transplantation (NODAT) is a serious and common complication following solid organ transplantation. NODAT has been reported to occur in 2% to 53% of all solid organ transplants. Kidney transplant recipients who develop NODAT have variably been reported to be at increased risk of fatal and nonfatal cardiovascular events and other adverse outcomes including infection, reduced patient survival, graft rejection, and accelerated graft loss compared with those who do not develop diabetes. Limited clinical studies in liver, heart and lung transplants similarly suggested that NODAT has an adverse impact on patient and graft outcomes. The following chapter presents an overview of the literature on the current diagnostic criteria for NODAT, its incidence after solid organ transplantation, suggested risk factors and potential pathogenic mechanisms. The impact of NODAT on patient and allograft outcomes and suggested guidelines for early identification and management of NODAT will also be discussed.

2. Definition and diagnosis of new onset diabetes after transplantation

Historically, post-transplant diabetes has been variably defined as having random glucose levels greater than 200 mg/dl fasting, glucose levels greater than 140 mg/dl, or the need for insulin or oral hypoglycemic agents in the post-transplant period. In 2003, the International Expert Panel consisting of experts from both the transplant and diabetes fields set forth the International Consensus Guidelines for the diagnosis and management of NODAT (Davidson et al., 2003; Wilkinson et al., 2005). It was recommended that the definition and

diagnosis of NODAT should be based on the definition of diabetes mellitus and impaired glucose tolerance (IGT) described by the World Health Organization (WHO) (Montori et al., 2002; Wilkinson et al, 2005). The current WHO and American Diabetes Association (ADA) guidelines for the diagnosis of prediabetic states (IFG and IGT) and diabetes mellitus are provided in Table 1 (modified from Davidson et al., 2003).

Criteria for the diagnosis of diabetes mellitus
- Symptoms[1] of diabetes mellitus + casual[2] PG concentrations $\geq$ 200 mg/dL (11.1 mM)

or
- FPG $\geq$ 126 mg/dL (7.0 mM). Fasting is defined as no caloric intake for at least 8 hours

or
- 2-hr PG $\geq$ 200 mg/dL (11.1 mM) during an oral glucose tolerance test[3]

A confirmatory laboratory test based on measurements of venous PG must be done on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.

Criteria for normal FPG and IFG or IGT

FPG
  WHO criteria
   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
  2003 ADA updated consensus report
   FPG < 100 mg/dL (5.6 mM) = normal fasting glucose
   FPG $\geq$ 100 mg/dl (5.6 mM) and < 126 mg/dl (7.0 mM) = IFG
or
OGTT
  2-hr PG < 140 mg/dl (7.8 mM) = normal glucose tolerance
  2-hr PG $\geq$ 140 mg/dl (7.8 mM) and < 200 mg/dl (11.1 nM) = IGT

WHO: World Health Organization; PG: plasma glucose; FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; OGTT: oral glucose tolerance test
[1] Classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
[2] Casual is defined as any time of day without regard to time since last meal.
[3] OGTT: the test should be performed as described by WHO, using a glucose load containing equivalent of 75 g anhydrous glucose dissolved in water.

Table 1. WHO and 2003 updated ADA criteria for the diagnosis of diabetes mellitus

3. Incidence

New onset diabetes mellitus after transplantation has been reported to occur in 4% to 25% of renal transplant recipients, 2.5% to 25% of liver transplant recipients, 4% to 40% of heart transplant recipients, and 30% to 35% of lung transplant recipients (Baid et al., 2001; Davidson et al., 2003; Knobler et al., 1998; Ye et al., 2010a). There has been scant literature on the incidence of diabetes mellitus after a successful pancreas transplant. In one-single center study persistent diabetes mellitus despite evidence of functioning pancreas allografts occurred in 19% of patients (22/144) at 39 months post-transplant (Dean et al., 2008).

The variation in the reported incidence may be due in part to the lack of a standard definition of the condition, the duration of follow-up, the presence of both modifiable and non-modifiable risks factors, and the type of organ transplants among others. In HCV-infected liver recipients, the prevalence of NODAT has been reported to range between 40% to 60% (Baid et al., 2001; Bigam et al., 2000; Knobler et al., 1998). While the prevalence of diabetes reported to the International Society of Heart Lung Transplant (ISHLT) are 19% at 1-year and 28% at 5 years for lung transplant recipients, and 15.4% at 1-year and 20% at 5-years for heart-lung transplant recipients (Trulock et al., 2007), a lower prevalence has been reported (Silverborn et al., 2005). In one single-center study consisting of 126 lung and heart-lung transplant recipients, diabetes has a reported prevalence of 6% at 1 year and 7% at 5 years. The lower prevalence of diabetes in this study was thought to be due in part to a lower frequency of cystic fibrosis patients (8.7% vs. 16.0% in the ISHLT database) and the exclusion of patients with pre-existing diabetes (Silverborn et al., 2005).

Similar to the nontransplant settings, the use of fasting plasma glucose (FPG) versus oral glucose tolerance test (OGTT) to define diabetes mellitus also changes the prevalence of NODAT. In a prospective study designed to evaluate the use of OGTT for risk-stratifying patients for NODAT, Sharif et al. demonstrated that among 122 renal transplant recipients without diabetes who had two FPG level measurements within the range of 100-125 mg/dl (5.6-6.9 mmol/l) for more than 6 months after transplantation, OGTTs revealed that 10% had overt diabetes mellitus, 9% had IGT alone, 18% had IFG alone (all defined by WHO criteria), and 14% had combined IFG and IGT (Sharif et al., 2006).

4. Risk factors for NODAT

Risk factors for the development of NODAT are categorized as non-modifiable and modifiable or potentially modifiable, the former category to facilitate the identification of high risk individuals, and the latter two categories to optimize the management of NODAT. Suggested risk factors for NODAT are summarized in Figure 1. It is noteworthy that most clinical studies evaluating the incidence and risk factors for NODAT have been performed in kidney and liver transplant recipients.

Limited studies in pancreas transplant recipients suggest that pre-transplant body mass index (BMI), high pretransplant insulin requirements and acute rejection episodes are risk factors for persistent post-transplant diabetes mellitus despite the presence of a functioning pancreas allograft (Dean et al., 2008).

Retrospective analysis of the UNOS/OPTN database demonstrated that the risk factors for NODAT after heart transplant are similar to those reported in kidney transplant recipients including older age, non-white race, higher BMI, recipient CMV positivity, tacrolimus (vs. cyclosporine) and steroid use (vs. no steroid) at discharge. Ischemic heart disease was also found to be associated with an increased incidence of NODAT (Ye et al., 2010b). In a single-center study consisting of 97 consecutive adult heart transplant recipients, a family history of diabetes and the need for insulin beyond the first 24 hours after transplantation were shown to be risk factors for the development NODAT (Depczynski et al., 2000).

4.1 Nonmodifiable risk factors
There has been ample literature suggesting that age, Hispanic and African American race and ethnicity are risks factors for NODAT (Cosio et al., 2001; Kasiske et al., 2003; P.T. Pham et al., 2007a, 2007b).
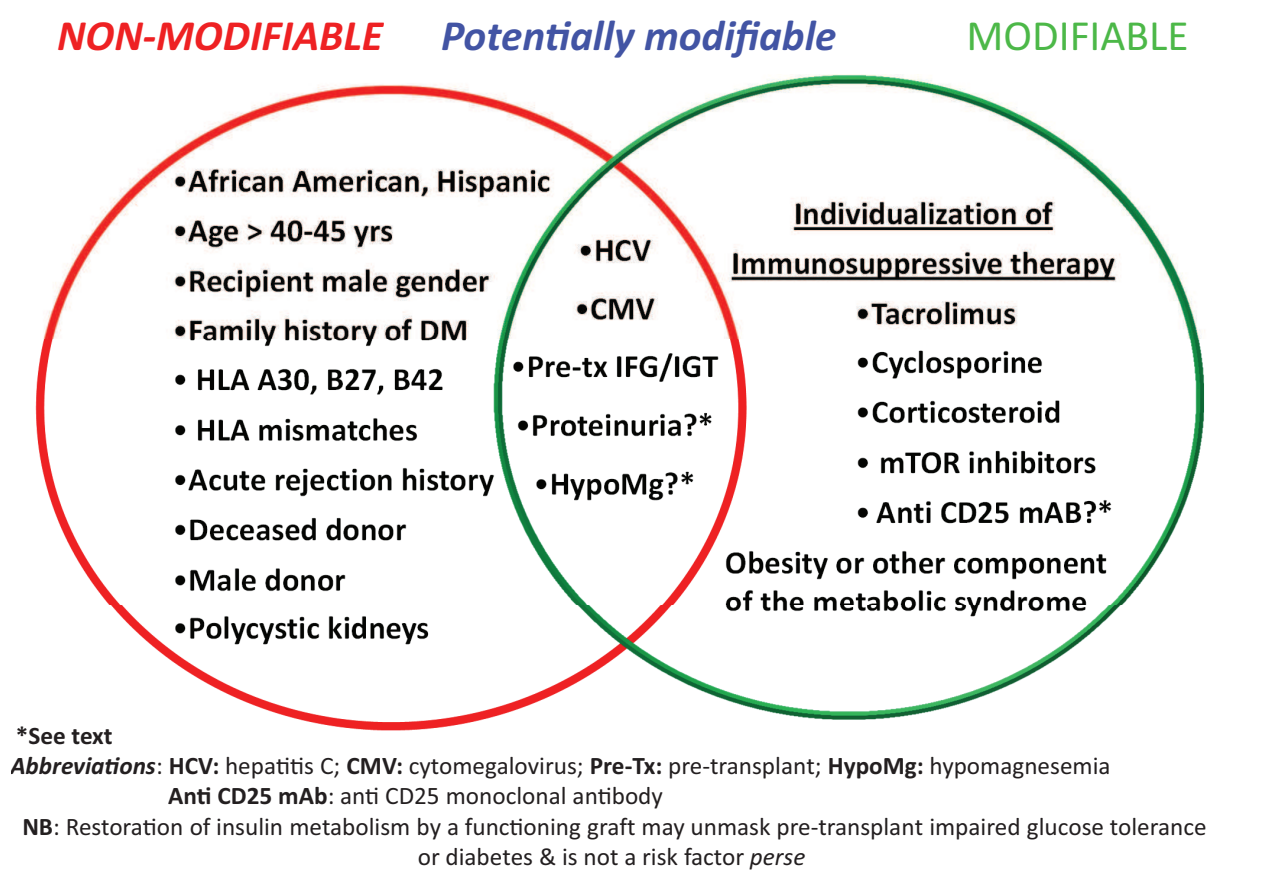
NON-MODIFIABLE   Potentially modifiable   MODIFIABLE

•African American, Hispanic
•Age > 40-45 yrs
•Recipient male gender
•Family history of DM
• HLA A30, B27, B42
• HLA mismatches
•Acute rejection history
•Deceased donor
•Male donor
•Polycystic kidneys

•HCV
•CMV
•Pre-tx IFG/IGT
•Proteinuria?*
•HypoMg?*

Individualization of
Immunosuppressive therapy
•Tacrolimus
•Cyclosporine
•Corticosteroid
• mTOR inhibitors
• Anti CD25 mAB?*
Obesity or other component
of the metabolic syndrome

*See text
Abbreviations: **HCV:** hepatitis C; **CMV:** cytomegalovirus; **Pre-Tx:** pre-transplant; **HypoMg:** hypomagnesemia
Anti CD25 mAb: anti CD25 monoclonal antibody
NB: Restoration of insulin metabolism by a functioning graft may unmask pre-transplant impaired glucose tolerance
or diabetes & is not a risk factor *perse*

Fig. 1. Risk Factors for NODAT

Similar to type 2 diabetes in the general population, both genetic and environmental factors have been suggested to play a role in the development of NODAT. There is strong evidence suggesting that individuals with a family history of diabetes among first-degree relatives have an increased risk of developing NODAT with one study reporting a seven fold increase in the condition (Davidson et al., 2003). The increased prevalence of NODAT associated with a family history of diabetes has been documented across all types of solid organ transplantation. In a Spanish multicenter cross-sectional study consisting of 1410 recipients of kidney transplants, 489 liver transplants, 207 heart transplants, and 72 lung transplants, a positive family history of diabetes was associated with a 50% increased in the risk of developing NODAT (odds ratio of 1.51) (Martinez-Castelao et al., 2005).

Other non-modifiable risk factors include recipient male gender, the presence of certain HLA antigens such as HLA A 30, B27, B42, increasing HLA mismatches, DR mismatch, deceased donor kidneys, male donor, and acute rejection history (Depczynski et al., 2000). Adult polycystic kidney disease (ADPKD) has been suggested to confer an increased risk of developing NODAT in some studies but not in others (P.T. Pham et al., 2007b). The pathogenic mechanism of ADPKD-associated NODAT has not been studied. Of interest, ADPKD patients with normal native kidney function have been shown to have insulin resistance and compensatory hyperinsulinemia (Vareesangthip et al., 1997).

Although not a risk factor per se, increased insulin clearance after a successful kidney transplant can unmask pre-transplant impaired glucose tolerance or pre-existing diabetes mellitus that manifests clinically as NODAT.

4.2 Modifiable risk factors
4.2.1 Corticosteroid-associated NODAT

The now well-established contributory role of corticosteroid on NODAT was first described by Starlz in 1964 in renal transplant recipients. The diabetogenic effect of corticosteroids has been suggested to be dose-dependent. Single-center studies have demonstrated that oral prednisolone dose reduction to 5 mg daily significantly improves glucose tolerance during the first year after transplantation (Hjelmesaeth et al., 1997) while a 0.01 mg/kg/day increase in prednisolone dose is associated with a 5% risk of developing NODAT (Hjelmesaeth et al., 2001).

In a small study involving 57 stable renal transplant recipients, Midtvedt and colleagues found that prednisolone dose reduction from a mean of 16 mg daily (range 10 to 30) to 9 mg (range 5 to 12.5) resulted in an average increase in insulin sensitivity index of 24% (Midtvedt et al., 2004). However, complete withdrawal of 5 mg/day 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. Nonetheless, in recent years several studies have suggested a potential beneficial effect of steroid-free immunosuppression on NODAT risk reduction (Luan et al., 2011).

In a retrospective analysis of the Organ Procurement Transplant Network/Scientific Registry of Transplant Recipient (OPTN/SRTR) database consisting of > 25,000 kidney transplant recipients engrafted between 1/2004 and 12/13/2006, Luan et al. demonstrated that steroid-free immunosuppression was associated with a significant reduction in the likelihood of developing NODAT compared with steroid-containing regimens (Luan et al., 2011). The cumulative incidence of NODAT within three years post-transplant were 12.3% in steroid-free vs. 17.7% in steroid-containing regimens, $p < 0.001$. Overall, steroid-containing regimens at the time of hospital discharge were associated with a 42% increased risk for NODAT. Notably, patients from programs that frequently adopted steroid-free regimens had reduced odds of NODAT compared with those from programs that commonly used steroid-contatining regimens.

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 found that patients who developed NODAT had received higher mean doses of prednisolone at 3 months compared with those who remained free of diabetes at a mean follow-up of 27 months (0.21 ± 0.03 vs. 0.19 ± 0.03 mg/kg/day, p< 0.01) (Depczynski et al., 2000).

4.2.2 Calcineurin inhibitor-associated NODAT: cyclosporine vs. tacrolimus

Although clinical trials comparing the incidence of NODAT in CSA- vs. Tac-treated patients have yielded mixed results, Tac has more consistently been shown to have a greater diabetogenic effect (Ekberg et al., 2007; P.T. Pham et al., 2007b; Woodward et al., 2003).

The DIRECT Study (Diabetes Incidence after Renal Transplantation: Neoral C2 monitoring versus Tacrolimus) was the first multi-center open label, randomized trial to assess glucose abnormalities in de novo kidney transplant patients who were randomized to cyclosporine microemulsion- (CsA-ME) or tacrolimus-based immunosuppression (Vincente et al., 2007). The incidence of NODAT or IFG (defined by WHO/ADA criteria) at 6-month post-transplant was significantly lower in CsA-ME- vs. tacrolimus- treated patients, (26% vs. 33.6%, p=0.046). Furthermore, a lower proportion of CsA-ME patients with NODAT required hypoglycemic medication or dual therapy with insulin and oral hypoglycemic agents compared with their tacrolimus-treated counterparts.

The greater diabetogenic effect of tacrolimus compared to CSA has been reported to occur across renal and nonrenal transplant groups. In a meta-analysis to evaluate the reported incidence of NODAT after solid organ transplantation, Heisel and colleagues found a higher incidence of insulin-dependent diabetes mellitus (IDDM) in Tac- vs. CSA-treated liver, heart, and lung transplant recipients (Heisel et al, 2004). In renal transplant recipients, IDDM occurred in 9.8% of Tac- vs. 2.7% of CSA-treated patients (p<0.00001). Similar trends were observed among recipients of non renal organ transplants (11.1% vs. 6.2%, respectively (p<0.003). Nonetheless, not all studies showed that Tac is more diabetogenic than cyclosporine (Meiser et al., 1998). It has been suggested that these study inconsistencies stemmed in part from the difference in the definitions of NODAT and the difference in calcineurin inhibitor dose and drug levels (Maes et al., 2001; Meiser et al., 1998). In a single-center study consisting of 139 renal transplant recipients without known pretransplant glucose abnormalities, Maes and colleagues have shown that high Tac trough levels, particularly levels greater than 15 ng/ml in the first month after transplant was a significant risk factor for persistent impaired fasting glucose or diabetes mellitus beyond the first year after transplantation (Maes et al., 2001). In a single-center study consisting of 45 OLT recipients treated with either CSA (n=9) or high- (n=15) vs. low- (n=13) dose Tac, the incidence of NODAT were 11%, 40% and 23%, respectively (Cai et al., 1998).

4.2.3 Interaction between tacrolimus and concomitant hepatitis C infection (HCV)

In a retrospective study of more than 400 kidney transplant recipients with no known pre-transplant diabetes, Bloom and colleagues have shown that among the HCV(+) cohort, NODAT occurred more often in the Tac- compared with the CSA-treated groups (57.8% vs. 7.7%, p< 0.0001) (Bloom et al., 2002). In contrast, among the HCV (-) cohort, the rates of NODAT were similar between the two calcineurin inhibitor (CNI) groups (Tac vs. CSA: 10% vs. 9.4%, respectively, p= 0.521). Whether concomitant exposure to tacrolimus and HCV plays a synergistic role in the development of NODAT remains speculative.

4.2.4 Effects of sirolimus on glucose metabolism

Early large randomized clinical trials suggested that sirolimus is devoid of diabetogenic effects either used alone or in combination therapy with CNI. However, the diabetogenicity of sirolimus has now been well-described. Teutenico et al. demonstrated that calcineurin inhibitors to sirolimus conversion therapy and tacrolimus withdrawal in a regimen consisting of tacrolimus and sirolimus were associated with a 30% increased incidence of impaired glucose tolerance (Teutenico et al., 2005). In one single-center study, tacrolimus and sirolimus combination therapy was found to be associated with a higher incidence of NODAT than tacrolimus alone immunosuppression (Sulanc et al., 2005). Subsequent large registry study also demonstrated an association between sirolimus and the development of NODAT. In an analysis of the USRDS database consisting of more than 20,000 primary kidney transplant recipients receiving sirolimus (Sir) or CNI (CsA or Tac) or both in various combination therapy with an antimetabolite (MMF or AZA), Johnston et al. demonstrated that patients treated with sirolimus in combination with a CNI (CsA or Tac) had the highest incidence of NODAT (Johnston et al., 2008). The authors further demonstrated that patients treated with (Sir + Tac) combination therapy had a hazard ratio of developing NODAT of 1.9 compared with those receiving (Tac + MMF/AZA), suggesting that sirolimus was associated with an increased risk for NODAT independent of any effect of tacrolimus.

4.2.5 Anti-CD25 monoclonal antibodies

In a single-center study consisting of 74 stable kidney transplant recipients with 3 month-follow-up, Bayes et al. demonstrated that basiliximab induction therapy is an independent risk factor for NODAT (OR: 3.28; p=0.041) (Bayes et al., 2007). Aasebo et al. similarly demonstrated that the use of basiliximab induction therapy significantly increased NODAT risk (n=264) (Aesebo et al., 2010). At 10 weeks post-transplant, NODAT, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) occurred in 51.5% in the basiliximab group compared with 36.9% in the group that did not receive basiliximab induction (p=0.017).

5. Potential pathogenic mechanisms of immunosuppressive drug--induced NODAT

5.1 Calcineurin inhibitors

Impaired insulin secretion has been suggested to contribute to the development of CNI-associated NODAT (Crutchlow & Bloom, 2007). Experimental studies have shown that CNIs impair the function of cultured β-cells by impairing insulin gene expression (Crutchlow et al., 2007; Van Hooff et al., 2004). In recipients of pancreas transplants, both calcineurin inhibitors CSA and Tac 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 Tac and CSA, as well as with the Tac peak level (Drachenberg et al., 1999). Cytoplasmic swelling and vacuolization, and marked decrease or absence of dense-core secretory granules in β-cells were demonstrated on electron microscopy. The islet cell damage was more frequent and severe in the Tac- (10/13) compared to the CSA-treated groups (5/13). Serial biopsies from two patients with hyperglycemia and evidence of islet cell damage receiving Tac immunosuppression demonstrated reversibility of the damage upon discontinuation of tacrolimus.

5.2 Sirolimus (mTOR inhibitors)

Suggested pathogenic mechanisms of sirolimus-induced hyperglycemia include sirolimus-associated impaired insulin-mediated suppression of hepatic glucose production, ectopic triglyceride deposition leading to insulin resistance, and direct β cell toxicity (Crutchlow & Bloom, 2007). However, studies on the effects of sirolimus on insulin action and secretion have yielded variable and conflicting results. Currently existing literature suggests that the effects of sirolimus on glucose metabolism appear to be cell-species- and dose-dependent (Subramanian & Trence, 2007).

5.2.1 Anti-CD25 monoclonal antibodies

The pathogenic mechanisms of anti-CD25-induced NODAT have not been established. However, suppression of regulatory T-cells has been suggested to play a contributory role (Aasebo et al., 2010). Studies in diabetes-prone mice have shown that anti-IL2-antibody treatment trigger insulinitis and early onset diabetes through inhibition of Foxp3-expressing CD25+ CD4+ regulatory T-cells (Setoguchi et al., 2005).

Suggested pathogenic mechanisms of immunosuppressive drug-induced NODAT are summarized in table 2.

Immunosuppressive agent	Pathogenic mechanism(s)	Comments
Corticosteroids	• ↓Peripheral insulin sensitivity • Inhibit pancreatic insulin production & secretion • ↑Hepatic gluconeogenesis • Promote protein degradation to free amino acids in muscle, lipolysis	•Dose-dependent •Impact of complete withdrawal of chronic low-dose steroids unclear •Potential ↓NODAT risk in steroid-free regimens
Cyclosporine	• ↓insulin secretion (CsA < Tac) • ↓insulin synthesis • ↓β-cell density	•Dose-dependent, •Diabetogenic effect ↑ with ↑ steroid dose*
Tacrolimus	• ↓insulin secretion (Tac > CsA) • ↓insulin synthesis	•Dose-dependent, •Diabetogenic effect ↑ with ↑ steroid dose*
Sirolimus	•↑Peripheral insulin resistance • Impair pancreatic β-cell response	↑Diabetogenicity when use with CNIs

Abbreviations: CNI: calcineurin inhibitors
* Demonstrated in some but not all studies

Table 2. Drug-Induced NODAT: potential pathogenic mechanism(s)

6. Obesity

Similar to the general population, obesity has been shown to be associated with the development of NODAT in most studies (Setoguchi et al., 2005). Analysis of the USRDS database revealed that obesity, defined as a BMI of $\geq$ 30 kg/m^2 is one of the strongest risk factors for NODAT (Relative risk of 1.73, P < 0.0001). Although some studies failed to demonstrate an association between obesity and the development of NODAT, obesity and its associated peripheral insulin resistance state is a known risk factor for type 2 diabetes. The mechanism whereby obesity induces insulin resistance is poorly understood. Nonetheless, the pattern of body fat distribution has been suggested to play a contributory role. Studies in healthy women showed that upper body or male-type obesity has a much greater association with insulin resistance and impaired glucose tolerance than lower body or female-type obesity (Kissebah et al., 1982). Similar studies in the transplant settings is lacking. It is speculated that intra-abdominal fat or waist-to-hip ratio may be more important risk factors for NODAT than total body weight or BMI (Davidson et al., 2003).

7. Hypertriglyceridemia / Hypertension

Early retrospective studies suggested that the greater the number of the metabolic syndrome components, the greater the risk for the development of NODAT (Eckel, 2007). In a recent retrospective analysis consisting of 640 nondiabetic renal transplant recipients Bayer et al. demonstrated that the prevalence of NODAT at 1-year increased with increasing number of

metabolic syndrome score 0: 0%, 1: 24%, 2: 29%, 3: 31%, 4: 35%, 5: 74%, p=0.001) (Bayer et al., 2010). Multivariate analysis incorporating the individual metabolic syndrome components as covariates demonstrated that of all the pre-transplant metabolic syndrome components, only low-density lipoprotein was independently associated with the development of NODAT.

The precise role of the metabolic syndrome or metabolic syndrome component(s) in the development of NODAT remains to be defined. Nonetheless, the overlapping metabolic risk factors for type 2 diabetes and cardiovascular disease (e.g. obesity, hyperglycemia, dyslipidemia, hypertension) warrants early identification and aggressive management of individual risk factors

8. Proteinuria

Early report from single-center study suggested an association between proteinuria on day 5 after transplantation and the development of NODAT (Kuypers et al., 2008). However, these findings have been challenged because proteinuria on day 5 may just reflect the highly concentrated urine associated with hyperglycemia-induced osmotic diuresis from the early posttransplant use of high dose corticosteroid or residual native kidney proteinuria. Furthermore, it has been shown that immediate posttransplant proteinuria generally resolves several weeks after transplantation (Myslak et al., 2006). Nonetheless, in a subsequent single-center retrospective study designed to evaluate the impact of early proteinuria (3 and 6 months after transplantation) and urinary albumin excretion (UAE) on NODAT, Roland et al. demonstrated that low-grade (<1g/day) and very low-grade (< /0.3 g/day) proteinuria were independent risk factor for NODAT (p=0.0042 and p=.00025, respectively) (Roland et al., 2008). Furthermore, there was a dose-dependent relationship across UAE categories with NODAT. NODAT-free survival was greater in patients with normoalbuminuria than in those with microalbuminuria, and greater in those with microalbuminuria than in those with macroalbuminuria (p=0.0326). The authors also demonstrated that pulse pressure was an independent risk factor for NODAT, suggesting that early low-grade proteinuria and pulse pressure may be markers of the metabolic syndrome or vascular damage or both.

9. Hypomagnesemia

In the general population, not only has hypomagnesemia been shown to be associated with type 2 diabetes, but numerous studies have also reported an inverse relationship between glycemic control and serum Mg levels (P.C. Pham et al., 2007). Similar to the nontransplant settings, hypomagenesemia has also been shown to be an independent predictor of NODAT in recipients of renal and liver transplants. In a single-center retrospective analysis consisting of 254 renal transplant recipients Van Laecke et al. demonstrated that hypomagnesemia during the first-month posttransplantation was associated with the development of NODAT independent of the immunosuppressive regimen used (van Laecke et al., 2009). While the association between the use of CNIs was strongly related to hypomagnesemia, NODAT disappeared after adjustment for Mg levels suggesting that the diabetogenic effect of CNIs is at least in part related to hypomagnesemia. Conversely, the use of mTOR inhibitors appeared to be a risk factor for NODAT after adjustment for Mg levels. The same group of authors subsequently demonstrated that both pretransplant

hypomagenesemia and hypomagnesemia in the first-month posttransplantation were independent predictors of NODAT in recipients of liver transplants (Van Laecke et al., 2010). Nonetheless, not all studies demonstrated that hypomagnesemia is a risk factor for NODAT. In one small single-center study consisting of 205 non-previously diabetic patients with > 1 year graft survival, neither the mean values of Mg nor the percentage of patients with hypomagnesemia differed between NODAT and non-NODAT patients (Santos et al., 2010).

Whether Mg supplementation and correction of Mg deficiency reduce the incidence of insulin resistance or NODAT remains to be studied.

10. Potentially modifiable risk factors

10.1 Impaired glucose tolerance before transplantation

Abnormal glucose metabolism has been reported to be a risk factor for the development of NODAT in some but not all studies. In a study consisting of 490 recipients of kidney transplants, Cosio et al. demonstrated that higher pretransplant glucose is a risk factor for NODAT at one year (Cosio et al., 2005). Using patients with pretransplant FPG levels between 90 and 100 as the reference group, patients with plasma glucose < 90 mg/dL have lower risk of NODAT (OR=.46, P=0.01). In contrast, the risk of NODAT increases as the pretransplant FPG levels increases (FPG =101-109, OR=1.5; and FPG = 110-125, OR=7.6, P < 0.0001). Among patients with IFG pretransplant, 70% had hyperglycemia at one year (IFG 43% and NODAT 27%). In one single-center study Eprinchard et al demonstrated that pretransplant IGT is a risk factor for NODAT with a relative risk of developing NODAT of 2.4 (Eprinchard et al., 2011).

10.2 HCV-associated NODAT

The association between HCV infection and impaired fasting glucose or the development of overt type 2 diabetes mellitus in the general population has long been suggested. Potential mechanisms of the diabetogenic effect of HCV infection include insulin resistance, decreased hepatic glucose uptake and glycogenesis, and direct cytopathic effect of the virus on pancreatic β cells (Bloom & Lake, 2006). Similar to the non-transplant settings, the link between hepatitis C and the development of NODAT has also been recognized in solid organ transplant recipients. The pathogenesis of HCV-associated NODAT, however, remains poorly understood. Clinical studies in recipients of orthotopic liver transplant (OLT) recipients 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 (Baid et al., 2001; Delgado-Borrego et al., 2004). Furthermore, patients who responded to antiviral therapy were observed to have improvement in glycemic control (Baid et al., 2001; Delgado-Borrego et al., 2004; Simo et al., 2006). In a small cohort of 17 non-diabetic HCV (+) and 33 non-diabetic HCV (-) OLT recipients, Baid and colleagues have shown that the presence of HCV infection was independently associated with a 62% increase in insulin resistance (P=0.0005) (Baid et al., 2001). It was suggested that the virus had a direct effect on insulin resistance as no difference in β cell function or hepatic insulin extraction between the HCV (+) and (-) groups was observed.

In a small study consisting of 16 renal transplant candidates with 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) (Kamar et al., 2003). It is conceivable that successful pre-transplant treatment of hepatitis C could potentially reduce the incidence of NODAT after kidney transplantation.

10.3 Cytomegalovirus-associated NODAT

The link between cytomegalovirus (CMV) infection and the development of NODAT was first reported in 1985 in a renal transplant recipient (Lehr et al., 1985). Limited studies suggested that both asymptomatic CMV infection and CMV disease are independent risk factors for the development of NODAT. In a study consisting of 160 consecutive non-diabetic renal transplant recipients who were prospectively monitored for CMV infection during the first three months after transplantation, Hjelmesaeth and colleagues found that asymptomatic CMV infection was associated with a four-fold increased risk of new-onset diabetes (adjusted RR= 4.00; p=0.025) (Hjelmasaeth et al., 2004). Patients with active CMV infection had a significantly lower median insulin release compared to their CMV negative counterparts, suggesting that impaired pancreatic β 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 β-cells (Hjelmasaeth et al., 2005).

11. Impact of NODAT on patient and allograft outcomes

11.1 Kidney transplants

Clinical studies evaluating the impact of NODAT on patient and allograft outcomes after solid organ transplantation have yielded variable results. Nonetheless, there has been ample literature suggesting that kidney transplant recipients who developed NODAT are at two- to three- fold increased risk of fatal and nonfatal cardiovascular disease events as compared with nondiabetic patients (Ojo, 2006; Hjelmasaeth et al., 2006). 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 (Ojo, 2006). 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 compared to "no diabetes", NODAT was associated with a 63% increased risk of graft failure (p< 0.0001), a 46% increased risk of death-censored graft failure (p< 0.0001) and an 87% increased risk of mortality (p< 0.0001) (Kasiske et al., 2003).

In contrast to earlier reports, a retrospective analysis of the UNOS/OPTN database (involving patients transplanted between 2004-2007) failed to demonstrate the negative impact of NODAT on transplant survival or CV mortality during a median follow-up of 548 days. The study consisted of >37,000 renal transplant recipients with a functioning transplant for at least 1 year. Risk stratification according to diabetes status (pre-transplant diabetes, NODAT) and acute rejection (AR) at 1 year demonstrated that pre-transplant diabetes is the major predictor of all-cause and cardiovascular mortality whereas acute rejection during the first year is the major predictor of death-censored transplant failure. In contrast, NODAT alone was not associated significantly with any study outcomes (Kuo et al., 2010). Nonetheless, the study results were regarded as inconclusive due to the wide confidence intervals and the relatively short duration of follow-up. It is noteworthy that in a large registry study consisting of more than 27,000 primary kidney transplant recipients

with graft survival of at least 1 year and with longer-term follow-up, Cole et al. demonstrated that patients with NODAT had decreased survival compared with those who developed neither NODAT nor acute rejection (HR 3.85; p < 0.0001) (Cole et al., 2008).

11.2 Non-renal solid organ transplants

Clinical studies evaluating the impact of NODAT on patient and allograft outcomes after non-renal solid organ transplantation have yielded variable results (Baid et al., 2001; John & Thuluvath, 2002; Valentine et al., 2001).

In a study consisting of 66 heart transplant recipients, post-transplant insulin resistance or post-transplant hyperglycemia (glucose levels > 8.9 mmol/L 2 hours after a standard oral glucose tolerance test) was found to be a predictive factor for transplant coronary artery stenosis (p $\leq$ 0.01) and death (p $\leq$ 0.005) during a 5-year post-tarnsplant follow-up period (Valentine et al., 2001). Patients with post-transplant hyperglycemia were also found to have a higher mean coronary artery intimal thickness than those without post-transplant hyperglycemia (0.35 $\pm$ 0.05 vs. 0.20 $\pm$ .02, respectively; p $\leq$ 0.05).

In a single-center study consisting of 435 liver transplant recipients John et al. demonstrated that cardiovascular complications, major and minor infections, neurologic and neuropsychiatric complications were twice as common in patients who developed NODAT (n= 46) compared with their age- and sex-matched counterparts without pre- or post-transplant diabetes (n=92) (John & Thuluvath, 2002). However, there was no difference in patient survival between the two groups at 1-, 2- and 5-years follow-up. In contrast, Baid et al. demonstrated that NODAT was an independent risk factor for mortality after liver transplantation (HR 3.67, p < 0.0001) particularly in those with hepatitis C. The cumulative mortality in HCV (+) NODAT (+) vs. HCV (+) NODAT (-) patients was 56% vs. 14%, respectively (p=0.001) (Baid et al., 2001).

12. Detection and management of diabetes mellitus in recipients of solid organ transplants

12.1 Pre-transplant baseline evaluation

Suggested guidelines for pre-transplant baseline evaluation of potential transplant candidates is shown in Figure 2. Patients with evidence of IGT or abnormal OGTT before transplantation should be counseled on lifestyle modifications including weight control, diet, and exercise. The goals for the life-style modification involved achieving and maintaining a weight reduction of at least 7 percent of initial body weight through a healthy low-calorie, low-fat diet and at least 150 minutes of physical activity per week.
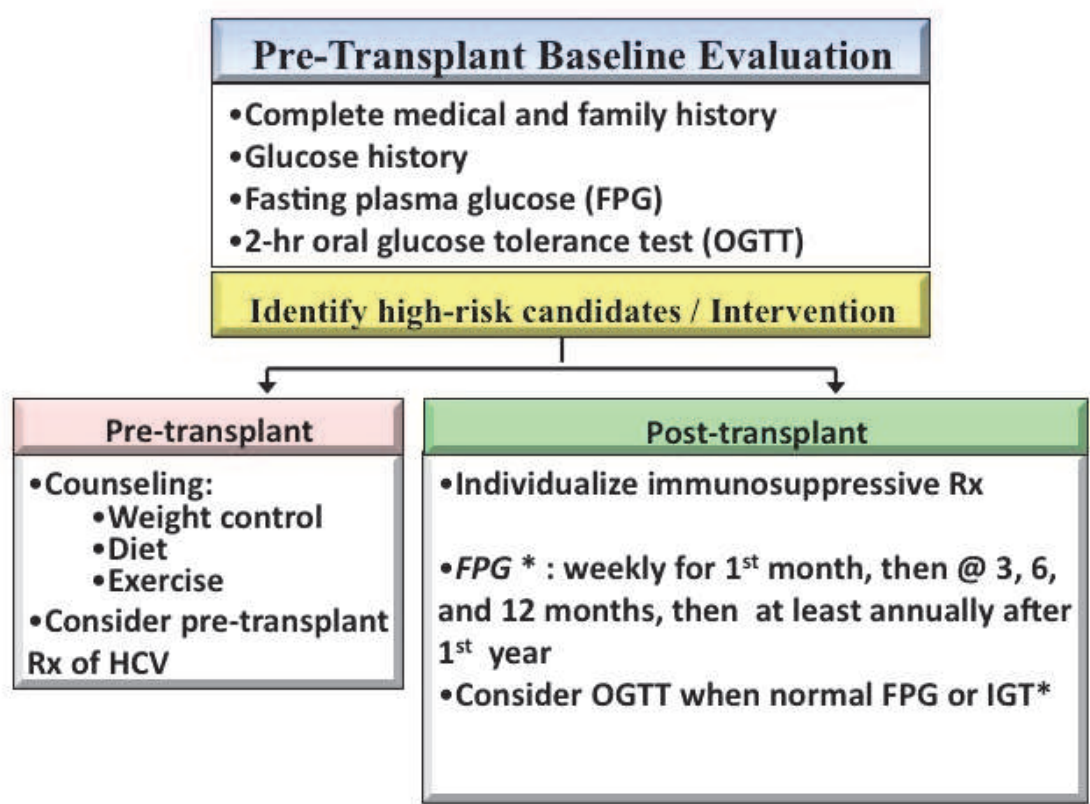
Pre-transplant treatment of HCV-infected renal transplant candidates should be considered. Selection of an immunosuppressive regimen should be tailored to each individual patient, weighing the risk of developing diabetes after transplantation against the risk of acute rejection.

12.2 Early detection of NODAT after transplantation

Studies investigating the best predictive tool for identifying patients at risk for developing NODAT early after transplantation are currently lacking. While fasting plasma glucose (FPG) is readily available in clinical practice it may be normal in kidney transplant recipients with abnormal glucose homeostasis. It has been suggested that transplant patients have an atypical form of insulin resistance and their plasma glucose often peeks before

lunch. Hence the use of FPG alone may preclude the accurate diagnosis of NODAT. Kuypers et al. demonstrated that a normal (vs. diabetic) OGTT on day 5 was associated with a significantly reduced risk for NODAT (odds ratio 0.03, P=0.0002) (Kuypers et al., 2008). However, it is noteworthy that while acute rejection has been suggested to increase the risk for NODAT, it usually does not occur before day 5. Obtaining OGTT and FPG at day 5, therefore, may preclude the subset of patients with higher risk of developing NODAT. Hence, it has been suggested that performing OGTT at 10-12 weeks post-transplantation might be useful as an alternative or supplementary test to day 5 OGTT (P.T. Pham & P.C. Pham, 2008).

The routine recommendation of performing an OGTT early after transplantation awaits further studies. Suggested pre-transplant baseline evaluation and post-transplant screening for NODAT is shown in Figure 2.

Pre-Transplant Baseline Evaluation
- Complete medical and family history
- Glucose history
- Fasting plasma glucose (FPG)
- 2-hr oral glucose tolerance test (OGTT)

Identify high-risk candidates / Intervention

Pre-transplant
- Counseling:
  - Weight control
  - Diet
  - Exercise
- Consider pre-transplant Rx of HCV

Post-transplant
- Individualize immunosuppressive Rx
- *FPG* * : weekly for 1st month, then @ 3, 6, and 12 months, then at least annually after 1st year
- Consider OGTT when normal FPG or IGT*

*2003 International Consensus Guidelines

Fig. 2. Sugested guidelines for pre-transplant baseline evaluation and post-transplant screening for NODAT

12.3 Management of established NODAT

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 American Diabetes Association (ADA).

Similar to the nontransplant settings, a target hemoglobin A1C level < 6.5%-7% is recommended. Fasting plasma glucose should be below 100 mg/dL (6.11 mmol/L), and a 2-hour postprandial plasma glucose should be below 140 mg/dL (7.77 mmol/L) (Mannon,

2008). Nonetheless, it should be noted that the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was discontinued prematurely because of a satistically significant increase in all-cause mortality in the intensive- compared with the standard- glycemic treatment groups (Gerstein et al., 2008). At 1 year, stable median A_{1C} levels of 6.4% and 7.5% were achieved in the intensive-therapy and standard groups, respectively. The intensive-therapy group had a relative increase in mortality of 22% and an absolute increase of 1.0% during a follow-up period of 3.5 years. Death from cardiovascular causes were similar between the two treatment groups. It is also notable that hypoglycemia requiring assistance and weight gain of more than 10 kg were more frequent in the intensive-therapy group (P< 0.001). Long-term follow-up of the ACCORD study demonstrated that intensive therapy failed to reduce the risk of advanced measures of microvascular outcomes but delayed the onset of micro- and macro-albuminuria and some measures of ocular complications and peripheral neuropathy which persisted over the 5 year study period despite the transition from intensive to conventional treatment of glycemia after 3.7 years (Ismail-Beigi et al., 2010).

Study similar to that of the ACCORD study in recipients of solid organ transplantation is lacking. Nonetheless, the determination of hemoglobin A1C target levels for solid organ transplant recipients should be individualized based on hypoglycemia risks.

13. Modifiable risk factor management strategy

13.1 Dietary modification and physical activity

The Diabetes Prevention Program has demonstrated that a structured diet and physical activity program that achieves and maintains modest weight loss for overweight adults with IGT can significantly reduce the development of diabetes. Defining realistic goals such as a target weight loss of 5-10% of total body weight and patient- centered approach to education may be invaluable in achieving success. Suggested non-insulin management of NODAT is shown in table 3.

13.2 Modification of immunosuppression

Modification of immunosuppression should be considered in high-risk patients. Corticosteroid dose reduction has been shown to significantly improve glucose tolerance during the first year after transplantation (Kasiske et al., 2003). However, any dose reduction should be weighed against the risk of acute rejection. Steroid-sparing regimen or steroid avoidance protocol should be tailored to each individual patient. Tac to CSA conversion therapy in patients who fail to achieve target glycemic control or in those with difficult to control diabetes has yielded variable results. The use of CNI and mTOR inhibitor combination therapy should probably be avoided. Belatacept -- a selective T cell costimulation blocker, is a promising new immunosuppressant that has been suggested to have better cardiovascular and metabolic risk profiles compared with cyclosporine (lower blood pressure, better lipid profiles and lower NODAT incidence) (Vanrenterghem et al., 2011).

13.3 Renin-angiotensin inhibition

A meta-analysis of 10 randomized controlled trials to assess the effects of renin angiotensin inhibition [five with angiotensin-converting enzyme inhibitors (ACEIs) and five with

Agents	Action	Adverse effects / Comments
INSULIN SENSITIZERS (e.g. Metformin, Butoformin, Phenformin)	↓ hepatic glucose production, ↑ glucose uptake by skeletal muscle	• Diarrhea, dyspepsia, lactic acidosis w/ renal insufficiency • No weight gain, no hypoglycemia
INSULIN SECRETAGOGUES ***Sulfonylureas (SUs)*** (e.g. Glipizide, Glyburide, Glimepiride) ***Meglitinides*** (e.g. Repaglinide, Nateglinide)	↑ pancreatic insulin secretion	***SUs***: weight gain, edema, hypoglycemia (esp. in renal insufficiency & elderly) ***Meglitinides***: weight gain, hypoglycemia (lower risk than SUs) Rapid onset & offset, hepatically excreted (use w/ renal insufficiency)
OTHERS W/ DIFFERENT ACTIONS		
Thiazolidinedione derivatives (TZD) [e.g. Pioglitazone, Rosiglitazone (the drug has been suspended in Europe since 2010, use with caution, see text)]	Bind to peroxisome proliferator-activated receptors (PPARs) & stimulate insulin sensitive genes	• Weight gain, peripheral edema (esp. w/ insulin), anemia, pulmonary edema, CHF, fractures • Slow onset of action, no hypoglycemia, no reliance on renal excretion, contraindicated in class III-IV CHF or hepatic impairment
Glucagon-like peptide-1 analogues (e.g. Exenatide, Liraglutide)	↑ pancreatic insulin secretion	Either favorable or neutral effect on weight gain (delays gastric emptying, ↑ satiety)
Dipeptidyl peptidase 4 inhibitors (e.g. Sitagliptin, Saxagliptin)	↑ Endogenous incretins	• Avoid vildagliptin in hepatic impairment & stage IV-V CKD, dose should be adjusted for renal insufficiency. • Watch for immunosuppresive drug interaction • Weight neutral, no hypoglycemia, ? β cell preservation

Table 3. Non-insulin drug therapy for NODAT

angiotensin receptor blockers (ARBs)] on the incidence of new cases of type 2 diabetes mellitus in patients with arterial hypertension and congestive heart failure demonstrated that renin-angiotensin inhibition with either ACEIs or ARBs consistently and significantly reduced the incidence of type 2 diabetes mellitus compared with placebo, or beta-blockers/diuretics or amlodipine (Scheen, 2004). This finding has not yet been validated in either transplant recipients or prospective trials in the general population (Bosch et al., 2006). Nonetheless, ACE-I and/or ARB are commonly used due to its well-established antiproteinuric, cardioprotective, and blood pressure lowering effect.

13.4 Pharmacological management

When lifestyle modification fails to achieve adequate glycemic control, medical intervention is recommended. Orally administered agents can be used either alone or in combination with other oral agents or insulin. The choice of pharmacologic therapy is based on the potential advantages and disadvantages associated with the different classes of oral agents. Table 3 summarizes the mechanisms of action and potential advantages and disadvantages of different classes of oral agents.

It is noteworthy that the results of the Dialysis Outcomes and Practice Patterns Study (DOPPS) demonstrated that in long-term hemodialysis patients rosiglitazone was associated with a significantly higher all-cause (hazard ration 1.59) and cardiovascular mortality and a 3.5 fold increase of hospitalizations due to myocardial infarction (Ramirez et al., 2009). In

contrast to the DOPPS study results, in an analysis of the national cohort study consisting of more than 5,000 dialysis patients with type 2 diabetes Brunelli et al. observed a lower incidence of all-cause mortality in patients not on insulin vs. insulin requiring diabetic patients (Brunelli et al., 2009). Similar studies in the transplant settings are lacking. Nonetheless, great caution should be exercised when rosiglitazone is used in the setting of kidney transplantation because all kidney transplant recipients should be regarded as having at least stage II-IV chronic kidney disease. It should be noted that rosiglitazone has been suspended in Europe since 2010

Incretin-based therapy appears to provide an attractive treatment option for patients with NODAT owing to its favorable effect on weight reduction /weight neutrality. Data on its safety and efficacy in renal transplant recipients are currently lacking. A randomized, placebo-controlled, double-blind, prospective trial to evaluate the safety and efficacy of vildagliptin in patients with NODAT is currently underway (Haidinger et al., 2010). Caution should be exercised when these agents are used in the transplant setting, particularly with regards to drug to drug interactions. Vildagliptin should be avoided in patients with hepatic impairment and stage IV-V chronic kidney disease and the dose of sitagliptin should be adjusted for renal insufficiency.

Finally, drug to drug interactions should be carefully considered. Interested readers are referred to the following references (Cheng & Fantus, 2005; Hatorp et al., 2003; Niemi et al., 2000).

14. Summary

NODAT is a common complication after solid organ transplantation and has variably been reported to have an adverse impact on patient and allograft outcomes. Risk stratification and intervention to minimize risk should be an integral part in the management of the transplant recipients. Clinicians must be familiar with the patients' immune history prior to manipulating their immunosuppressive therapy.in an attempt to ameliorate NODAT risk. When lifestyle modification fails to achieve adequate glycemic control, medical intervention is often necessary.

The routine care of patients with NODAT should include an evaluation of hemoglobin A1C level every three months and regular screening for diabetic complications. It should be noted that hemoglobin A1C cannot be accurately interpreted within the first three months post transplantation due to various factors including possible blood transfusions in the early posttransplant period and the presence of anemia or impaired allograft function. Blood transfusions may render the test invalid until new hemoglobin is formed and the presence of anemia and kidney impairment can directly interfere with the A1C assay. An artifactual reduction in A1C level has been reported in islet cell transplant recipients taking dapsone for pneumocystis carinii (P. jiroveci) prophylaxis. The cause is yet unknown, but a reduction in red blood cell lifespan and/or hemolysis has been implicated (Froud et al., 2007).

Fasting lipid profile should be measured annually. In transplant recipients with multiple CVD risk factors, more frequent monitoring of lipid profile should be performed at the discretion of the clinicians. Statins or the HMG-CoA reductase inhibitors are the most widely used lipid lowering agents in both the nontransplant and transplant settings. Table 4 summarizes the suggested guidelines for the management of NODAT (P.T. Pham et al., 2007c; Qaseem et al., 2011).

Non-pharmacological

> *Dietary modification*
> Dietitian referral
> Diabetic dyslipidemia: diet low in saturated fats and cholesterol & high in complex carbohydrates & fiber
> AHA[1] guidelines: limiting cholesterol (< 200 mg/day for those with DM), < 7% calories from saturated fats, 2-3% calories from trans-fatty acids, < 2,400 mg sodium a day, > 25g/day of dietary fiber & 2 servings of fish a week
>
> *Lifestyle modification*
> Exercise
> Weight reduction or avoidance of excessive weight gain
> Smoking cessation

Modification of immunosuppressive medications[2]

> Rapid steroid taper, steroid-sparing or steroid avoidance protocols
> Tacrolimus to cyclosporine conversion therapy
> Avoid CNI and mTOR inhibitors combination therapy

Pharmacological therapy

> Acute, marked hyperglycemia (may require in-patient management)
> Consider insulin drip when glucose > 400 mg/dL[3]
> Chronic hyperglycemia: treat to target HbA1C < 6.5%[4]
> Oral glucose-lowering agent monotherapy or combination therapy[5] and/or insulin therapy
> Consider diabetologist referral if HbA1C remains > 9.0%

Monitoring of patients with NODAT

> HbA1C every 3 months
> Screening for microalbuminuria
> Regular ophthalmologic exam
> Regular foot care
> Annual fasting lipid profile
> Aggressive treatment of dyslipidemia nd hypertension

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[1]AHA: American Heart Association
[2]Clinicians must be familiar with the patients'immune history prior to manipulating their immunosuppressive therapy
[3] The American College of Physicians expert panel recommends not using intensive insulin therapy to normalize blood glucose in general surgical and medical intensive care unit (SICU/MICU) patients with or without diabetes (reference 84). Studies in the transplant settings are lacking. The determination of target blood glucose for transplant recipients should be individualized at the discretion of the clinician.
[4]See text

Table 4. Management of NODAT

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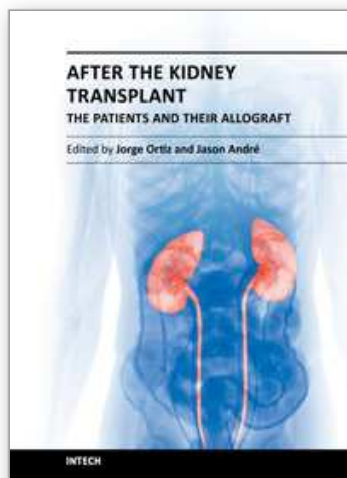
After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipient's tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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