New-Onset Diabetes After Kidney Transplantation: Prevalence, Risk Factors, and Management

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New-Onset Diabetes After Transplantation (NODAT) is an increasingly recognized severe metabolic complication of kidney transplantation causing lower graft function and survival and reduced long-term patient survival mainly due to cardiovascular events. The real incidence of NODAT after kidney transplantation is difficult to establish, because different classification systems and definitions have been employed over the years. Several risk factors, already present before or arising after transplantation, in particular the employed immunosuppressive regimens, have been related to the development of NODAT. However the responsible pathogenic mechanisms are still far to be perfectly known. Awareness of NODAT and of the NODAT-related factors is of paramount importance for the clinicians in order to individuate higher risk patients and arrange screening strategies. The risk of NODAT can be reduced by planning preventive measures and by tailoring immunosuppressive regimens according to the patient characteristics. Once NODAT has been diagnosed, the administration of specific anti-hyperglycemic therapy is mandatory to reach a tight glycemic control, which contributes to significantly reduce posttransplant mortality and morbidity.

Keywords: Kidney transplantation, Posttransplant complications, Diabetes mellitus, Immunosuppressive therapy, Insulin, Antihyperglycemic agents.

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Diabetes is a well-known complication of transplantation, and its development is associated with lower graft function and survival and reduced long-term patient survival mainly because of cardiovascular events (*1–3*). The real incidence of new-onset diabetes after transplantation (NODAT) is difficult to establish, mainly because different classification systems have been used over the years. The NODAT has been related to several risk factors, and the used immunosuppressive medications such as calcineurin inhibitors (e.g., cyclosporine and tacrolimus) and corticosteroids play an important role on its pathogenesis (*4*). In nondiabetic renal transplant recipients, the reported incidence of NODAT ranges between 4% and 25% (*5*), while preexisting diabetes contributes to increase the risk of posttransplant complications and poor outcome (*6*). The complications related to NODAT impose a careful preoperative assessment of the diabetic risk and a close monitoring of patients after transplantation, to tailor therapy accordingly and to avoid inappropriate immunosuppressive therapy administration.

This article reviews the more recent evidence available concerning the development of NODAT in the renal transplant population, the contributing risk factors, and the therapeutic approaches that may help to reduce diabetes-related complication after renal transplantation.

NODAT IN KIDNEY TRANSPLANT RECIPIENTS: CLINICAL IMPLICATIONS AND SCREENING STRATEGIES

Several studies have assessed the clinical impact of NODAT on outcome after renal transplantation. Over the past 10 years, NODAT has been well established as an independent predictor for lower patient survival (*3*) increasing the risk of all-cause mortality up to 87% and determining a higher rates of graft failure and death-censored graft failure when compared with the risk of nondiabetic patients (*7*). Two recent studies confirmed the strong association between NODAT and reduced patient survival (*2*, *8*). Joss et al. (*8*) reported in 787 renal transplants a 5- and 10-year survival of 86.1% and 67.1%, respectively, for patients who developed NODAT, which was significantly worse than the 90.9% and 81.9% survival of nondiabetics ($P<0.01$), while there was no significant difference in graft survival. Bee et al. (*2*) in 388 renal transplants confirmed a significant difference in

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long-term survival between patients with NODAT and nondiabetics. Five- and 10-year survival was 85.7% and 72.0%, respectively, for patients with NODAT, compared with 96.1% and 89.3% for those without diabetes ($P<0.001$). Furthermore, there was a significant difference in graft survival: 5- and 10-year graft survival was 89.4% and 81.0%, respectively, for patients with NODAT compared with 94.0% and 85.2% for those without diabetes ($P=0.045$).

Approximately 6% of dialysis patients waiting for renal transplantation develop diabetes annually (*9*). On the basis of this evidence, it is of paramount importance to detect diabetic individuals to permit appropriate therapeutic intervention before transplant. Moreover, it should be considered that dialysis patients may have a diminished insulin metabolism associated with kidney dysfunction that could mask a preexisting diabetes in otherwise normoglycemic patients. In this population, 2-hr oral glucose tolerance test (OGTT) may help to detect diabetes mellitus (*10*). Pretransplant OGTT also plays an important role in identifying prediabetes state such as impaired glucose tolerance or impaired fasting glucose, which are associated with more than a 2.5-fold increase in the incidence of NODAT (*11*), compared with normoglycemic status, and in addition, they represent a risk to develop cardiovascular diseases after transplant (*12*), mostly related to carotid atherosclerosis (*13*).

Several studies have shown that OGTT before transplantation could be a useful tool to identify glucose derangements, therefore providing an opportunity to prevent the onset of NODAT, suggesting a healthier lifestyle and proposing a less diabetogenic protocol after transplantation (*14*, *15*).

NODAT is diagnosed according to the American Diabetes Association criteria: symptoms of diabetes along with casual plasma glucose concentration ≥200 mg/dL (casual being defined as any time of the day without regard to time since last meal) or fasting glucose ≥126 mg/dL (fasting defined as no caloric intake for at least 8 hr). Moreover, all renal transplant recipients found to have a fasting glucose between 100 and 125 mg/dL should subsequently undergo an OGTT which might reveal diabetes if 2-hr plasma glucose is ≥200 mg/dL, or glucose intolerance if it ranges between 140 and 199 mg/dL (*16*).

Because glucose abnormalities may be related to surgical stress and exposure to immunosuppressive medications (*17*), NODAT is diagnosed when there is persistent hyperglycemia after hospital discharge in patients without preexistent diabetes. On the basis of this assumption, the screening test to detect NODAT should be performed in the time frame between 1 and 12 months posttransplant, because by 4 weeks after transplantation patients are clinically stable and on stable doses of immunosuppression, and the highest incidence of NODAT occurs within the first year posttransplant (*7*, *9*). Patients who may have developed transient hyperglycemia only in the immediate posttransplant period because of surgical stress and high-dose corticosteroid therapy are not considered (*18*). However, one should keep in mind that, although transient hyperglycemia in the first month after transplantation cannot be used as a parameter to diagnose NODAT, it represents a strong independent predictor of NODAT at 1 year (*18*). On the basis of these data, the ''Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group'' recommends instead frequent early screening tests for abnormal glucose metabolism, in particular fasting plasma glucose, oral glucose tolerance, and/or glycosylated hemoglobin (HbA1C) weekly for 4 weeks, every 3 months for 1 year, and annually thereafter (*19*).

The best predictive screening test to diagnose NODAT is still a matter of debate. Fasting blood glucose represents a reliable tool to detect NODAT, because it is easy to use in a clinical setting; however, Caillard et al. (*14*) demonstrated that fasting glucose diagnosed diabetes in only three quarters of kidney recipients, but there is a remaining one quarter of patients in whom diabetes was diagnosed by OGTT, which is more sensitive and specific than fasting glucose. This discrepancy is easy to understand, in fact fasting glucose is primarily determined by a feedback interaction between liver and beta cells, whereas postprandial glucose is mostly dependent on glucose uptake by insulin-sensitive tissues such as muscle and liver (*20*). Recently, HbA1C has been implicated in the diagnosis of NODAT. Although HbA1C should be used along with fasting blood glucose to select recipients who should undergo OGTT after transplantation (*21*), it could be underestimated in uremic patients before transplant (*22*) (Table 1).

TABLE 1. NODAT: diagnostic, screening, and management strategies

	Before transplantation	After transplantation
Screening	Assessment of diabetes risk factors 75 g OGTT	FPG, OGTT, and/or HbA1c at least – Weekly for 4 wk – Every 3 mo for 1 yr – Annually, thereafter
Treatment	Counseling on weight control, diet, and exercise	– Minimize immunosuppressive regimen – Follow-up of all patients, especially those with prediabetes *For patients who developed NODAT:* – Diabetes education – Appropriate antidiabetic therapy – Monitoring macro and microvascular complications – Evaluate and control comorbid conditions, such as blood hypertension, dyslipidemia, hyperuricemia, and other

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin; NODAT, new–onset diabetes after transplantation.

RISK FACTORS FOR NODAT

Several factors are believed to predispose renal transplant patients to NODAT and should be evaluated to prevent the development of posttransplant diabetes. Although the pathogenic mechanisms are still not perfectly known, the knowledge of these risk factors is of paramount importance to individualize the higher risk patients and tailor the therapeutic strategy accordingly.

PATIENTS' CHARACTERISTICS

Aging plays an important role in the development of NODAT. Transplant recipients older than 45 years were found to be 2.2 times more likely to develop NODAT than younger recipients (*23*), and the evidence of an age-increased risk has been further confirmed (*7*). Furthermore, African Americans and Hispanics were reported to be at higher risk for NODAT than whites (*7*, *24*). An increased risk has also been reported in Asiatic cohorts (*25*, *26*). A higher risk of NODAT has also been described for recipients of kidneys from male donors (*7*).

Obesity represents a consistent risk factor for NODAT and, in fact, data coming from "The United States Renal Data System" revealed that obese patients have a relative risk for NODAT of 1.73% (*7*). Similar to obesity, overweight conditions are also at risk for NODAT (*27*). However, it should be considered that although many patients experience considerable weight gain during the first year after transplantation, the incidence of NODAT did not correlate significantly with the amount of weight gain (*27*). The underlying mechanism is poorly understood, although it is known that obesity in itself is associated with peripheral insulin resistance, a predisposing risk factor for type 2 diabetes. Moreover, adipose tissue is implicated in the secretion of adipokines that may play a role in the incidence of NODAT. It was reported that for every 1 μg/mL decrease in serum adiponectin concentration, the risk of developing NODAT increases by 13% (*28*). Obesity is also associated with an increase in serum inflammatory markers that in turn cause insulin resistance. Ibernon et al. (*29*) reported that a pretransplant decrease in low serum mannose-binding lectin (a liver-synthesized innate immune molecule) is associated with insulin resistance and therefore with increased risk of NODAT.

GENETIC BACKGROUND

Similar to type 2 diabetes, the genetic background may contribute to the development of NODAT, and although the influence of different genetic factors has already been evaluated, the determination of a genetic susceptibility for all patients still requires further study. Over the years, several human leukocyte antigens (HLAs), such as *HLA-B42* (*24*) and *HLA-B27* (*30*), have been analyzed and considered as predictive factors for NODAT. More recently, *HLA-B13* and *HLA-B15* phenotypes have been identified as independent predictors of NODAT (*2*). Previous reports have detected that a family history of type 2 diabetes increases up to seven times the risk for NODAT (*24*, *30*). Moreover, several genetic polymorphisms have been considered as contributing to diabetes. A study performed in 70 kidney transplant recipients has shown a significantly higher frequency of posttransplant diabetes in patients with the vitamin D receptor *TaqI t* allele than in the control group with the *TT* genotype (*31*). Bamoulid et al. (*32*) have also identified the interleukin-6 gene promoter polymorphism at position −174(G→C) to be associated with the later development of NODAT. In particular, the risk for NODAT was significantly higher in homozygous (GG) wild-type patients than in homozygous (CC) mutant patients. Furthermore, the incidence of NODAT increased linearly with the interleukin-6 production capacity. Ghisdal et al. (*33*) in a large cohort of predominantly white renal transplant patients analyzed 11 well-established type 2 diabetes susceptibility genes and the occurrence of NODAT within 6 months after transplantation, finding *TCF7L2* as the only polymorphism significantly associated with NODAT in the whole cohort (odds ratio: 1.55 [P=0.02] for CT genotype and odds ratio: 1.79 [P=0.04] for TT genotype).

More recently, Yang et al. (*34*) evaluated the genetic risk factors for NODAT in Hispanic kidney transplant recipients. Among 14 alleles in nine genes, hepatocyte nuclear factor 4 alpha AA (rs2144908), hepatocyte nuclear factor 4 alpha TT (rs1884614), and insulin receptor substrate 1 AA+AG (rs1801278) remained significantly associated with NODAT in kidney transplant patients with Hispanic ethnicity. Ergün et al. (*35*) evaluated the relationship between the enzyme endothelial nitric oxide synthase gene intron 4 polymorphism and NODAT in kidney allograft recipients. This enzyme is implicated in the synthesis of nitric oxide which mediates insulin-induced uptake and metabolism of glucose in skeletal muscle. Having a 4a allele of the endothelial nitric oxide synthase gene intron 4 polymorphism was found to be an independent risk factor for the development of NODAT.

VIRAL INFECTIONS

The association of viral infections and NODAT has a long been suggested, although the pathogenetic mechanisms linking this association are poorly understood and further perspective study needs to clarify this issue. The United States Renal Data System registry supplied evidence of a significant increase in 1-year incidence of NODAT in hepatitis C virus (HCV)-positive patients compared with HCV-negative patients (*7*). Moreover, Kamar et al. (*36*) demonstrated that successful pretransplant treatment of hepatitis C with interferon could potentially reduce the incidence of NODAT after kidney transplantation.

The diabetogenic effect of HCV may be explained by the HCV properties to cause insulin resistance, mostly decreasing hepatic insulin sensitivity with a consequent increase in hepatic glucose production. Although still not fully clarified, the main pathogenic mechanism determining insulin resistance involves the serine phosphorylation on the insulin receptor substrate (IRS)-1 and impairment of the Akt signaling pathway; the specific target of this pathway is related to virus genotype. Although all HCV genotypes can induce insulin resistance, genotypes 1 or 4 are more prone than those with genotype 3 to develop insulin resistance (*37*). The latter, in particular the core protein of genotype 3a, seems to down-regulate peroxisome proliferator-activated receptor-γ and up-regulate the suppressor of cytokine signal 7 (SOCS-7), whereas the core protein of genotype 1b activates mammalian target of rapamycin and SOCS-3; all these

mechanisms cause the phosphorylation of the IRS-1 (*38*). In addition, increased production of SOCS is related to phosphorylation of the Akt and phosphatidylinositol 3 kinase pathways, which in turn inhibits the production of glucose transporter 4 and, therefore, glucose uptake (*39*). HCV infection is associated with an increase in tumor necrosis factor-α that have been shown to be major stimuli of Ser 307 phosphorylation of IRS-1 through the activation of both c-Jun N-terminal kinase and inhibitor κB kinase-β. Tumor necrosis factor-α stimulates phosphorylation of Ser residues of both IRS-1 and IRS-2 in hepatocytes (*40*, *41*). Moreover, HCV seems to have a direct cytopathic effect on pancreatic beta cells contributing also to insulin secretion derangements (*42*).

Besides HCV, the role of cytomegalovirus infection as a risk factor for NODAT is debated. Hjelmesaeth et al. (*1*) found a higher risk for the development of NODAT in both symptomatic and asymptomatic patients with cytomegalovirus.

IMMUNOSUPPRESSIVE REGIMENS

The relationship between NODAT and the immunosuppressive medications used after transplantation has been well documented (*4*), and immunosuppressive drugs accounted for up to 74% of the risk of NODAT development (*27*, *43*).

The agents most strongly associated with NODAT are corticosteroids and tacrolimus (*4*, *7*, *44*, *45*). Increased insulin resistance and weight gain are widely thought to be the main mechanisms involved in corticosteroid-induced NODAT (*44*). The association between corticosteroids and NODAT is mostly dependent on cumulative dosages and therapy duration (*46*). Although avoidance, minimization, or early withdrawal of corticosteroids seem as favorable options to reduce the incidence of corticosteroid-induced NODAT (*4*), data from randomized controlled trials regarding this strategy are scarce and in general demonstrate modest reductions in the rate of metabolic complications, including NODAT, but higher rates of acute rejections (*47*). Thus, the adoption of steroid-free maintenance immunosuppression seems to be suitable only for selected patients at low immunological risk.

In fact, although withdrawal or avoidance of prednisolone/prednisone ameliorated glucose metabolism, it was associated with an increase in the risk of graft rejection and chronic allograft nephropathy (*48*). In addition, as reported by Woodle et al. (*49*), the steroid withdrawal did not significantly reduce the incidence of NODAT but it contributes to improve the glycemic control and decrease the amount of insulin in the withdrawal arm. Decreasing prednisolone below 5 mg/dL may represent a good compromise in risk of rejection and metabolic derangements (*19*). Conversely, the calcineurin inhibitors exert their diabetogenic properties through the inhibition of insulin secretion, as demonstrated in both animal models and human studies (*50*, *51*). Tacrolimus has been reported to have a greater diabetogenic effect than cyclosporine. Woodward et al. (*9*) found a 2-year posttransplant incidence of NODAT of almost 18% and 30%, respectively, among patients receiving cyclosporine or tacrolimus. More recently, the DIRECT Study, the first multicenter open label, randomized trial to assess the glucose abnormalities in de novo kidney transplant patients, randomized to cyclosporine- or tacrolimus-based immunosuppression, confirmed a significantly decrease of NODAT at 6 months posttransplant in cyclosporine-treated compared with tacrolimus-treated patients (*45*). In particular, a recent study performed by Tavira et al. (*52*) identified KCNQ1 gene variants as determinants of the risk of developing NODAT in tacrolimus-treated patients. It is intriguing to report that the diabetogenicity of tacrolimus depends also on ethnicity; in fact, several studies conducted in Chinese population reported a low prevalence of NODAT in tacrolimus-treated patients (*25*, *26*).

In an attempt to reduce the risk of NODAT, the conversion of calcineurin inhibitors to sirolimus has been suggested. Nevertheless, sirolimus showed to have higher diabetogenic property, through a mechanism involving a defect in the compensatory pancreatic β-cell response and a fall in insulin sensitivity (*53*). Moreover, Johnston et al. (*54*) found sirolimus to be independently associated with NODAT in a cohort 20,124 adult recipients without preexisting diabetes undergoing a first kidney transplant. Compared with patients treated with cyclosporine and either mycophenolate mofetil or azathioprine, sirolimus-treated patients were at increased risk for NODAT, whether it was used in combination with cyclosporine (hazard ratio [HR]: 1.6; confidence interval [CI]: 1.36–1.90), tacrolimus (HR: 1.66; CI: 1.42–1.93), or an antimetabolite (mycophenolate mofetil or azathioprine—HR: 1.36; CI: 1.09–1.69). An increased risk for NODAT was also recorded in patients treated with tacrolimus in combination with either mycophenolate mofetil or azathioprine. In this group of patients, the diabetogenic risk was even higher than in patients treated with sirolimus in combination with either mycophenolate mofetil or azathioprine (HR: 1.36; CI: 1.09–1.69 vs. HR: 1.4; CI: 1.29–1.52).

Impaired glucose homeostasis has been recorded also in renal transplant recipients receiving basiliximab, a CD25 antibody indirectly suppressing T-cell proliferation, as induction therapy at transplantation. In the basiliximab group, 51.5% of patients developed NODAT, impaired glucose tolerance, or impaired fasting glucose, versus 36.9% of patients in the group without induction therapy, but the pathogenic mechanism remains unknown (*55*). A better metabolic risk profile has been described in two recent phase III studies evaluating the role of belatacept, a costimulation blocker that selectively inhibits T-cell activation, compared with cyclosporine A-based regimen (*56*). The patient populations included patients who did not have diabetes at baseline. NODAT (assessed 12 months after transplantation) occurred less often in the belatacept compared with the cyclosporine A groups, in a prespecified pooled analysis of the two studies ($P<0.05$).

OTHER RISK FACTORS

Still doubtful risk factors for NODAT are represented by proteinuria and hypomagnesemia. Roland et al. (*57*) found an association between the grade of proteinuria after kidney transplant and the development of NODAT. Patients at highest risk had early low-grade proteinuria.

However, proteinuria after kidney transplant is not always associated with transplant in itself, but it could be a consequence of the immunosuppressive therapy, or a residual native kidney proteinuria; furthermore, it generally

resolves some weeks after transplantation (*58*), for which reason it cannot be definitively accepted as a reliable predictive factor for NODAT.

The relation between hypomagnesemia and NODAT is still not clear because conflicting results have been reported (*59*, *60*). It should be noticed that magnesium homeostasis is necessary to preserve insulin secretion, cellular transport of glucose, and insulin-insulin receptor interactions (*61*). Van Laecke et al. (*60*) found hypomagnesemia as an independent predictor of NODAT, whose occurrence seemed to be induced by calcineurin inhibitors (*60*), which cause obligatory renal loss and decrease transcriptional expression of the magnesium transporter in the distal collecting tubule (*62*). Conversely, Osorio et al. (*59*) demonstrated that delayed calcineurin inhibitors' introduction along with the use of sequential therapy with anti-CD25 antibodies was associated with higher magnesemia levels during the first year posttransplantation, but no differences in magnesium were observed among patients who developed NODAT compared with the non-NODAT cohort. However, the differences in the results reported in these retrospective studies are presumably because of different methodologies used as to when and how magnesium levels were ascertained. A recent randomized controlled trial (*63*) has helped to clarify this issue and confirmed early posttransplantation hypomagnesemia to be a predictor of NODAT.

Finally, several evidence have been supplied regarding the role of autosomic-dominant polycystic kidney disease as a risk factor for NODAT (*64*, *65*). Patients with autosomic-dominant polycystic kidney disease were at a three-fold increased risk for development of posttransplant diabetes mellitus within the first year after renal transplantation (*64*).

INTERVENTION

The best therapeutic approach should be started with prevention, trying to optimize modifiable risk factors, such as obesity and immunosuppressive therapy, and encouraging an healthy lifestyle (Table 1).

As already known, physical activity plays an important role in ameliorating glucose metabolism in obesity; in the same manner, regular exercise along with an appropriate nutrition therapy have shown to improve glucose metabolism and prevent the development of NODAT in kidney recipients who experienced hyperglycemia during the first month after transplant (*66*).

When lifestyle modifications fail to reach adequate glycemic control, medical intervention is necessary. The selection of antihyperglycemic agents and/or insulin therapy should be made according to the pharmacological properties of compounds (efficacy and safety) and clinical characteristics of patients (stage of disease, body weight, kidney, and liver function). Posttransplantation hyperglycemia may develop acutely, resembling type 1 diabetes, and immediate intervention with fluids, electrolytes, and insulin administration may be needed to avoid serious consequences, whereas the majority of cases of NODAT resemble type 2 diabetes and it may therefore be appropriate to start therapy with oral antidiabetic compounds. The mechanism of action of oral antidiabetic compounds targets insulin sensitivity (metformin, pioglitazone, and rosiglitazone), insulin secretion (sulfonylureas and meglitinides), or reduce glucose absorption (acarbose; Fig. 1).

Among insulin sensitizers, it should be noted that metformin should be prescribed with great caution, given the increased risk of lactic acidosis in patients with impaired kidney function. Given its cardiovascular protective and antidiabetic properties (*67*), it may exert an important beneficial effect in kidney recipients at risk for metabolic syndrome; its use is recommended for this reason, and in the context of renal or renal allograft insufficiency (e.g., epidermal growth factor receptor 30–60 mL/min), metformin, because of a strong linear relationship between kidney function and plasma metformin levels, could be prescribed based on these plasma levels (*68*), but unfortunately they are not widely available and are infrequently used for this purpose.

In the same manner, compounds as glyburide, metformin, and acarbose whose active metabolites have a renal excretion (*69*) need to be used only after a careful evaluation of kidney function.

In addition, it should be taken into account that the pharmacokinetics of some antidiabetic drugs may be

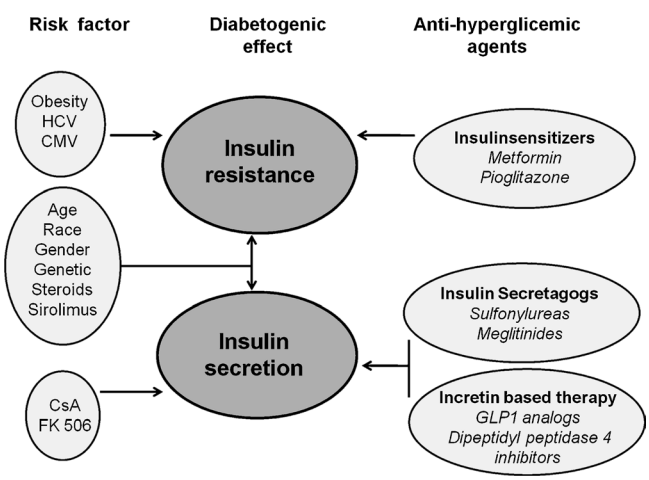

FIGURE 1. New-onset diabetes after transplantation (NODAT): influence of pre- and posttransplant risk factors over insulin resistance and insulin secretion, the targets of the main antihyperglycemic agents used.

modified by the interaction with immunosuppressant, and in this regard, Pollock et al. (*70*) found that cyclosporine may interfere with glyburide in animal study.

A new horizon is supplied by incretin-based therapy, although data on its safety and efficacy are still unknown. However, vildagliptin should be avoided in patients with hepatic impairment or severe renal dysfunction, while the dose of sitagliptin should be adjusted for renal insufficiency (*71*).

With regard to this topic, there is an ongoing randomized controlled trial evaluating the efficacy and safety of vildagliptin in 32 renal transplant recipients with new diagnosis of NODAT (www.clinicaltrials.gov—NCT 00980356). Given the importance of pretransplant metabolic state, an ongoing trial is evaluating the efficacy of treatment with sitagliptin before transplant in preventing the onset of NODAT (www.clinicaltrials.gov - trial identifier NCT00936663). Whenever lifestyle changes and oral therapy fail to keep an acceptable glucose control, insulin therapy needs to be started using a wide variety of rapid-acting, intermediate-acting, and long-acting insulin preparations currently available (*72*).

Although targeted metabolic control has not been tested specifically in the kidney transplant population, it is reasonable to assume that patients affected by NODAT may have similar benefits compared with patients with either type 1 or 2 diabetes, in whom tight glycemic control significantly reduces mortality and morbidity.

Target HbA1C should be 7.0% to 7.5% in patients with NODAT, trying to avoid value less than 6.0%, especially if hypoglycemic events are common (*19*).

Similar to patients with type 1 or 2 diabetes, HbA1C should be monitored every 3 months, keeping in mind that severe anemia or advanced renal failure may influence the result. In addition, self-monitoring blood glucose may also be a useful tool in improving glucose metabolism in patients with NODAT, as it occurs in the general diabetic population (*73*).

CONCLUSIONS

NODAT is a serious complication after kidney transplantation, associated with worse patient and graft survival. Despite the efforts made up until now, the available data are usually based on retrospective and observational studies, often with limited cohorts of patients. The pathophysiological basis of NODAT has to be further investigated and clarified, and prospective studies evaluating the causes and mechanisms of impaired insulin secretion associated or not to insulin resistance in this specific cohort of patients are needed.

Several risk factors, already present before or arising after transplantation, have been related to the development of NODAT, but again the pathogenic mechanisms are far to be known. In this background, screening strategies play an important role; knowledge of the various risk factors is mandatory for the clinicians to adopt preventing measures and tailor the immunosuppressive regimen, simultaneously evaluating the risk of acute rejection. Once NODAT has been diagnosed, and lifestyle cannot warrant glycemic control, the antihyperglycemic therapy has to take into account patient characteristics and the pharmacological properties of antidiabetic compounds, to achieve a tight glycemic control without impairing renal function. If validated in the ongoing trial, new compounds will become available soon.

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REFERENCES

1. 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: 588.
2. Bee YM, Tan HC, Tay TL, et al. Incidence and risk factors for development of new-onset diabetes after kidney transplantation. *Ann Acad Med Singapore* 2011; 40: 160.
3. Cosio FG, Pesavento TE, Kim S, et al. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. *Kidney Int* 2002; 62: 1440.
4. Luan FL, Steffick DE, Ojo AO. New-onset diabetes mellitus in kidney transplant recipients discharged on steroid-free immunosuppression. *Transplantation* 2011; 91: 334.
5. Pham PT, Pham PM, Pham SV, et al. New onset diabetes after transplantation (NODAT): An overview. *Diabetes Metab Syndr Obes* 2011; 4: 175.
6. Kuo HT, Sampaio MS, Vincenti F, et al. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: An analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. *Am J Kidney Dis* 2010; 56: 1127.
7. Kasiske BL, Snyder JJ, Gilbertson D, et al. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; 3: 178.
8. Joss N, Staatz CE, Thomson AH, et al. Predictors of new onset diabetes after renal transplantation. *Clin Transplant* 2007; 21: 136.
9. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant* 2003; 3: 590.
10. Nam JH, Mun JI, Kim SI, et al. beta-Cell dysfunction rather than insulin resistance is the main contributing factor for the development of postrenal transplantation diabetes mellitus. *Transplantation* 2001; 71: 1417.
11. Iida S, Ishida H, Tokumoto T, et al. New-onset diabetes after transplantation in tacrolimus-treated, living kidney transplantation: Long-term impact and utility of the pre-transplant OGTT. *Int Urol Nephrol* 2010; 42: 935.
12. Jardine AG, Gaston RS, Fellstrom BC, et al. Prevention of cardiovascular disease in adult recipients of kidney transplants. *Lancet* 2011; 378: 1419.
13. Alvarez A, Fernandez J, Porrini E, et al. Carotid atheromatosis in nondiabetic renal transplant recipients: The role of prediabetic glucose homeostasis alterations. *Transplantation* 2007; 84: 870.
14. Caillard S, Eprinchard L, Perrin P, et al. Incidence and risk factors of glucose metabolism disorders in kidney transplant recipients: Role of systematic screening by oral glucose tolerance test. *Transplantation* 2011; 91: 757.
15. Mathew JT, Rao M, Job V, et al. Post-transplant hyperglycaemia: A study of risk factors. *Nephrol Dial Transplant* 2003; 18: 164.
16. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2004; 27(suppl 1): S5.
17. Chakkera HA, Weil EJ, Castro J, et al. Hyperglycemia during the immediate period after kidney transplantation. *Clin J Am Soc Nephrol* 2009; 4: 853.
18. Cosio FG, Kudva Y, van der Velde M, et al. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; 67: 2415.
19. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; 9(suppl 3): S1.
20. Davies MJ, Raymond NT, Day JL, et al. Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 2000; 17: 433.
21. Valderhaug TG, Jenssen T, Hartmann A, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. *Transplantation* 2009; 88: 429.
22. Bergrem HA, Valderhaug TG, Hartmann A, et al. Undiagnosed diabetes in kidney transplant candidates: A case-finding strategy. *Clin J Am Soc Nephrol* 2010; 5: 616.
23. Cosio FG, Pesavento TE, Osei K, et al. Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int* 2001; 59: 732.

24. Sumrani NB, Delaney V, Ding ZK, et al. Diabetes mellitus after renal transplantation in the cyclosporine era—An analysis of risk factors. *Transplantation* 1991; 51: 343.
25. Chow KM, Szeto CC, Li PK. Good metabolic control using tacrolimus-based immunosuppressants in primary cadaveric renal transplantation in Chinese–a preliminary report. *Clin Transplant* 2002; 16: 39.
26. Cheung CY, Wong KM, Chan HW, et al. Paired kidney analysis of tacrolimus and cyclosporine microemulsion-based therapy in Chinese cadaveric renal transplant recipients. *Transpl Int* 2006; 19: 657.
27. Rodrigo E, Fernandez-Fresnedo G, Valero R, et al. New-onset diabetes after kidney transplantation: Risk factors. *J Am Soc Nephrol* 2006; 17(12 Suppl 3): S291.
28. Bayes B, Granada ML, Pastor MC, et al. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *Am J Transplant* 2007; 7: 416.
29. Ibernon M, Moreso F, Moreno JM, et al. Low serum mannose-binding lectin as a risk factor for new onset diabetes mellitus after renal transplantation. *Transplantation* 2009; 88: 272.
30. Hjelmesaeth J, Hartmann A, Kofstad J, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 1997; 64: 979.
31. Numakura K, Satoh S, Tsuchiya N, et al. Clinical and genetic risk factors for posttransplant diabetes mellitus in adult renal transplant recipients treated with tacrolimus. *Transplantation* 2005; 80: 1419.
32. Bamoulid J, Courivaud C, Deschamps M, et al. IL-6 promoter polymorphism -174 is associated with new-onset diabetes after transplantation. *J Am Soc Nephrol* 2006; 17: 2333.
33. Ghisdal L, Baron C, Le Meur Y, et al. TCF7L2 polymorphism associates with new-onset diabetes after transplantation. *J Am Soc Nephrol* 2009; 20: 2459.
34. Yang J, Hutchinson II, Shah T, et al. Genetic and clinical risk factors of new-onset diabetes after transplantation in Hispanic kidney transplant recipients. *Transplantation* 2011; 91: 1114.
35. Ergün I, Keven K, Sengül S, et al. Endothelial nitric oxide synthase gene intron 4 polymorphism predicts new onset diabetes mellitus after transplantation in kidney allograft recipients treated with cyclosporin A. *Int Urol Nephrol* 2011; 43: 543.
36. 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.
37. Moucari R, Asselah T, Cazals-Hatem D, et al. Insulin resistance in chronic hepatitis C: Association with genotypes 1 and 4, serum HCV RNA level, and liver fibrosis. *Gastroenterology* 2008; 134: 416.
38. Pazienza V, Clement S, Pugnale P, et al. The hepatitis C virus core protein of genotypes 3a and 1b downregulates insulin receptor substrate 1 through genotype-specific mechanisms. *Hepatology* 2007; 45: 1164.
39. Del Campo JA, Romero-Gomez M. Steatosis and insulin resistance in hepatitis C: A way out for the virus? *World J Gastroenterol* 2009; 15: 5014.
40. Pittas AG, Joseph NA, Greenberg AS. Adipocytokines and insulin resistance. *J Clin Endocrinol Metab* 2004; 89: 447.
41. Kanety H, Feinstein R, Papa MZ, et al. Tumor necrosis factor alpha-induced phosphorylation of insulin receptor substrate-1 (IRS-1). Possible mechanism for suppression of insulin-stimulated tyrosine phosphorylation of IRS-1. *J Biol Chem* 1995; 270: 23780.
42. Bloom RD, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. *Am J Transplant* 2006; 6: 2232.
43. Montori VM, Basu A, Erwin PJ, et al. Posttransplantation diabetes: A systematic review of the literature. *Diabetes Care* 2002; 25: 583.
44. Kamar N, Mariat C, Delahousse M, et al. Diabetes mellitus after kidney transplantation: A French multicentre observational study. *Nephrol Dial Transplant* 2007; 22: 1986.
45. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 2007; 7: 1506.
46. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; 75(10 Suppl): SS3.
47. Augustine JJ, Hricik DE. Steroid sparing in kidney transplantation: Changing paradigms, improving outcomes, and remaining questions. *Clin J Am Soc Nephrol* 2006; 1: 1080.
48. Pascual J, Zamora J, Galeano C, et al. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev* 2009: CD005632.
49. Woodle ES, First MR, Pirsch J, et al. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann Surg* 2008; 248: 564.
50. Paty BW, Harmon JS, Marsh CL, et al. Inhibitory effects of immunosuppressive drugs on insulin secretion from HIT-T15 cells and Wistar rat islets. *Transplantation* 2002; 73: 353.
51. Duijnhoven EM, Boots JM, Christiaans MH, et al. Influence of tacrolimus on glucose metabolism before and after renal transplantation: A prospective study. *J Am Soc Nephrol* 2001; 12: 583.
52. Tavira B, Coto E, Diaz-Corte C, et al. KCNQ1 gene variants and risk of new-onset diabetes in tacrolimus-treated renal-transplanted patients. *Clin Transplant* 2011; 25: E284.
53. 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.
54. Johnston O, Rose CL, Webster AC, et al. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol* 2008; 19: 1411.
55. Aasebo W, Midtvedt K, Valderhaug TG, et al. Impaired glucose homeostasis in renal transplant recipients receiving basiliximab. *Nephrol Dial Transplant* 2010; 25: 1289.
56. Vanrenterghem Y, Bresnahan B, Campistol J, et al. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation* 2011; 91: 976.
57. Roland M, Gatault P, Al-Najjar A, et al. Early pulse pressure and low-grade proteinuria as independent long-term risk factors for new-onset diabetes mellitus after kidney transplantation. *Am J Transplant* 2008; 8: 1719.
58. Myslak M, Am H, Morales P, et al. Interpreting post-transplant proteinuria in patients with proteinuria pre-transplant. *Am J Transplant* 2006; 6: 1660.
59. Osorio JM, Bravo J, Perez A, et al. Magnesemia in renal transplant recipients: Relation with immunosuppression and posttransplant diabetes. *Transplant Proc* 2010; 42: 2910.
60. Van Laecke S, Van Biesen W, Verbeke F, et al. Posttransplantation hypomagnesemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. *Am J Transplant* 2009; 9: 2140.
61. Chaudhary DP, Sharma R, Bansal DD. Implications of magnesium deficiency in type 2 diabetes: A review. *Biol Trace Elem Res* 2010; 134: 119.
62. Nijenhuis T, Hoenderop JG, Bindels RJ. Downregulation of Ca(2+) and Mg(2+) transport proteins in the kidney explains tacrolimus (FK506)-induced hypercalciuria and hypomagnesemia. *J Am Soc Nephrol* 2004; 15: 549.
63. Stevens RB, Lane JT, Boerner BP, et al. Single-dose rATG induction at renal transplantation: Superior renal function and glucoregulation with less hypomagnesemia. *Clin Transplant* 2012; 26: 123.
64. de Mattos AM, Olyaei AJ, Prather JC, et al. Autosomal-dominant polycystic kidney disease as a risk factor for diabetes mellitus following renal transplantation. *Kidney Int* 2005; 67: 714.
65. Hamer RA, Chow CL, Ong AC, et al. Polycystic kidney disease is a risk factor for new-onset diabetes after transplantation. *Transplantation* 2007; 83: 36.
66. Sharif A, Moore R, Baboolal K. Influence of lifestyle modification in renal transplant recipients with postprandial hyperglycemia. *Transplantation* 2008; 85: 353.
67. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352: 854.
68. Lalau JD, Lacroix C, Compagnon P, et al. Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 1995; 18: 779.
69. Marchetti P. New-onset diabetes after liver transplantation: From pathogenesis to management. *Liver Transpl* 2005; 11: 612.
70. Pollock SH, Reichbaum MI, Collier BH, et al. Inhibitory effect of cyclosporine A on the activity of oral hypoglycemic agents in rats. *J Pharmacol Exp Ther* 1991; 258: 8.
71. Srinivasan BT, Jarvis J, Khunti K, et al. Recent advances in the management of type 2 diabetes mellitus: A review. *Postgrad Med J* 2008; 84: 524.
72. Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 1995; 18: 361.
73. American Association of Clinical Endocrinologists. The American Association of Clinical Endocrinologists Medical Guidelines for the Management of Diabetes Mellitus: The AACE system of intensive diabetes self-management—2000 update. *Endocr Pract* 2000; 6: 43.