New-Onset Diabetes After Renal Transplantation

Risk assessment and management

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New-onset diabetes after transplantation (NODAT) is a serious and frequent metabolic complication after renal transplantation. This entity is currently well defined since the publication of the International Consensus Guidelines in 2003. Here, we review the factors contributing to the risk of NODAT and the strategies related to modifiable factors, with emphasis on practical issues. Recognizing these factors may help clinicians to evaluate prospectively appropriate prevention strategies to minimize the risk of NODAT.

Over the past 50 years, the concept of NODAT has evolved in terms of name and definition. Before 2003, de novo diabetes that developed after transplantation was described in various terms, most frequently "posttransplantation diabetes mellitus," and suffered from a lack of consensus regarding its definition. The most commonly used clinical definition was the requirement of insulin for a minimum period posttransplantation (often 30 days). This definition, however, identified only the most severe cases, leaving out the majority of patients with glucose metabolism disorders. International Consensus Guidelines on NODAT were published in 2003. They recommended that the diagnosis of NODAT should be based on the American Diabetes Association (ADA) criteria for type 2 diabetes published in 2003 (1,2). Since then, a follow-up report from the International Expert Committee further lowered the inferior limit of fasting plasma glucose (FPG) (100 mg/dL) that corresponds to impaired fasting glucose (IFG), based on epidemiologic predictive data (3). In addition, since 2009, the International Expert Committee recommended the use of a standardized A1C assay for diabetes diagnosis (A1C level ≥6.5%), a position that has been endorsed by ADA in 2010 (4). The Expert Committee stated that A1C assay cannot be used in conditions that change red cell turnover. This is the case of end-stage renal disease (ESRD) patients and newly transplanted kidney patients. For instance, the posttransplant period is frequently associated with anemia (due to surgical blood loss, iron deficiency, immunosuppressive drugs, graft dysfunction, and abrupt discontinuation of erythropoietin administration), resulting in spurious A1C results (5,6). Likewise, glucose levels rather than A1C must be used as screening in case of rapid onset of diabetes, a situation encountered after high-dose glucocorticoid administration (7). Taking these data together, we suggest the use of modified ADA 2003 criteria to define NODAT and IFG in kidney transplant recipients (3).

INCIDENCE AND IMPACT OF NODAT IN RENAL TRANSPLANT PATIENTS

—The reported incidence of NODAT greatly depends on the length of follow-up, diagnostic criteria, and immunosuppression regimen. The true incremental incidence of diabetes occurs mainly during the first 6 months posttransplantation, when patients are treated with high doses of immunosuppression. After 6 months, the annual incidence of diabetes is similar to that observed in patients on the waiting list (~6% per year) (8). Thus, late-onset cases of NODAT may be difficult to distinguish from genuine cases of type 2 diabetes. The most accurate incidence of NODAT under calcineurin inhibitor (CNI) therapy is provided by the prospective study of Vincenti et al. (9), reporting an incidence of NODAT reaching 20.5% within the first 6 months postrenal transplantation.

Renal transplant recipients with NODAT exhibit similar complications as those seen in the general population with type 2 diabetes, but at an accelerated rate (10). As a consequence, NODAT is associated with worse outcomes after renal transplantation, such as a higher risk of major cardiovascular events, graft failure, death-censored graft failure, and death (11,12). In addition, this metabolic complication substantially increases medical costs (8).

RISK FACTORS

Risk factors shared with type 2 diabetes in the general population

Reports from large databases, such as the United States Renal Data System (USRDS; a national organization that collects, analyzes, and distributes information about ESRD in the U.S.) and the Organ Procurement Transplant Network/United Network of Organ Sharing (OPTN/UNOS; organizations that are collecting medical data on donor and transplant recipients), have identified several independent risk factors associated with NODAT. As observed in type 2 diabetes in the general population, older age is a strong independent risk factor of NODAT. There is a 90% increase of relative risk (RR) in renal transplant patients aged 45–59 and a 160% increase in patients ≥60 (versus 18–44 years as a reference). The RR of NODAT is increased by 32–68% in black patients and by 35% in Hispanic patients in comparison with white patients. Overweight or obese patients have a higher risk of developing NODAT, with an RR of 1.4 for patients with a BMI between 25 and 30 kg/m^2 and an RR of 1.7–1.8 for patients with a BMI >30 kg/m^2. The RR of NODAT associated with a positive hepatitis C virus (HCV)

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serology ranges from 1.3 to 1.4 (12,13). While no prospective study has evaluated the impact of pretransplant clearance of HCV on the incidence of NODAT, two retrospective reports suggest that this strategy could be beneficial (14,15).

With regard to cytomegalovirus (CMV), a group showed that both ganciclovir-treated and asymptomatic CMV infection episodes are independent risk factors of NODAT (16,17). These results have not been confirmed by other groups (18,19). Likewise, there is no clear relationship between positive CMV serological status and the risk of type 2 diabetes in the general population (20).

The role of a family history of diabetes in predicting NODAT is unclear, as it has not been evaluated in large registry reports. However, a family history of type 2 diabetes emerged as a significant risk factor associated with NODAT in multivariate analysis of several studies (16,21). Retrospective studies reported a higher incidence of NODAT in patients with a metabolic syndrome at baseline. Patients with an increasing number of criteria are more likely to develop NODAT (74% of patients with five pretransplant criteria developed NODAT) (22,23). The risk of NODAT increases stepwise with pretransplant FPG level (FPG 101–110, odds ratio [OR] 1.5; FPG 110–125, OR 7.6) (24). The 2-h plasma glucose level after an oral glucose tolerance test (OGTT) correlates with the risk of NODAT (OR 1.26 per 1 mmol/L or 18 mg/dL) (25). Pretransplantation hypertriglyceridemia was also shown to correlate with NODAT (26).

Early studies evaluating the possible association of NODAT with single nucleotide polymorphisms of various genes are limited by small sample size and the absence of replication cohort, precluding any robust conclusions. After 2007, the association between NODAT and type 2 diabetes–associated genes have been reported in larger cohorts (Table 1). Since the first genome-wide association study (GWAS) in 2007, >40 confirmed loci have been associated with type 2 diabetes in the general population. The effect size of genetic variants so discovered was quite small, however, with an OR ranging from 1.10 to 1.20 for most of them. One of the largest ORs was 1.55 and was observed in nonobese patients with genetic polymorphism rs7903146 (T allele), a common variant in the *TCF7L2* (transcription factor 7-like 2) gene (27). This allele has been associated with impaired insulin secretion, incretin effect, and enhanced rate of hepatic glucose production in humans (28). Our group showed that this polymorphism was independently associated with NODAT occurring in the first 6 months posttransplantation, in a large white cohort (N = 1,076) (29). Another group found a significant association with the same variant, in a cohort of 589 Korean transplant recipients (30). *TCF7L2* as well as six other genes linked to type 2 diabetes in GWAS are acting through the Wnt signaling pathway involved in pancreas development, islet function, and insulin production and secretion. Wnt ligands might also be involved in the cross-talk between adipocytes and pancreatic β-cells. Investigations of these links should eventually help identify new therapeutic drug targets (31). Currently, *TCF7L2* is not routinely genotyped in order to stratify the risk of diabetes and to support personalized medicine. As stated above, the >40 diabetes-predisposing genetic variants discovered as of today only explain 10% of the observed heritability of diabetes, which is of little help in individual prediction (27). Recently, a study showed that the addition of genotypes (20 single nucleotide polymorphisms from GWAS) to phenotype-based risk models yielded only a marginal improvement in accuracy for estimating the absolute risk of type 2 diabetes and that an isolated genetic score was not discriminant (32). Currently, the search is focused on less common variants associated with type 2 diabetes in the general population, which might be more suited to support customized management of patients. Such variants yielding a stronger effect size might also be associated with NODAT in renal transplant patients. Thus, although the association of *TCF7L2* with NODAT highlights a major common mechanistic pathway with type 2 diabetes, we do not currently recommend genotyping *TCF7L2* for individual risk prediction of NODAT today.

Hypomagnesemia induced by CNIs (more common with tacrolimus) is due to renal magnesium wasting occurring through transcriptional inhibition of the renal magnesium transporter in the distal collecting tubule. Recently, posttransplantation hypomagnesemia was found to be an independent predictor of NODAT in both renal and liver transplant (26,33). This finding is in line with data from the general population where hypomagnesemia cross-sectionally associates with insulin resistance in obese children and with a metabolic syndrome in both diabetic and nondiabetic adults (34,35). These findings obviously do not prove causality, and hypomagnesemia might merely represent a surrogate marker or be a consequence of insulin resistance, inflammation, or endothelial dysfunction, which are all risk factors for diabetes in the general population. Although magnesium supplementation has previously demonstrated a beneficial impact on insulin resistance in the general population, randomized, controlled trials assessing the impact of early posttransplantation magnesium supplementation on glucose metabolism, which are ongoing, will hopefully shed light on this still controversial issue (36).

Specific factors related to transplantation

Although the type of donor (deceased versus living) is not an independent risk factor for NODAT, immunosuppression is a major factor contributing to the risk of NODAT. The diabetogenic effect of glucocorticoids, mainly due to insulin resistance, is mediated by both impaired insulin-dependent glucose uptake in the peripheral tissues and enhanced gluconeogenesis in the liver. High-dose glucocorticoid regimens used during the 1970s were associated with a very high incidence of so-called "steroid diabetes," which declined when cyclosporine was introduced as an immunosuppressant in the 1980s. However, pulse glucocorticoid therapy still given in the context of acute rejection treatment remains an independent risk factor of NODAT (29,37). A recent meta-analysis of 30 randomized controlled trials showed that glucocorticoid withdrawal (discontinuation after some months) was not associated with a reduction of NODAT incidence, whereas avoidance (no steroids at all after transplantation) resulted in less NODAT requiring any treatment. However, both steroid-sparing strategies were associated with higher acute rejection rates and higher risk of graft loss excluding death (38). Therefore, in patients at high risk of NODAT, a glucocorticoid minimization strategy should be balanced with the immunological risk profile to avoid acute rejection and graft loss.

CNIs are diabetogenic by inducing a defect in insulin secretion by interfering with the nuclear factor of activated T-cell signaling in pancreatic β-cells. This pathway triggers the expression of genes critical for β-cell function, including at least six genes mutated in hereditary forms of monogenic diabetes (39). Tacrolimus induces a reversible suppression of insulin secretion at the level of insulin mRNA

Table 1—*Candidate gene studies evaluating genetic susceptibility of NODAT*

Gene (official symbol)	Polymorphism	*N*	Reference	Association with NODAT
Glucokinase (*GCK*)	All exons/introns	58	Nam et al. (61)	One had one new mutation in exon 5, one had a mutation in intron 7
Apolipoprotein C-III (*APOC3*)	SstI	110	Rodrigo et al. (62)	No
Apolipoprotein E (*APOE*)	ε2/ε3/ε4	110	Rodrigo et al. (62)	No
Interferon-gamma (*IFNG*)	+874	278	Babel et al. (63)	AA genotype is associated with NODAT*
Interleukin 10 (*IL10*)	−1082	278	Babel et al. (63)	No
Vitamin D receptor (*VDR*)	TaqI	70	Numakura et al. (18)	NODAT associated with TaqI
	ApaI			No
	BsmI			No
	G866A			No
CYP3A5	A6986G	70	Numakura et al. (18)	No
ATP-binding cassette, subfamily B, member 1 (*ABCB1*, alias *MDR1*)	C3435T	70	Numakura et al. (18)	No
	G2677(A/T)			No
Uncoupling protein 2 (*UCP2*)	G866A	70	Numakura et al. (18)	No
Peroxisome proliferator–activated receptor-gamma (*PPARG*)	Pro12Ala	70	Numakura et al. (18)	No
Adiponectin (*ADIPOQ*)	T45G	70	Numakura et al. (18)	No
	G276T			No
	A349G			No
Angiotensin I converting enzyme (*ACE*)	I/D	70	Numakura et al. (18)	No
		42	Rodríguez-Moreno et al. (64)	No
Angiotensinogen (*AGT*)	M235T	42	Rodríguez-Moreno et al. (64)	TT genotype associated with NODAT*
Interleukin 6 (*IL6*)	−174 (G>C)	349	Bamoulid et al. (65)	CC genotype: decreased risk of NODAT
	−174 (G>C)	335	Sánchez-Velasco et al. (66)	No
	−174 (G>C)	278	Babel et al. (63)	No
Tumor necrosis factor (*TNF*, encoding for *TNF-α*)	G-238A	61	Gençtoy et al. (67)	(AA+GA) genotypes of G-238A: higher fasting insulin level and HOMA-IR*
	−308	278	Babel et al. (63)	No
Transforming growth factor-beta 1 (*TGFB1*, alias *TGF β*)	codon10–869 (T/C)	61	Gençtoy et al. (67)	No
Transcription factor 7-like 2 (*TCF7L2*)	rs7903146	589	Kang et al. (30)	OR CT genotype: 1.71
		1,076	Ghisdal et al. (29)	OR CT genotype: 1.7; TT genotype: 2.42
		234	Kurzawski et al. (68)	No
		303	Yang et al. (69)	No
Solute carrier family 30, member 8 (*SLC30A8*)	rs13266634	589	Kang et al. (30)	OR CC genotype: 1.96
Hematopoietically expressed homeobox (*HHEX*)	rs1111875	589	Kang et al. (30)	OR CC genotype: 1.81
	rs7923837			OR GG genotype: 1.84
	rs5015480			OR CC genotype: 1.97
CDK5 regulatory subunit associated protein 1-like (*CDKAL1*)	rs10946398	589	Kang et al. (30)	OR CC genotype: 2.02
Cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/B*)	rs10811661	589	Kang et al. (30)	OR TT genotype: 1.66
Potassium voltage-gated channel, KQT-like subfamily, member 1 (*KCNQ1*)	rs2237892	589	Kang et al. (30)	OR TT genotype: 1.61
Calpain 10 (*CAPN10*)	rs5030952	372	Kurzawski et al. (70)	OR CT genotype: 2.45
Hepatocyte nuclear factor 4 α (*HNF4A*)	rs2144908	303	Yang et al. (69)	OR AA genotype:1.96
	rs1884614			OR TT genotype: 2.44
Insulin receptor substrate 1 (*IRS1*)	rs1801278	303	Yang et al. (69)	OR AA+AG genotypes: 2.71

N, number of patients included. HOMA-IR, homeostasis model assessment–insulin resistance. *Association significant in univariate analysis only.

transcription, mediated by the binding of the drug to FK506 binding protein-12 and a subsequent inhibition of calcineurin in the β-cells (40). The high level of FK506 binding protein-12 present in pancreatic β-cells might explain why tacrolimus more profoundly inhibits insulin secretion than cyclosporine. Registry analyses, meta-analyses, and the prospective study of Vincenti et al. (9) showed that the risk of NODAT was significantly higher in patients on tacrolimus versus cyclosporine (12,13,41,42). The risk of NODAT related to tacrolimus is dose dependent and high trough levels enhance this risk, in particular during the early posttransplant period (37,43). The impact of the reduction of trough levels has not been evaluated prospectively. Cyclosporine is also diabetogenic but to a lesser extent. Indeed, studies comparing belatacept (a molecule that inhibits T-cell activation) with a cyclosporine-based regimen showed that NODAT developed in 6.7% of patients on cyclosporine versus 3.5% of belatacept patients at 12 months (P = 0.018) (44,45). Based on early studies reporting a high difference of incidence of NODAT between the two available CNIs, we started to switch patients with NODAT under tacrolimus to cyclosporine in our center. We showed that 42% of switched patients experienced a resolution of NODAT, whereas this never occurred in patients remaining on tacrolimus, after a follow-up of 1 year (46). Three other single-center retrospective studies reported, like our group, either a complete resolution or a significant improvement of NODAT after conversion from tacrolimus to cyclosporine in renal allograft recipients (47–49). In this context, we did set up a prospective, randomized, multicenter trial in order to further investigate this strategy (EudraCT no. 2006–001765–42).

There is now strong evidence that *m*-TOR (mammalian target of rapamycin) inhibitors cause alterations in glucose metabolism. This diabetogenic effect is probably due to a combination of an insulin secretion defect (toxicity to β-cells) and insulin resistance. Sirolimus has been associated with an increased risk of NODAT in large North American and European cohorts. The risk is particularly high when sirolimus is associated with a CNI (50,51). In one study, the discontinuation of CNI with replacement by sirolimus failed to improve glucose metabolism of kidney transplant recipients and was even associated with a worsening of insulin resistance and an inappropriately low insulin response (52). Experimental and clinical data on everolimus, the other *m*-TOR on the market, are more scant.

MANAGEMENT OF NODAT

Pretransplant evaluation

Currently, pretransplant risk assessment should be based on the phenotype and the medical history of the patient. The following factors associated with a higher risk of NODAT should be considered: an age >45 years old, a familial history of type 2 diabetes, a personal history of NODAT with previous graft or a gestational diabetes, IFG, impaired glucose tolerance, criteria for metabolic syndrome, a BMI >30 kg/m^2, and a positive hepatitis C serology. The screening should include an evaluation of the glucose metabolism status by FPG and/or OGTT. A recent large study (N = 889) has underlined the low sensitivity of FPG in detecting pretransplant glucose metabolism abnormalities in patients with ESRD because of insulin resistance. An FPG screening should be performed in all candidates, followed ideally by an OGTT in patients with FPG between 92 and 125 mg/dL (±50% of patients). This should allow the identification of >80% of pretransplant diabetes (53). The use of A1C is not recommended for the screening given the low sensitivity of the test in ESRD patients (53,54). Patients should be screened for risk factors before transplantation in order to prospectively tailor their immunosuppression and minimize the risk of NODAT. Patients at risk should be counseled on the importance of lifestyle intervention, including weight control, diet, and physical activity; as such strategy is efficient in patients at risk for type 2 diabetes. However, it must be acknowledged that we lack robust data showing that immunosuppression tailoring helps to prevent NODAT.

Posttransplant monitoring of glucose metabolism status

Recent guidelines recommend screening all kidney transplant recipients with FPG, OGTT, and/or A1C assay at least weekly for 4 weeks, every 3 months for 1 year, and annually thereafter (55). Although these guidelines do not counsel about what screening test to use, a recent large (N = 1,637, mainly white patients) prospective study performing systematic FPG, OGTT, and A1C assay at 10 weeks after renal transplantation provides rationale to use specific cutoff values in this population. NODAT was identified by FPG in only 49% of patients, and by OGTT in the remaining 51% (modified 2003 ADA criteria). Sensitivity analyses showed that performing the OGTT in patients with FPG between 95 and 125 mg/dL or with A1C ≥5.8% allows this test to be limited to 49 and 41% of patients, respectively, while still detecting ≥80% of NODAT. However, the authors did not report the mean hemoglobin level of patients and did not assess the sensitivity of the A1C cutoff value in the subpopulation of recipients with anemia (56). Therefore, screening with FPG levels should be performed at the intervals described above, and an OGTT could be considered in patients with IFG at 3 and 6 months (as the higher risk of NODAT is present during the first 6 months after transplantation). Additionally, A1C could be assayed at 3 and 6 months, and then yearly, to improve NODAT diagnostic accuracy.

NODAT patients should be monitored with A1C assay measured routinely every 3 months and with FPG at each visit. Although there is no study evaluating whether achieving a specific A1C target translates into a better survival, maintaining patients with NODAT <7% is reasonable (1). The cautious interpretation of A1C in patients with anemia should be once more emphasized. Self-monitoring of blood glucose should ideally be performed in patients treated by insulin or oral hypoglycemic agents, as in type 2 diabetic patients (1).

Management of immunosuppression

We suggest an algorithm for the management of immunosuppression in order to both minimize the risk of developing NODAT and improve established NODAT, based on published data (see section SPECIFIC FACTORS RELATED TO TRANSPLANTATION) and our own experience (Fig. 1). The choice of immunosuppression should first take into account the immunological risk of the patients in order to avoid acute rejection. In patients with a low immunological risk and a high risk of NODAT, the first choice might be a cyclosporine- or belatacept-based immunosuppressive regimen. In patients with a high immunological risk (see Fig. 1 for definition), tacrolimus is still preferred (57,58). In patients who develop NODAT, a reduction in the exposure to diabetogenic drugs such as CNIs and glucocorticoids should be done carefully and progressively. Likewise, mycophenolic acid (MPA) should be closely monitored to avoid rejection in the context

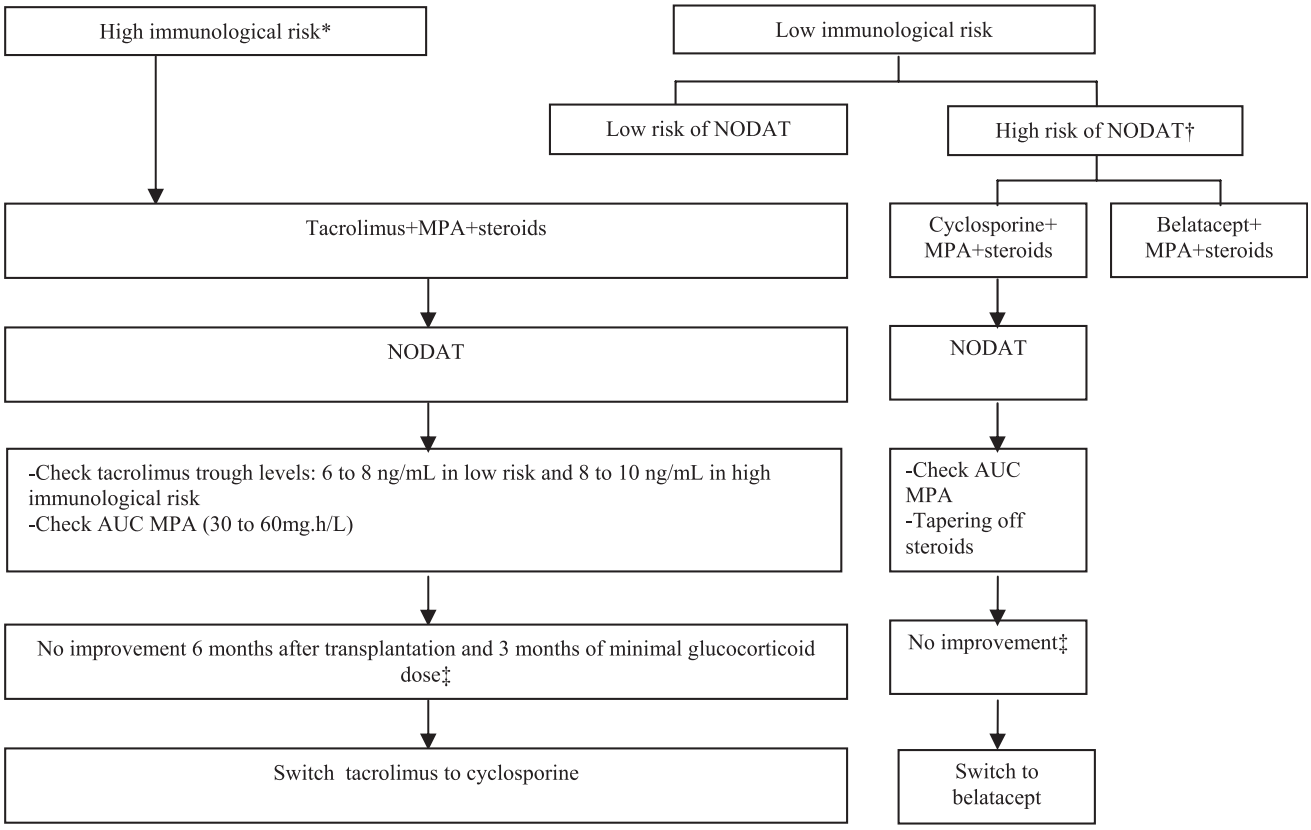

Figure 1—*Management of immunosuppression to minimize the risk of developing NODAT and to improve established NODAT. *Third or fourth transplantation, second transplantation if the first was lost <2 years, presence of anti-HLA antibodies/high panel-reactive antibody, five to six HLA mismatches. †Age >45 years, black or Hispanic ethnicity, familial history of type 2 diabetes, personal history of gestational diabetes or NODAT, metabolic syndrome, abnormal pretransplant fasting or 2-h postload OGTT plasma glucose, BMI >30 kg/m^2, positive hepatitis C serology. ‡NODAT requiring insulin or A1C level >7% with glucose-lowering agent.*

of glucocorticoid tapering. Area under the curve of MPA should be maintained between 30 and 60 mg · h · L^{-1} (59). In tacrolimus-treated patients whose diabetes is difficult to control (A1C >7% and/or insulin requirement), a switch to cyclosporine might be considered in cases of high immunological risk, whereas a switch to belatacept might also be considered in cases of low immunological risk. Given the lower MPA exposure under cyclosporine than under tacrolimus, area under the curve of MPA should be closely monitored in switched patients.

Pharmacological management of hyperglycemia

Currently, it is considered that patients with an A1C assay ≥6.5% should start glucose-lowering agents (54). As for type 2 diabetes, a stepwise approach should be adopted. The first step includes hygienodietetic recommendations (weight control, diet, and exercise). The second step is the initiation of an oral agent in monotherapy. The choice of the drug should take into account the patient-specific factors, graft function (some drugs or active metabolites are eliminated by the kidney), specific side effects, and potential pharmacokinetic interactions with immunosuppressive drugs (mainly interaction with CNI or *m*-TOR through metabolization by cytochrome P450, family 3, subfamily A, polypeptide 4/5 [CYP3A4/5]). Recommendations for all available glucose-lowering agents (beside insulin) are summarized in Table 2 (1,55,60). Almost all oral agents can be used, except for the first-generation sulfonylureas (because they accumulate and induce hypoglycemic episodes) and biguanides (because they induce lactic acidosis). Biguanides should be avoided if the glomerular filtration rate is <60 mL/min. Gliquidone, the most-prescribed agent for kidney transplants in our institution, is efficient, well tolerated, and has no interaction with immunosuppressive drugs. The third step is a combination of oral agents with different mechanisms of actions. Combination therapy has not been investigated and compared in kidney allograft recipients. The last step is the initiation of insulin with or without oral agents. If individualized goals for glucose control are not achieved within 2–4 months, lifestyle interventions should be reassessed and patients should move to the next step.

CONCLUSIONS—In summary, NODAT and IFG should be defined according to the modified ADA 2003 criteria for the diagnosis of type 2 diabetes. A1C assay is not recommended for the diagnosis. A1C assay should be used for the monitoring of NODAT, with a target <7%. A1C assay should, however, be interpreted with caution in recipients with anemia. NODAT and type 2 diabetes share many risk factors: older age, higher BMI, African or Hispanic ethnicity, family history, presence of a metabolic syndrome feature, positive HCV serology, T-variant of the *TCF7L2* gene, and hypomagnesemia. The majority of NODAT cases appear during the first 6 months posttransplantation, when patients

Table 2—*Glucose-lowering agents used in kidney transplant patients with NODAT*

Class	Drug	Avoid/dose adjustment	Drug-drug interaction
First-generation sulfonylureas	All	Avoid	Increase CsA levels
Second-generation sulfonylureas	Glipizide, Gliclazide	—	Increase CsA levels
	Gliquidone	—	—
	Glibenclamide (Glyburide)	Avoid if GFR <50 mL/min/1.73 m^2	Increase CsA levels
	Glimepiride	Start with 1 mg/d	Increase CsA levels
	Glisentide	Avoid if advanced CKD	—
Biguanides	Metformin	Avoid if GFR <60 mL/min/1.73 m^2	—
	Phenformin	Avoid	—
α-Glucosidase inhibitors	Acarbose, Miglitol	Avoid if GFR <30 mL/min/1.73 m^2	—
Meglitinides	Repaglinide	Cautious titration (start 0.5 mg if GFR <40 mL/min/1.73 m^2)	Increased levels of repaglinide with CsA
	Nateglinide	Cautious use if GFR <60 mL/min/1.73 m^2	Increased levels of nateglinide with CsA
Thiazolidinediones	Pioglitazone,	Avoid if heart failure	—
	Rosiglitazone	Avoid if heart failure	—
Incretin mimetic	Exenatide	Avoid if GFR <30 mL/min/1.73 m^2	—
Analog of amylin	Pramlintide	Avoid if GFR <20 mL/min/1.73 m^2	—
DDP-4 inhibitor	Sitagliptin	Reduce dose to 50 mg/d (GFR 50–30 mL/min/1.73 m^2), 25 mg (GFR <30 mL/min/1.73 m^2)	Metabolized by CYP3A4/5*
	Vildagliptin	Avoid if dialyzed, caution if GFR <60 mL/min/1.73 m^2 (need more data)	No interaction with CYP3A4/5 substrates
	Saxagliptin	2.5 mg daily if GFR <50 mL/min/1.73 m^2	Metabolized by CYP3A4/5*

Exenatide and pramlintide are administered subcutaneously. CKD, chronic kidney disease; CsA, cyclosporine; DDP-4, dipeptidyl peptidase 4; GFR, glomerular filtration rate. *Possible increase in the levels of cyclosporine, tacrolimus, and *m*-TOR inhibitors.

are treated with high doses of immunosuppression. Thus, immunosuppressive drugs (CNIs, glucocorticoids, and *m*-TOR inhibitors), by inducing an insulin secretion defect and insulin resistance, probably act as triggers for glucose metabolism abnormalities in patients at risk. The predictive value of a phenotypic score as well as the place of biomarkers like the *TCF7L2* polymorphism or the magnesium level remain to be evaluated prospectively. Likewise, interventional strategies that might decrease the risk of NODAT and are focused on modifiable risk factors (BMI, metabolic syndrome components, and immunosuppression mainly) should be prospectively investigated. In patients at risk for NODAT or with confirmed NODAT, exposure to diabetogenic immunosuppressive drugs should be reduced carefully and be balanced with the risk of acute rejection.

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