Twelve-Month and Five-Year Analyses of Risk Factors for New-Onset Diabetes After Transplantation in a Group of Patients Homogeneous for Immunosuppression

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ABSTRACT

Objective. In the case of new-onset diabetes after transplantation (NODAT) development, it is suitable to reduce calcineurin inhibitors and corticosteroids. But change of immunosuppression can be counterproductive and can cause development of rejection and leads to further NODAT aggravation.

Methods. We retrospectively evaluated risk factors after kidney transplantation. Comparison groups were homogeneous in terms of administered immunosuppression, and individual monitored parameters were not distorted by the immunosuppression administered.

Results. In the 12-month analysis we identified these risk factors for NODAT: age at the time of transplantation, 50–59 years ($P = .0034$); age at the time of transplantation, $\geq$60 years ($P < .0001$); positive family anamnesis for diabetes mellitus type 2 ($P < .0001$); body mass index at the time of transplantation, $\geq$30 kg/m^2 ($P = .0236$); prediabetes before transplantation ($P < .0009$); and proteinuria, >0.15 g/d ($P < .0002$). In the 5-year analysis, we identified patients who were diagnosed with NODAT after the 1st year. We identified age $\geq$50 years at the time of transplantation to be an independent risk factors for NODAT.

Conclusions. It is advisable to carry out the oral glucose tolerance test even in patients with physiologic levels of fasting glycemia.

NEW-ONSET DIABETES AFTER TRANSPLANT (NODAT) is associated with increased mortality and morbidity, and, in particular, higher rates of cardiovascular disease and infection, which are the leading causes of death in renal transplant recipients. International consensus guidelines regarding the definition of new-onset diabetes mellitus after transplantation were published in 2003 [1,2]. That diagnostic clarification was important because the use of various definitions before that publication made it difficult to assess the incidence of NODAT or the importance of different risk factors. Except for the glycated hemoglobin (Hb_{A1c}), which should not be used before 3 months after transplantation, the guidelines use standard World Health Organization (WHO) and American Diabetes Association (ADA) criteria for diagnosis of diabetes mellitus and impaired glucose tolerance [3]. The Hb_{A1c} is not recommended before 3 months after transplantation, because the test may not be valid until new hemoglobin has been synthesized and glycated for the appropriate period in the diabetogenic post-transplantation setting [2]. Diagnostic criteria for NODAT are presented in Table 1.

The real incidence of NODAT after kidney transplantation is difficult to establish, because different classification systems and definitions have been used over the years. Several risk factors, already present before or arising after transplantation, in particular, the immunosuppressive regimens used, have been related to the development of

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Table 1. American Diabetes Association Diagnostic Criteria for Diabetes Mellitus

Diagnostic Criteria for Diabetes Mellitus
Symptoms of diabetes mellitus: polyuria, polydipsia, unexplained weight loss
OR
Fasting blood glucose ≥7 mmol/L
OR
Glycemia ≥111 mmol/L in the 2nd hour of OGTT

Abbreviation: OGTT, oral glucose tolerance test.

NODAT. However the responsible pathogenic mechanisms are still far from perfectly known. Awareness of NODAT and of NODAT-related factors is of paramount importance for clinicians to distinguish 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 antihyperglycemic therapy is mandatory to reach a tight glycemic control, which contributes to significantly reducing post-transplantation mortality and morbidity [4].

A specific algorithm for immunosuppressive protocol and immunosuppressive regimens in risk patients should eliminate NODAT outbreak. Naturally, to avoid rejection, it is necessary to take the immunologic risk into consideration when choosing immunosuppression. Cyclosporine is suitable in patients with low risk of rejection and high risk of NODAT outbreak. Conversely, tacrolimus is recommended in patients with high risk of rejection [5,6]. In case of NODAT development, it is suitable to reduce calcineurin inhibitors (CNIs) and corticosteroids, but it is then beneficial to increase (or add to treatment) mycophenolate mofetil to maintain sufficient immunosuppression. In patients who are treated with tacrolimus and in whom NODAT is controlled with difficulty, there is an alternative to change the treatment to cyclosporine. In the case of a patient in the early post-transplantation period, or in a patient with high immunologic risk (history of acute rejection, present acute rejection,

Table 2. Risk Factors for NODAT Development [16]

Nonmodifiable Risk Factors for NODAT	Modifiable Risk Factors for NODAT
Age at time of transplantation	Immunosuppression (corticosteroids, CNI, mTORi)
Population (African-American, Hispanic)	Obesity
Positive family history for DM2	Hypertriacylglycerolemia
Male sex	Arterial hypertension
HLA A30, B27, B42	Hypomagnesemia
Higher number of HLA mismatches	Prediabetes before transplantation
Polycystic kidney disease	Viral hepatitis C
	Cytomegalovirus infection
	Basiliximab in induction
	Proteinuria

Abbreviations: NODAT, new-onset diabetes after transplantation; DM2, diabetes mellitus type 2; CNI, calcineurin inhibitors; mTORi, mammalian target of rapamycin inhibitors.

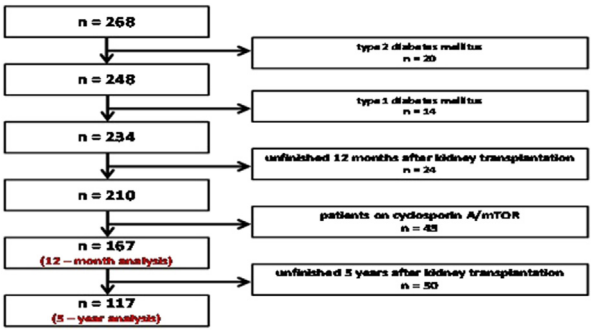

Fig 1. Inclusion of patients.

secondary and higher kidney transplantation, etc) change of immunosuppression (tacrolimus to cyclosporine) can be counterproductive. Reduction of immunosuppression in high-risk patients can cause development of rejection, and consequent treatment of rejection eventually leads to further NODAT deterioration.

For that reason we focused on patients who were treated with tacrolimus, mycophenolate mofetil (or mycophenolate sodium), and corticosteroids throughout the whole monitored period and, in this homogeneous group regarding immunosuppression, identified risk factors for NODAT (both avoidable and unavoidable).

MATERIALS AND METHODS

We retrospectively evaluated selected risk factors for NODAT in 167 patients (all of European racial ancestry) after primary kidney transplantation (KT) from a dead donor (in the years 2003–2012) at the Transplant Center Martin.

In each patient we determined age at the time of transplantation, sex, family history of diabetes mellitus type 2 (DM2; parents, siblings, grandparents), compatibility index and number of HLA mismatches, presence of risk HLAs (A30, B27, B42), and basic diagnosis of kidney failure (we differentiated patients with adult-onset polycystic kidney disease [APKD]), and we identified recipients who received kidneys from expanded-criteria donors (ECDs). We recorded the presence of avoidable risk factors 12 months after KT and 5 years after KT. We further recorded the type of immunosuppression and average levels during the monitored period, and average dose of prednisone, and we also determined if the patient had been treated with methylprednisolone pulses (except for induction therapy) and the dose size. We monitored weight, body mass index (BMI), and weight gain 12 months and 5 years after transplantation. We also recorded average levels of triacylglycerols and cholesterol and the presence of arterial hypertension. And we determined average levels of magnesemia and proteinuria during the 1st 12 months and 5 years from transplantation. From each patient's history we also recorded the presence of fasting hyperglycemia/impaired glucose tolerance (prediabetes), cytomegalovirus (CMV) viremia (determined by means of polymerase chain reaction [PCR]) in each month during the 1st 12 months and 5 years after transplantation, and we identified patients with hepatitis C virus (HCV) RNA PCR positivity. Twelve months and 5 years after transplantation, we evaluated graft function by means of estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease–Epidemiology Collaboration formula. In each patient we