Pretransplant Risk Score for New-Onset Diabetes After Kidney Transplantation

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OBJECTIVE—New-onset diabetes after kidney transplantation (NODAT) has adverse clinical and economic implications. A risk score for NODAT could help identify research subjects for intervention studies.

RESEARCH DESIGN AND METHODS—We conducted a single-center retrospective cohort study using pretransplant clinical and laboratory measurements to construct a risk score for NODAT. NODAT was defined by hemoglobin A_{1c} (HbA_{1c}) ≥6.5%, fasting serum glucose ≥126 mg/dL, or prescribed therapy for diabetes within 1 year posttransplant. Three multivariate logistic regression models were constructed: *1*) standard model, with both continuous and discrete variables; *2*) dichotomous model, with continuous variables dichotomized at clinically relevant cut points; and *3*) summary score defined as the sum of the points accrued using the terms from the dichotomous model.

RESULTS—A total of 316 subjects had seven pretransplant variables with $P < 0.10$ in univariate logistic regression analyses (age, planned corticosteroid therapy posttransplant, prescription for gout medicine, BMI, fasting glucose and triglycerides, and family history of type 2 diabetes) that were selected for multivariate models. Areas under receiver operating curves for all three models were similar (0.72, 0.71, and 0.70). A simple risk score calculated as the sum of points from the seven variables performed as well as the other two models in identifying risk of NODAT.

CONCLUSIONS—A risk score computed from seven simple pretransplant variables can identify risk of NODAT.

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New-onset diabetes after kidney transplantation (NODAT) occurs frequently in the 1st year after transplant (incidence 15–25%) and has a significant impact on allograft and patient survival, health care costs, and quality of life (1–4). In a large, retrospective study of U.S. Renal Data System data, NODAT was associated with a 60% increase in subsequent graft failure, an almost 90% increase in death rates (3), and frequent diabetes complications (5). NODAT incurs an extra Medicare payment of $21,500 per case by 2 years' posttransplant (4).

These are compelling reasons for prevention. However, clinical trials of prevention strategies may have greater power if conducted among patients at highest risk. Because the incidence of NODAT is 5 to 6 times higher the 1st year after transplant (15–25%), compared with the annual incidence thereafter (4–6%), pretransplant risk factors may play significant roles in the development of NODAT. Previous studies have identified many risk factors for NODAT including older age, minority race, higher BMI, corticosteroid use, family history of type 2 diabetes (T2DM), hepatitis C seropositivity, male donor, and elevations in pretransplant fasting glucose and triglycerides (1–3).

We previously found inpatient hyperglycemia and its treatment with insulin immediately after transplantation to predict NODAT (6). Ideally, we could identify those at highest risk of NODAT well before transplantation to provide early intervention. Our aim was therefore to construct a risk score for NODAT using simple pretransplant clinical and laboratory tests. Such a score could help identify patients at highest risk of NODAT for intervention or enrollment in prevention clinical trials.

RESEARCH DESIGN AND METHODS

Study cohort

We conducted a retrospective cohort study of all adult, nondiabetic patients undergoing a first kidney transplant at the Mayo Clinic Arizona between June 1999 and January 2008. All patients had at least a 1-year follow-up posttransplant. After institutional review board approval, we identified the study cohort by systematic chart review. Absence of diabetes before transplantation was documented in the form submitted to United Network for Organ Sharing, with the information obtained from documentation provided by a medical care provider before transplant. Additionally, all patients had a fasting plasma glucose <126 mg/dL and HbA_{1c} <6.5% at pretransplant testing.

Immunosuppression after kidney transplantation

We used steroid-based maintenance immunosuppression before June 2003, and afterward we used rapid steroid withdrawal maintenance immunosuppression except in patients who required prednisone for nontransplant indications or who were at high risk of rejection for immunologic reasons (positive cross-match); thus, the cohort included patients prescribed or not prescribed maintenance prednisone. Induction therapy with rabbit antithymocyte

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immunoglobulin or basiliximab was used in rapid steroid withdrawal patients and some patients who were continued on maintenance steroids. All patients received a 5-day tapering course of glucocorticoids (methylprednisolone intravenously 500 mg on day 1, 250 mg on day 2, 125 mg on day 3, oral prednisone 60 mg on day 4, and 30 mg on day 5, then discontinued if in the rapid steroid withdrawal group). Patients requiring ongoing steroid therapy received the same initial 5-day corticosteroid treatment with tapering of prednisone over 8–12 weeks to maintenance with 5 mg prednisone daily. Tacrolimus was initiated when serum creatinine dropped >30%; the day of tacrolimus initiation was variable for each patient. All patients, including those with delayed graft function, began tacrolimus before discharge. Mycophenolate mofetil and tacrolimus were the maintenance immunosuppressants for all patients who did not require ongoing steroid therapy.

Definition of NODAT

NODAT was diagnosed if a patient had HbA_{1c} ≥6.5%, fasting venous plasma glucose ≥126 mg/dL, or was receiving diet or medical therapy for diabetes between 1 month and 1 year posttransplant. HbA_{1c} ≥6.5% has recently been adopted as a new diagnostic criterion for diabetes (7), and we used these composite diagnostic criteria previously (6). The time period for development of NODAT (1 month to 1 year posttransplant) was chosen because patients are clinically stable and on stable doses of immunosuppression by 4 weeks' posttransplant, and this period excludes patients who developed transient hyperglycemia in the immediate posttransplant period as a result of stress of surgery and/or high-dose corticosteroid therapy. Additionally, the highest incidence of NODAT occurs within the 1st year posttransplant (3,4).

Data analyses

In addition to demographic, anthropometric, and pretransplant laboratory assessments, we ascertained pretransplant if corticosteroids would be used posttransplant for nontransplant indications or as maintenance immunosuppression. Logistic regression was used to determine the risk of NODAT associated with pretransplant patient characteristics. We first constructed univariate models to determine the association of individual pretransplant variables with development of NODAT. Variables significant at $P < 0.10$ in univariate models were then included in multivariate analyses. We conducted two multivariate analyses: *1*) a standard model, in which continuous variables and discrete variables were included without categorization; and *2*) a dichotomized model, where variables were assigned binary values, using clinically relevant cut points.

Three models of the pretransplant risk score were then created from the multivariate logistic regression models: *1*) a standard model, in which both continuous and discrete variables were included and weighted according to the β-coefficients in the multivariate logistic model; *2*) a dichotomous model, in which continuous variables were dichotomized based on clinically relevant cut points (values below and above the cut point were assigned a value of 0 and 1, respectively) and were weighted according to the β-coefficients in the multivariate logistic model; and *3*) a summary score calculated as the sum of the points accrued by each individual using the dichotomized measures from the dichotomous model. Receiver operating curves (ROCs) were created for each of the three models to compare the accuracy of each in predicting NODAT. Statistical analyses were conducted with Stata statistical software, version 10.0 (StataCorp, College Station, TX) or SAS version 9.2.

RESULTS—From June 1999 to January 2008, 318 nondiabetic patients underwent kidney transplantation. Patient characteristics and their associations with NODAT are described in Tables 1 and 2, respectively. Median hospital stay after transplantation was 4 days. Maintenance immunosuppression was predominantly tacrolimus and mycophenolate mofetil: 93 and 86% were prescribed tacrolimus at 4 and 12 months' posttransplant, respectively. The 1-year incidence of NODAT was 27% (85/318).

In univariate logistic regression analysis of 316 patients in whom all variables were measured, seven pretransplant risk factors—older age, higher pretransplant fasting glucose, triglycerides and BMI, family history of T2DM, use of gout medicines, and use of corticosteroids posttransplant (ascertained pretransplant)—were associated with higher risk of NODAT ($P < 0.10$). Risk factors with $P \geq 0.10$ were not included: minority race, dialysis modality pretransplant, donor type, duration of dialysis, uric acid, and hepatitis C seropositivity.

Multivariate logistic regression models were built using the seven variables (Table 3). Pretransplant age, fasting glucose, fasting triglycerides, and use of corticosteroids posttransplant were associated with increased risk of NODAT in multivariate analyses in both the standard model and in the dichotomized model (Table 3).

The risk calculators created from the multivariate analyses were as follows:

Table 1—*Clinical characteristics of the study participants*

Variable	Study cohort (N = 318)
Age (mean ± SD) (years)	49 ± 15
Female sex (%)	43
Race/ethnicity (%)	
White	71
African American	7
American Indian	6
Hispanic	14
Other	2
Family history of T2DM (%)	19
Dialysis modality pretransplant (%)	
Hemodialysis pretransplant	62
Peritoneal dialysis pretransplant	12
Preemptive transplant	25
Hepatitis C seropositivity (%)	4
Deceased donor (%)	36
Pretransplant BMI (mean ± SD) (kg/m^2)	27 ± 6
Pretransplant fasting glucose (mean ± SD) (mg/dL)	92 ± 11
Use of gout medicines (%)	12
Pretransplant triglycerides (median [intraquartile range]) (mg/dL)	157 (110–234)
Corticosteroid therapy posttransplant (%)	42

Table 2—*Association of variables and development of NODAT*

Variable	Total number	Number (%) with NODAT
Age ≥50 years at time of transplant		
No	148	30 (20)
Yes	170	55 (32)
Pretransplant BMI ≥30 kg/m^2		
No	234	56 (24)
Yes	84	29 (35)
Pretransplant fasting glucose ≥100 mg/dL		
No	246	55 (22)
Yes	72	30 (42)
Planned corticosteroid maintenance posttransplant		
No	183	41 (22)
Yes	135	44 (33)
Family history of T2DM		
No	259	64 (25)
Yes	59	21 (36)
Pretransplant triglycerides ≥200 mg/dL		
No	212	44 (21)
Yes	106	41 (39)
Pretransplant use of gout medicine		
No	281	69 (25)
Yes	37	16 (43)

Standard model (continuous and dichotomized variables weighted with β-coefficients)

Probability of NODAT = 1/ 1 + e(−fn[**x**]) where f[**x**] = −9.6288 + 0.02397 · age (years) at transplant + 0.5624 (if family history of T2DM) + 0.7624 (if steroid maintenance) + 0.03021 · pretransplant fasting glucose (mg/dL) + 0.0259 · pretransplant BMI (kg/m^2) + 0.4467 · $\log_2$ pretransplant triglyceride (mg/dL) + 0.7481 (if gout medicine used pretransplant).

Dichotomous model (variables dichotomized and weighted with β-coefficients)

Probability of NODAT = 1/ 1 + e(−fn[**x**]) where f[**x**] = −2.4684 + 0.5396 (if transplant age ≥50 years) + 0.4914 (if family history of T2DM) + 0.7410 (if steroid maintenance) + 0.7285 (if pretransplant fasting glucose ≥100 mg/dL) + 0.3693 (if pretransplant BMI ≥30 kg/m^2) + 0.8440 (if pretransplant triglyceride ≥200 mg/dL) + 0.7917 (if gout medicine used pretransplant).

Summary score model (variables dichotomized and counted)

One point was assigned to each of the following: age above 50 years, family history of T2DM, pretransplant assignment to corticosteroid maintenance protocol, pretransplant fasting glucose ≥100 mg/dL, pretransplant BMI ≥30 kg/m^2, pretransplant triglycerides ≥200 mg/dL, and use of gout medicine. Summary score for each patient ranged from 0 to 7. The risk of developing NODAT increases with higher score.

Areas under the ROC for predicting NODAT were 0.72, 0.71, and 0.70 for the three models, respectively, and not significantly different from each other (Fig. 1).

The summary scores were also grouped as low (0 or 1), intermediate (2 or 3), or a high-risk group (4, 5, or 6); prediction of NODAT by group is shown in Fig. 2.

CONCLUSIONS—A simple risk score using the sum of seven dichotomized pretransplant risk factors is as good at predicting NODAT as a standard multivariate model using continuous variables in this sample from one institution. A score of 0–7, calculated from pretransplant age, family history of T2DM, BMI, fasting glucose and triglycerides, use of gout medicine, and predicted use of corticosteroids posttransplant (nontransplant indications or immunologic indications) predicted incidence of NODAT at 1 year posttransplant. The risk of NODAT ranged from 7%, for a score of 0, to 56%, for a score of ≥4. A simple summary score is valuable because it demonstrates the additive nature of the individual variables and integrates the impact of single baseline variables on development of NODAT.

We constructed three logistic regression models for predicting NODAT, ranging from a model that used continuous variables as such to a simple score that adds the number of variables having values above a cut point. We included a dichotomous model as an intermediate, in which each variable was dichotomized but weighted according to its importance rather than weighted equally as in the summary score. We anticipated that the continuous model would provide the best predictive power and the summary score the least. Although this was the case, surprisingly there were no important or statistically significant differences in the predictive abilities of the three models, as judged by areas under the ROC (Fig. 1). On the basis of these results, the simplest model can be used at the bedside for rapid evaluation without extensive computation. Before applying this to other populations or settings, however, we recommend validation in that population or setting.

Serum uric acid and gout have been identified as risk factors for T2DM but have not been reported as risk factors for NODAT. Interestingly, serum uric acid itself did not predict NODAT, but gout medication did. Most patients with end-stage renal disease undergoing dialysis have elevated serum uric acid levels because of renal failure and inadequate clearance by dialysis, but do not develop gout. Rather, other factors predict gout in patients with end-stage renal disease, including African American ethnicity, older age, BMI, female sex, hypertension, and alcohol use (8). In end-stage renal disease patients undergoing dialysis therapy, gout is a risk factor for mortality (8) but has not been reported as an independent risk factor for diabetes. Alternatively, the medicines for gout may themselves be diabetogenic, but we are unaware of evidence for this. This question should be pursued in studies that are large enough to include users of different types of gout medicines.

These risk scores were developed primarily for future application in clinical trials to evaluate measures to prevent NODAT. Like many other risk calculators, these were created for a specific population of patients scheduled to undergo kidney transplantation and may not apply to general patient populations. However, the risk scores may eventually prove to be clinically useful in patients similar to those in our cohort. Of the pretransplant risk factors for NODAT that emerged from this study, only BMI, fasting glucose, and triglycerides are amenable to

Table 3—*Logistic regression models: association of continuous variables and dichotomized variables to development of NODAT*

Variable	Model 1: standard model with continuous and discrete variables			Model 2: continuous variables dichotomized		
	Definition	Univariate*	Multivariate*	Definition	Univariate*	Multivariate*
Age at transplant	Age per 10 year increase	1.33 (1.11–1.59), 0.002	1.27 (1.04–1.55), 0.02	Age at transplant ≥50 years	1.88 (1.13–3.14), 0.02	1.72 (0.97–3.02), 0.06
Pretransplant BMI	Per 1 unit increase	1.05 (1.01–1.10), 0.02	1.03 (0.98–1.08), 0.30	BMI ≥30 kg/m^2	1.68 (0.98–2.88), 0.06	1.45 (0.80–2.61), 0.22
Predicted steroid maintenance immunosuppression	Yes	1.67 (1.02–2.76), 0.04	2.14 (1.24–3.71), 0.007	Yes	1.67 (1.02–2.76), 0.04	2.10 (1.22–3.61), 0.008
Pretransplant fasting glucose (mg/dL)	Per 10 mg/dL increase	1.45 (1.16–1.83), 0.001	1.35 (1.06–1.73), 0.02	≥100 mg/dL	2.48 (1.42–4.33), 0.001	2.07 (1.12–3.85), 0.02
Pretransplant fasting triglyceride	Log transformed (per twofold higher)	1.61 (1.19–2.17), 0.002	1.56 (1.13–2.17), 0.008	≥200 mg/dL	2.41 (1.44–4.02), 0.001	2.33 (1.33–4.06), 0.003
Pretransplant use of gout medicine	Yes	2.34 (1.16–4.74), 0.02	2.11 (0.98–4.54), 0.06	Yes	2.34 (1.16–4.74), 0.02	2.21 (1.01–4.81), 0.05
Family history of T2DM	Yes	1.68 (0.92–3.08), 0.09	1.76 (0.91–3.39), 0.09	Yes	1.68 (0.92–3.08), 0.09	1.64 (0.85–3.13), 0.14

*Table values are odds ratio (95% CI), *P* value for the given variable.

Figure 1—*Comparison of the ROCs of the three models.*

modification. Treatment for gout, although a significant risk factor, is more likely a marker of genetic and metabolic abnormalities, some of which may be modifiable by dietary and other measures. Use of corticosteroid therapy posttransplant may or may not be modifiable, depending on its indications.

Whether lifestyle modification or medicines will reduce the risk for NODAT remains an important question. The Diabetes Prevention Program and other clinical trials showed that T2DM could be delayed or prevented (9–13). Because NODAT has a significant impact on graft survival, patient survival, and cost, prevention of NODAT may be very valuable. The next step will be to test risk factor modifications in clinical trials. If prevention of NODAT in patients at risk is possible, the simple risk score could be used to identify those pretransplant patients at the greatest need of intervention. The question of which patients should be enrolled in such clinical trials or given interventions, however, depends on more than their estimated risk. Although our simple risk score separated those with low risk (12% developed NODAT) from those at high risk (56% developed NODAT), the majority of the cases (50 of 85) occurred in those at intermediate risk (Fig. 2). Thus, if safe, effective, and affordable interventions were available, consideration should be given to providing them to all transplant patients. On the other hand, if the only effective interventions had serious side effects or other costs, they might be appropriate only for those at higher risk.

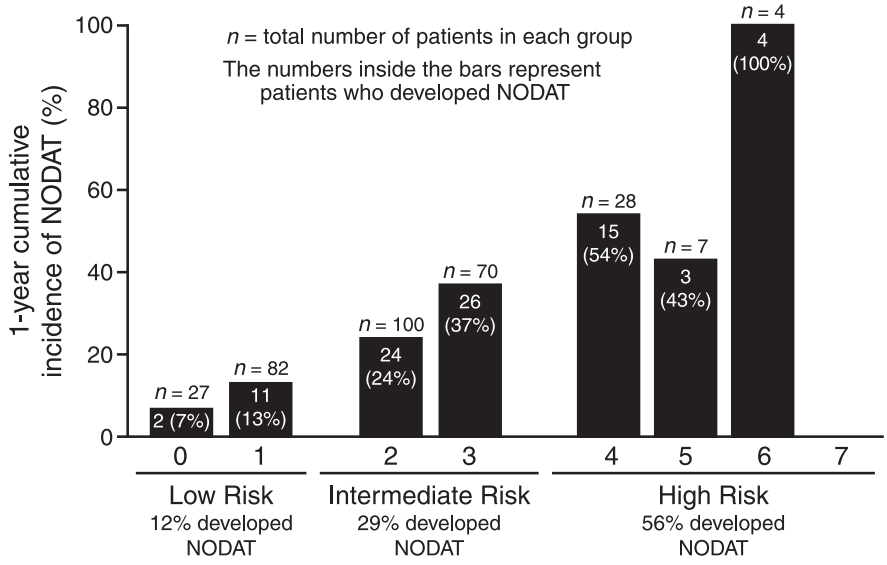

Figure 2—*Association of the pretransplant risk score with development of NODAT.*

There are a number of limitations to our study. First, we used a composite definition of NODAT (fasting venous glucose ≥126 mg/dL, HbA_{1c} ≥6.5%, or drug therapy for diabetes) rather than the American Diabetes Association diagnostic criteria. Although our criteria have been used previously (6), our definition differed from the 2010 American Diabetes Association criteria (7) by not using an oral glucose tolerance test. However, HbA_{1c} ≥6.5% has recently been suggested as the sole diagnostic criterion for diabetes (14). Had we used an oral glucose tolerance test, it is likely that some of our patients would have been excluded for having pretransplant diabetes and some additional ones would have been diagnosed with NODAT. Second, because precise time to event was not available, we used logistic regression rather than time-to-event analysis to develop our risk score. This was appropriate because of the short time period to event (within 1 year) and no loss to follow-up before 1 year posttransplant. Finally, this study was performed in a single center with a cohort of 318 patients. These results should be replicated in other kidney transplant populations.

In conclusion, kidney transplantation is widely acknowledged to be the best therapy for end-stage renal disease, but its advantages are severely undermined by NODAT. NODAT diminishes patient and allograft survival and quality of life and increases the cost of care. The use of a simple summary risk score can identify patients at highest risk of NODAT so that interventions may begin. The pretransplant risk factors for future NODAT overlap with those for T2DM in general, thus emphasizing the need for future clinical intervention studies similar to the Diabetes Prevention Program to decrease NODAT.

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