Risk Factors for Development of New-Onset Diabetes Mellitus After Kidney Transplantation

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Background. New-onset diabetes mellitus after kidney transplantation (NODM) is an important co morbid condition that is associated with inferior graft and patient survival. The objective of this study was to identify donor, recipient and transplant factors, and choices of immunosuppression associated with development of NODM using Organ Procurement Transplant Network/United Network of Organ Sharing database (OPTN/UNOS).

Methods. From January 2004 to December 2005, 15,309 adult kidney transplants alone with at least one follow-up report as of March 2006 were identified in the OPTN/UNOS database. Among these, 1,581 patients developed NODM during the follow-up period. We examined the risk factors of NODM using multivariate Cox regression analysis using the time to diagnosis of NODM as a time-varying end point. Other events such as graft loss, patient death, and lost to follow-up were censored.

Results. NODM was reported in 10% in our study population with mean follow-up time of 306 days. After adjusting for other known factors, independent factors associated with the development of NODM included recipient age (29% increase of relative risk [RR] for every 10-year age increment), obesity (RR=1.39 for body mass index [BMI] 25–30 and RR=1.85 for BMI>30 vs. BMI<25), tacrolimus use (RR=1.50), hepatitis C virus (HCV) positivity (RR=1.42), and African-American recipients (RR=1.32). Alemtuzumab was associated with a lower risk of NODM (RR=0.52).

Discussion. Using OPTN/UNOS database, we identified risk factors for development of NODM. Some of these factors are potentially modifiable, including obesity, HCV infection, and the use of tacrolimus. Clinical trials are needed to assess whether modifying these "modifiable risk factors" will indeed prevent NODM.

Keywords: Kidney transplant, Diabetes mellitus, Post transplant complications, Outcomes.

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Over the last several years, the number and severity of acute rejection episodes in kidney transplantation, have been reduced and short-term graft survival has greatly improved (*1*). However, a similar improvement in long-term graft survival has not been observed and posttransplant complications remain common (*1*). Among these, new-onset diabetes mellitus after transplantation (NODM) is a recognized complication associated with reduction in both graft and patient survival (*2*). The reported incidence of NODM ranges from 4–20%. The wide variability may reflect different diagnostic criteria for NODM, type of transplant, immunosuppression regimens, donor and recipient characteristics, and duration of follow-up (*2–4*).

Since June 30, 2004, the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) has been collecting data on the presence of diabetes via recipient follow-up forms. Using these data, we evaluated adult primary renal transplant recipients to identify risk factors associated with the development of NODM.

MATERIALS AND METHODS

Our study population was restricted to nondiabetic adult patients (age >20 years) who received their first kidney transplants alone between January 2004 and December 2005 with at least one follow-up report. A total of 15,309 adult kidney transplants alone were identified in the OPTN/UNOS database as of March 23, 2006. Among these, 1,581 patients developed NODM during the follow-up period.

Statistical Analysis

Baseline recipient, donor, and transplant factors according to the presence of NODM are compared using the chi-square test. Survival rate was estimated using the Kaplan-Meier product limit method. The log-rank test was used for comparison of the survival curves. For diabetes mellitus (DM)-free survival, primary endpoint was the time to diagnosis of NODM as a time-varying event: $P(T>t)=S(t)$ where P is the probability of a patient whose graft is functioning through time (T) without the development of NODM (t) and S is the survival function. Other events such as patient death, graft loss, and lost to follow-up were censored in DM-free survival analysis. Univariate and multivariate DM-free survival analyses were performed using Cox proportional hazard model. For multivariate analysis, missing values were imputed as mean values for continuous variables (age and body mass index [BMI]) and as modals for categorical variables (race, hypertension, hepatitis C virus [HCV] antibody test, type of donor, the number of mismatched human leukocyte antigen [HLA]-A and -B antigens, and immunosuppressive drugs). Missing data occurred less than 5% of the time. All reported *P* values were two-tailed.

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RESULTS

A total of 15,309 adult patients received a kidney transplant between January 2004 and December 2005 and, among them, 1,581 developed NODM. The prevalence of NODM according to recipient, donor, and transplant variables are listed in Table 1.

Table 2 shows unadjusted and adjusted relative risks for developing NODM. Statistically significant risk factors in univariate analyses were included in multivariate analysis. After adjusting for potential confounding variables using multivariate analysis, factors that highly correlated with the development of NODM included older age ($P<0.001$), hypertension prior to transplant ($P<0.001$), black race ($P<0.001$), BMI >30 ($P<0.001$), HCV antibody positivity in the recipient ($P<0.001$), tacrolimus use vs. other immunosuppressant ($P<0.001$), whereas alemtuzumab induction therapy was associated with a decreased risk of NODM. However, extended criteria donor, number of HLA mismatches, and type of donor were no longer associated with an increased relative risk for the development of NODM after adjusting for other factors.

DM-free survival curves according to two major risk factors for developing NODM are shown in Figures 1 and 2. Decreased DM-free survival rate with increasing BMI can be seen in Figure 1. Unadjusted DM-free survival rates at 12 and 24 months were: 91.1% and 85.2% for BMI <25; 88.2% and 76.5% BMI 25–30; and 84.4% & 74.1% BMI >30 ($P<0.001$). The effect of obesity continued to be significant after adjusting for other risk factors as shown in Table 2 (RR=1.51 for BMI 25–30 vs. <25, $P<0.001$ and RR=1.93 BMI>30 vs. <25, $P<0.001$). For patients treated with tacrolimus during the initial hospital stay DM-free survival rates at 12 and 24 months were 87.5% and 77.9% compared with 91.6% and 84.5% for patients not treated initially with tacrolimus ($P<0.001$; Fig. 2). The effect of tacrolimus use continued to be significant after adjusting for other risk factors (Table 2, RR=1.50 vs. no tacrolimus use group; $P<0.001$).

TABLE 1. Prevalence of new-onset diabetes mellitus (NODM) according to recipient, donors, and transplant factors

	Total (%)	Percent with NODM	*P* value
Recipient			
Sex			0.03
Male	9,028 (59.0)	10.8	
Female	6,281 (41.0)	9.7	
Age			<0.001
21–30	1,973 (12.9)	4.3	
31–40	3,030 (19.8)	7.5	
41–50	3,892 (25.4)	9.9	
51–60	3,690 (24.1)	13.4	
>60	2,724 (17.8)	14.3	
Body mass index (kg/m^2)			<0.001
≤25	6,498 (42.5)	7.8	
25–30	4,967 (32.4)	11.3	
>30	3,533 (23.1)	14.1	
Missing	311 (2.0)	5.1	
Race			<0.001
White	8,541 (55.8)	9.2	
Black	3,567 (23.3)	12.8	
Hispanic	1,821 (11.9)	10.9	
Asian	785 (5.1)	11.3	
Others	595 (3.9)	9.1	
Hypertension			<0.001
No	3,428 (22.4)	8.0	
Yes	11,881 (77.6)	11.0	
HCV antibody test			<0.001
Negative	12,178 (79.6)	10.6	
Positive	646 (4.2)	15.5	
Not done/missing	2,485 (16.2)	7.5	
Donor			
ECD			<0.001
No	13,859 (90.5)	10.0	
Yes	1,450 (9.5)	13.3	<0.001
Deceased	8,732 (57.0)	11.1	
Living	6,577 (43.0)	9.3	
HLA-A, -B mismatch			0.054
0	2,195 (14.3)	9.3	
1	1,232 (8.1)	10.6	
2	3,634 (23.7)	9.7	
3	4,256 (27.8)	10.3	
4	3,992 (26.1)	11.4	
Calcineurin inhibitor			<0.001
Tacrolimus	11,178 (73.0)	11.0	
Cyclosporin	2,012 (13.1)	8.9	
None	2,119 (13.8)	8.1	
Induction			<0.001
None	4,249 (27.8)	11.4	
Thymoglobulin	5,643 (36.9)	10.5	
IL-2	4,328 (28.3)	10.3	
Alemtuzumab	1,089 (7.1)	5.5	

NODM, new-onset diabetes mellitus; HCV, hepatitis C virus; ECD, extended criteria donor; IL, interleukin.

DISCUSSION

NODM is a common and important complication after renal transplantation (*5*). A recent meta-analysis of observational studies and randomized controlled trials reported that the incidence of NODM in the first year after kidney transplantation varied from 2 to 50% (*4*). The differences in reported rates of NODM may in part be due to the varying definitions of diabetes, the duration of follow up, the type and dose of immunosuppressant, and the prevalence of predisposing risk factors (*3*). A recent study done by Kasiske et al. evaluated many of these risk factors using the United States Renal Data System/Medicare database (*2*). Although this was the largest study of its kind, only about 20% of transplant patients in the United States were included in the analysis. It is recognized that Medicare beneficiaries have a higher prevalence of risk factors for NODM compared with the non-Medicare primary population. The overall incidence of NODM in our study was 10% during the mean follow-up of 10 months compared to 16.0% at one year in the Medicare study. This difference is due to the different baseline characteristics among these two groups rather than the type of insurance as confirmed by the multivariate result showing that Medicare insurance is not an independent risk factor for NODM (data not shown).

Our study confirmed several risk factors for NODM that were previously reported in clinical trials and retrospec-

TABLE 2. Estimation of unadjusted and adjusted relative risks of developing NODM using univariate and multivariate Cox regression analyses

	Unadjusted		Adjusted	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
Recipient factors				
Female vs. male	0.87 (0.79–0.97)	0.01	0.92 (0.83–1.01)	0.10
Age (year)/10	1.29 (1.24–1.34)	<0.001	1.29 (1.24–1.34)	<0.001
Hypertension, yes vs. no	1.40 (1.23–1.59)	<0.001	1.26 (1.11–1.44)	<0.001
Black vs. others	1.38 (1.23–1.54)	<0.001	1.32 (1.17–1.48)	<0.001
BMI 25–30 vs. <25	1.51 (1.35–1.71)	<0.001	1.39 (1.24–1.57)	<0.001
BMI >30 vs. <25	1.93 (1.71–2.19)	<0.001	1.84 (1.63–2.08)	<0.001
HCV antibody, positive vs. negative	1.60 (1.31–1.96)	<0.001	1.42 (1.15–1.74)	0.001
Donor factors				
ECD vs. SCD	1.37 (1.18–1.59)	<0.001	1.07 (0.92–1.26)	0.37
Living vs. deceased	0.82 (0.74–0.90)	<0.001	0.97 (0.87–1.08)	0.62
No. of HLA-A,-B mismatch	1.05 (1.01–1.09)	0.01	1.01 (0.97–1.05)	0.63
Tacrolimus at discharge vs. others	1.45 (1.29–1.63)	<0.001	1.50 (1.33–1.68)	<0.001
Alemtuzumab vs. others	0.52 (0.40–0.67)	<0.001	0.52 (0.40–0.68)	<0.001

NODM, new-onset diabetes mellitus; RR, relative risk; CI, confidence interval; BMI, body mass index; HCV, hepatitis C virus; ECD, extended criteria donor; SCD, standard criteria donor; HLA, human leukocyte antigen.

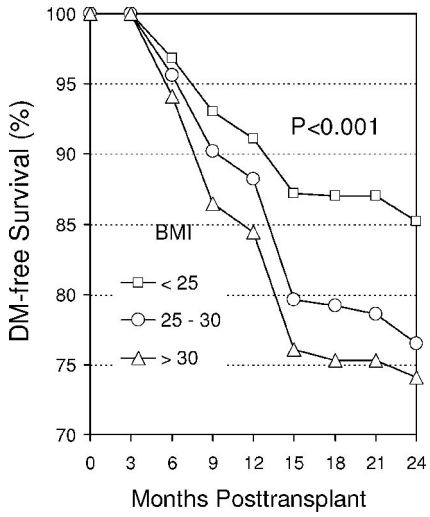

FIGURE 1. Impact of recipient body mass index (kg/m^2) on the new onset of diabetes.

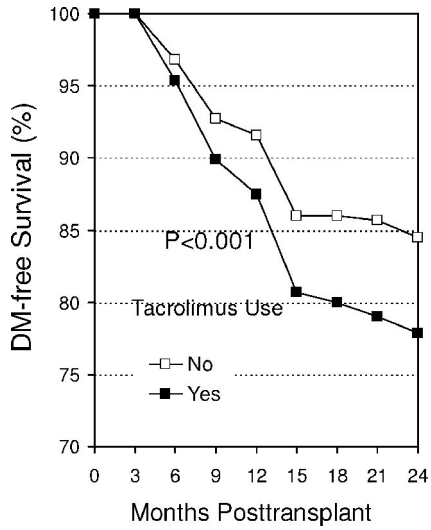

FIGURE 2. Association of tacrolimus maintenance immunosuppression at discharge and new onset of diabetes.

tive studies of registry data. Of all risk factors, only obesity, hepatitis C infection, and the type of immunosuppressive medications used are potentially modifiable. Obesity and hepatitis C infection are known factors associated with inferior transplant outcomes (*6*, *7*). Whether or not, modifying these "modifiable risk factors" would indeed result in a decrease in the incidence of NODM is not known. The type of transplant was shown to be a risk factor in univariate analysis but was not an independent risk factor in the multivariate analysis. This may be due to older recipients being more likely to receive extended donor criteria kidney compared to younger recipients. Recently, two groups have published the association between polycystic kidney disease and NODM (*8*, *9*). However, in this study, we did not find this association (result not shown). The relative risk of NODM was 49% greater in patients treated with tacrolimus compared those who were not discharged with tacrolimus. This corresponded to 2% difference in prevalence among the two groups. This finding is consistent with those of randomized controlled trials, where the incidence of NODM is consistently higher among patients treated with tacrolimus compared to cyclosporine (*10*). It was previously noted that the high incidence of NODM in tacrolimus treated recipients in early clinical trials may be in part due to the high targeted trough levels. Our study was performed using a very recent cohort of kidney transplant recipients. Even in the mid-2000s, when the target level of tacrolimus is lower than previously targeted levels, the risk of developing NODM from tacrolimus has been relatively unchanged. In contrast to the effects of tacrolimus, the use of alemtuzumab was associated with a 48% lower

relative risk of NODM compared to no induction. We are not aware of a direct effect of alemtuzumab on glucose metabolism. One potential explanation was that the use of alemtuzumab induction was more common use in calcineurin inhibitor or steroid minimization regimens, which may in turn resulted in a lower risk of NODM. Tan et al. conducted a large study on living donor transplant who received Alemtuzumab and tacrolimus monotherapy and reported an incidence of posttransplant insulin-dependent diabetes mellitus of only 0.5% (*11*). Further investigations including a multicenter trial are needed to address this question especially in deceased donor transplant.

The impact of NODM on patient and graft survival are well recognized in many studies including the above-mentioned study by Kasiske et al. (*2*). Due to the recent introduction of NODM in the UNOS follow-up forms, the effect of NODM on long-term patient and graft survival cannot be studied at this time. The data accumulating in the coming years will provide evidence on the impact of NODM on these outcomes.

This study has some important limitations. First, this retrospective analysis is subjected to flaws inherent to the nature of registry database such as reporting bias or error. For example, given the known association of tacrolimus and NODM, transplant centers may be more likely to diagnose NODM in recipients treated with tacrolimus compared to those treated with cyclosporin. Second, the definition of NODM varies according to the definition used among transplant centers in the United States. Due to the recent introduction of NODM in the OPTN/UNOS follow-up form, the follow-up time to development of NODM is relatively short and therefore, risk factors for development of late onset NODM can not be assessed nor the impact of NODM on graft and patient survival. Resolution of NODM after the manipulation of immunosuppressive medication, weight loss and life style changes was not captured in our analysis. Other important cointerventions such as angiotensin-converting enzyme inhibitors and statins use are not reported in the database and could not be examined. We also excluded the pediatric recipients from our study; therefore the results reported in this paper may not be applicable to the pediatric transplant population.

In conclusion, new-onset diabetes is still common in the U.S. kidney transplant population. Our study using OPTN/UNOS database confirmed certain known risk factors for NODM. These included demographic factors such as male gender and African American race. Potentially modifiable factors for NODM include obesity, pretransplant HCV infection, and the use of tacrolimus.

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