

Risk Factors and Outcomes of New-Onset Diabetes After Transplant: Single-Centre Experience

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Abstract

Objectives: We sought to study the prevalence, risk factors, and long-term prognosis of posttransplant diabetes mellitus.

Materials and Methods: We studied all patients with end-stage renal disease without diabetic nephropathy who received a kidney transplant and were followed-up at our center since 1983 (n=218; age, 44.3 ± 13.1 y). Patients with new-onset diabetes after transplant were compared to kidney transplant recipients without risk factors for diabetes mellitus. Patients with new-onset diabetes after transplant were divided into subgroups according to time of onset (early; < 90 d vs late, ≥ 90 d).

Results: In total, 73/218 patients (33%) developed new-onset diabetes after transplant. Patients with new-onset diabetes after transplant were significantly older (51.2 ± 11.4 vs 40.7 ± 12.5 y; $P < .001$) and had a tendency to have a higher body mass index (29.6 ± 8.7 vs 21.6 ± 7.8 kg/m²; $P = .05$) than those that did not have new-onset diabetes after transplant. In multivariate analysis, age ($P < .001$), hepatitis C virus infection ($P < .05$), family history of diabetes mellitus ($P < .03$), and tacrolimus use ($P < .001$) were independent risk factors. Five- and 10-year death censored patient survival rates were worse in those that had new-onset diabetes after transplant compared with controls (log rank, 0.04), whereas there was no difference in outcomes between the early and late subgroups.

Conclusions: The prevalence of new-onset diabetes after transplant was 33%. Age, body weight at time of transplant, tacrolimus use, family history of diabetes mellitus, and hepatitis C virus infection are independent risk factors for new-onset diabetes after transplant. New-onset diabetes after transplant has a negative effect on patient survival, irrespective of the time of onset and duration of diabetes.

Key words: Kidney transplant, Diabetes mellitus, Outcomes

Introduction

Diabetes mellitus was first described as a complication of kidney transplants over 40 years ago.¹ Despite the importance of this condition to the outcome of transplant recipients, their precise incidence is difficult to determine. This is due to the fact that there has been, until recently, no consensus regarding the definition of new-onset diabetes after transplant (NODAT). Thus different studies have used various diagnostic criteria.² Consequently, the reported incidence of NODAT varies between 2% and 53%, whereas the prevalence of diabetes in the general population is estimated at 4%.^{3, 4} Kasiske and associates studied 11 659 medicare beneficiaries who received their first kidney transplants between 1996 and 2000 and reported a cumulative incidence of NODAT of 9%, 16%, and 24% at 3, 12, and 36 months.⁵ Woodward and associates studied medicare beneficiaries transplanted between 1994 and 1998 and estimated the true incremental incidence of NODAT to be 8% to 10% during the first posttransplant year.⁶

New-onset diabetes after transplant has specific adverse effects on transplant outcome. In controlled studies, posttransplant NODM has been associated

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with an increased incidence of infectious⁷ and cardiovascular complications,^{8, 9} as well as, most pertinently, impaired long-term graft function and reduced patient and graft survival.⁵⁻¹⁶ One large-scale study reported that the relative risk of graft loss 12 years after kidney transplant was 3.72 times higher in patients who had developed NODAT than in those with normal glucose metabolism.¹¹

Several factors for developing posttransplant diabetes mellitus have been identified in single-center, observational, or case control studies. These include age,⁶ race,⁶ ethnicity,⁹ family history,^{10, 11} hepatitis C,² obesity,^{1, 6, 12} donor source (deceased vs living),^{6, 9} acute rejection,^{1, 3, 9-11, 13-16} type of immunosuppressive agents used to prevent and treat rejection,^{1, 3, 9-11, 14, 15, 17} and the dosage of corticosteroids.^{2, 11, 12, 18-20} Transplant with a deceased-donor kidney also may increase the risk.²¹ We studied our center's kidney transplant population to determine the incidence and clinical correlates of NODAT after transplant.

Materials and Methods

Patient population

We studied all patients who received a deceased-donor or a living-donor kidney transplant who were then followed-up at our unit (Al-Moayyed Nephrology and Transplant Unit, Salmaniya Medical Complex, Manama, Bahrain) between January 1983 and December 2009. Patients with graft failure or death within 1 month after transplant, or graft loss caused by technical complications and patients who had a diagnosis of diabetes mellitus before transplant (either as native kidney disease or comorbidity) were excluded. The study was approved by the ethics committee of the institution before the study began, and that the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from all patients.

Definition of posttransplant diabetes mellitus

The presence of NODAT was determined retrospectively through medical chart review and defined as 2 random blood sugar values ≥ 11.1 mmol/L and/or fasting blood sugar values ≥ 7.0 mmol/L, taken on separate occasions, per WHO guidelines.²² We confirmed the diagnosis of diabetes by defining treatment with oral hypoglycemic

agents or insulin continued for more than 30 days after transplant and/or the persistence of untreated hyperglycemia for more than 30 days. Blood glucose values are routinely collected at least weekly for 0 to 3 months, every 2 to 4 weeks for months 3 to 6, and every 3 months thereafter.

Clinical variables

We examined several clinical characteristics to determine whether they were associated with the presence or absence of NODAT. These characteristics included patient age; race and sex; year of transplant; dialysis before transplant; obesity (defined as a continuous variable and as body mass index [BMI] ≥ 30) at the time of transplant and 6 months after transplant; type of donor (deceased vs living); the number of human leukocyte antigen mismatches; induction therapy; type and dosage of maintenance-immunosuppression therapy; calcineurin inhibitor (CNI) trough levels; dosage and cumulative dosage of corticosteroid therapy; biopsy-proven rejection episodes; cytomegalovirus; hepatitis C antibody status at time of transplant; and presence or absence of hypertension (defined as any treatment for high blood pressure and/or a systolic value > 140 mm Hg or a diastolic value > 90 mm Hg within 2 years of transplant).

Immunosuppressive regimen

Primary immunosuppressive treatment included corticosteroids, CNIs (cyclosporine [CsA] or tacrolimus [Tac]), and an antiproliferative agent (azathioprine or mycophenolate mofetil). Methylprednisolone was given 500 mg intravenously on the day of the operation and on first day after surgery, 250 mg on the day after surgery, and maintained at gradually decreasing dosages to 15 to 20 mg/d at the third month, and 5 mg/d at the fourth month. Target Tac and CsA levels for the first 3 months were 10 to 15 ng/mL and 200 to 300 ng/mL, and 5 to 10 ng/mL and 100 to 150 ng/mL thereafter. Anti-IL2 receptor antibodies (basiliximab) were used as an induction treatment in all patients.

During the course of the study of patients who developed NODAT, 3 patients were switched from CsA to Tac before developing NODAT. Once posttransplant diabetes mellitus had been diagnosed, 2 patients were switched from Tac to CsA, but this did not result in resolution of NODAT. In the group of patients who did not develop NODAT, $< 15\%$ of

patients had CNI switched (primarily from CsA to Tac for cosmetic indications such as hirsutism, gingival hypertrophy [90%], and after a rejection episode [10%]). There were no cases where calcineurin discontinuation occurred. Acute rejection episodes confirmed by an allograft biopsy, were initially treated with pulse methylprednisolone (1 g/d for 3 consecutive days) intravenously, and if resistant, anti-thymocyte globulin was used.

Laboratory assessments

Renal allograft function was formally assessed on days 7, 30, 90, and 360 by measuring serum creatinine concentration, estimated creatinine clearance using the Cockcroft-Gault formula, while proteinuria was measured on 24-hour urine collection after 12 and 24 months. Lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) were measured at the time of grafting, at 3 and 12 months.

Statistical analyses

Data are expressed as means $\pm$ SD. Mean values in the 2 groups, NODAT and no NODAT, were compared by the *t* test or by nonparametric tests if the data were not normally distributed. The chi-square test was used to compare categorical variables. Patient and graft survival were calculated using Kaplan-Meier survival curves, and the log-rank test was used to compare survival curves. Multivariate analysis was used to determine independent risk factors for developing NODAT. Logistic regression was used for multivariate analysis of a combination of categorical and continuous variables. Values for *P* less than .05 were considered statistically significant. Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 19.0, IBM Corporation, Armonk, New York, USA).

Results

After excluding patients with diabetes before transplant (*n*=83) and patients who failed within the first 30 days after transplant (*n*=5) or with missing information (*n*=26), there were analyzable data on 218 adult kidney transplant recipients between 1983 and 2009 (Table 1). The majority of our patient population consisted of Bahraini individuals (86.2%).¹

The patient population included 205 live-donor and 13 deceased-donor recipients. The mean age of the patients was 44.3 ± 13.1 years, 60.6% were men, body weight and BMI at the time of transplant were 57 ± 13 kg and 24.5 ± 4.1 kg/m². Time spent on dialysis before transplant was 13 ± 17 months. Seventy-seven percent of the patients had been treated with hemodialysis before transplant, and 11 patients received their second transplant. Hepatitis C virus infection was present in 12 patients (5.5%). Primary immunosuppressive treatment for the majority consisted of CsA-based (63.3%) or Tac-based regimen (32.1%) combined with (34.4%) or mycophenolate mofetil (65.6%). The remaining patients were treated with CNI-free protocol (sirolimus, prednisolone, and azathioprine; *n*=4) combined with steroids.

During follow-up, NODAT occurred in 73 patients (33.5%). The mean interval between transplant and the onset of NODAT was 43 ± 94 days and the median time to NODAT diagnosis was 24.2 days (range, 3 d to 10.7 y). The onset occurred within the first 3 months in 76.3% of patients; between 3 and 12 months in 13.2% of cases, and beyond 1 year in 10.5% of cases. The average values for random blood sugar at the time of diagnosis for recipients with NODAT was 11.5 ± 6.2 mmol/L as compared with the mean blood glucose value in follow-up of 5.1 ± 1.1 mmol/L in recipients who did not develop NODAT (*P* < .001). The average value for random blood sugar at the time of transplant for recipients who subsequently developed NODAT was 5.1 ± 1.3 mmol/L, and 5.5 ± 1.4 mmol/L for individuals who did not develop NODAT (*P* = .1).

Of the patients who developed NODAT, 56% required oral agents for treatment, and 38% required insulin therapy, and 3 patients required a combination of insulin and oral hypoglycemic agents. There was no association between the time of diagnosis and the agent used for treatment. There was no difference in weight, age, sex, and pretransplant random glucose of patients who required insulin compared with those who required oral medications only. However, patients who required insulin to control hyperglycemia had significantly higher plasma glucose concentrations at the time of diagnosis (14 vs 10.5 mmol/L; *P* < .002) than those that did not. The Hb A1c in those treated with insulin was significantly higher than those treated with oral medications only (Hb A1c 9.5% vs 6.9; *P* < .01).

Table 1. Univariate Analysis of Patient Demographics and Transplant-Related Parameters Between Patients With (n=73) and Without (n=145) NODAT

Parameter	NODAT (n=73)	No-NODAT (145)	P Value
Age (y)	51.2 ± 11.4	40.9 ± 12.3	< .0001
Sex: male/female (%)	67.1/32.9	57.2/42.8	.2
Weight at transplant (kg)	82.1 ± 16.9	70.2 ± 15.1	.03
BMI	29.4 ± 9.6	26.9 ± 6.1	.2
Race (%)			
Bahraini	90.4	84.1	.4
Non-Bahraini	9.6	15.9	
Causes of ESRD (%)			
Glomerulonephritis	9.6	23.3	.2
Vascular	5.5	3.4	
ADPKD	17.8	7.6	
Tubulointerstitial nephritis	13.4	12.5	
Unknown origin	49.3	45.2	
Miscellaneous	4.4	8.0	
Family history of diabetes	62.2	45.3	.04
HLA > 3 mismatches (%)	29	23	.7
Renal replacement therapy (%)			
Hemodialysis	95.9	96.2	.3
Peritoneal dialysis	4.1	3.8	.3
Pre-emptive	12.3	9.7	.1
Time on renal replacement therapy (mo)	11.3 ± 10.9	15.1 ± 20.3	.3
Positive hepatitis C status (%)	9.8	3.8	.02
Deceased/living donor (%)	95.8/4.2	93.0/7.0	.6
Retransplant (%)			
First/second	98.6/1.4	93.1/6.9	.07
Biopsy-proven acute rejection (%)	19.6	15.1	.05
Follow-up time (mo)	85.4 ± 72.1	74.9 ± 70.3	.3
	Posttransplant Diabetes Mellitus (n=73)	No Posttransplant Diabetes Mellitus (n=145)	P Value
Primary immunosuppressive regimen (n, %)			
Tac-based group	32 (43.8)	42 (28.9)	.02
CsA-based group	41 (56.2)	99 (68.2)	
Steroid-azathioprine	-	4 (2.8)	
Blood concentrations tacrolimus (ng/mL)			
Predose trough on POD 14	19.6 ± 6.8	15.8 ± 6.3	.04
Predose trough on POD 30	10 ± 4.6	9.7 ± 3.8	.3
Predose trough on POD 90	9.2 ± 3.4	9.1 ± 4.1	.7
Blood concentrations CsA (ng/mL)			
Predose trough on POD 14	181 ± 24	176 ± 40	.2
Predose trough on POD 30	150 ± 38	144 ± 34	.8
Predose trough on POD 90	132 ± 30	129 ± 37	.1
Predose trough on POD 180	112 ± 30	115 ± 31	.3
Daily corticosteroid dose (mg/d)			
POD 7	38.1 ± 7.4	29.4 ± 6.2	.07
POD 14	30.4 ± 7.7	25.7 ± 6.3	.3
POD 30	22.3 ± 6.8	22.1 ± 4.9	.9
POD 90	9.9 ± 2.7	9.6 ± 2.6	1.0
Cumulative steroid doses after 90 days (mg)	3.7 ± 0.3	3.0 ± 0.2	.05

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CsA, cyclosporine; ESRD, end-stage renal disease; HLA, human leucocyte antigen; NODAT, new-onset diabetes after transplant; POD, postoperative day; Tac, tacrolimus

On univariate analysis, risk factors associated with the development of NODAT were age, family history of diabetes mellitus, body weight at the time of transplant, the presence of HCV infection, and use of Tac (Table 1). Transplant characteristics including recipient sex, donor source, causes of ESRD, pre-emptive transplant, time on dialysis before transplant, incidence of acute rejection, and ethnicity were not different between groups (Table 1). New-onset diabetes after transplant was significantly more frequent in patients on Tac treatment than in those patients on CsA (43.8% vs 28.9%; $P < .05$)

(Table 2). New-onset diabetes after transplant occurred more frequently among HCV-positive patients than it did in HCV-negative patients (9.8% vs 3.8%; $P = .02$). When the incidence of NODAT was analyzed according to HCV status and the type of CNI treatment, the highest NODAT incidence was observed in HCV-infected patients using Tac (60%). Thirty-six percent of all patients received high-dose steroids at least once for presumed acute rejection. Patients who developed NODAT were more likely to have received at least 1 course of high-dose corticosteroids, but this did not reach statistical

Table 2. Multivariate Analysis of Parameters Between Patients With (n=73) and Without (n=145) NODAT

Risk Factors—Multivariate Analysis	Hazard Ratio	CI 95%	P Value
Age	2.04	2.01-2.08	.0001
Body weight at transplant (kg)	1.03	1.02-1.07	.01
Tac (as opposed to CsA)	1.52	1.12-2.83	.007
Family history of diabetes mellitus	1.43	1.1-1.96	.01
Positive hepatitis C serology	1.64	1.2-1.4	.01

Abbreviations: CsA, cyclosporine; NODAT, new-onset diabetes after transplant; Tac, tacrolimus

Table 3. Patient Glucose Status According to CNI

Glucose Status	CsA-ME (n=41)	Tac (n=32)	P Value
Family history of diabetes (%)	66.1.7	62.1	.2
Mean duration of treatment (mo)	13.4 ± 5.93	13.0 ± 5.69	.1
NODAT incidence (%) (95% CI)	4.6 (1.9-7.3)	9.2 (6.3-12.9)	.04
Median interval between transplant and diagnosis of NODAT (mo)	3.9 (0.2-16.1)	1.9 (0.03-16.1)	.06
Diagnosis of NODAT (%), n			
≤ 3 months after transplant	50.5 (21)	77.8 (26)	.04
> 3 months after transplant	49.5 (20)	22.2 (8)	

Abbreviations: CNI, calcineurin inhibitor; CsA, cyclosporine; NODAT, new-onset diabetes after transplant

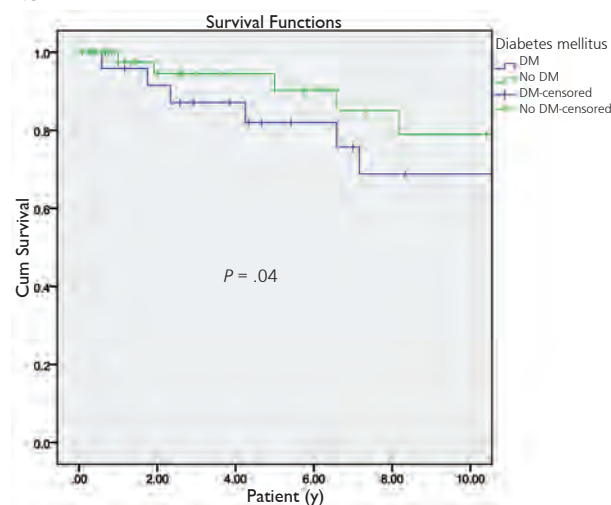
significance ($P = .05$). There was no difference in NODAT between patients treated with azathioprine or mycophenolate mofetil ($P > .05$).

For the analysis, the CNI prescribed at discharge was used if the patient's blood glucose status was normal; but in patients with NODAT, the CNI being taken on the day the NODAT was diagnosed was input. A total of 41 and 26 patients were receiving CsA and Tac (Table 3). The mean treatment duration was similar for both groups (13.4 ± 5.9 mo for CsA, 13.0 ± 5.7 mo for Tac); however, the Tac group developed NODAT significantly earlier than did the CsA group ($P = .04$). At the last study visit, 97.5% of the patients were still receiving steroids, a majority of them received a mycophenolic acid drug (98.1%), and 3.6% were being treated with sirolimus. Median dosages of CNIs and steroids and CNI trough blood levels are described in Table 1.

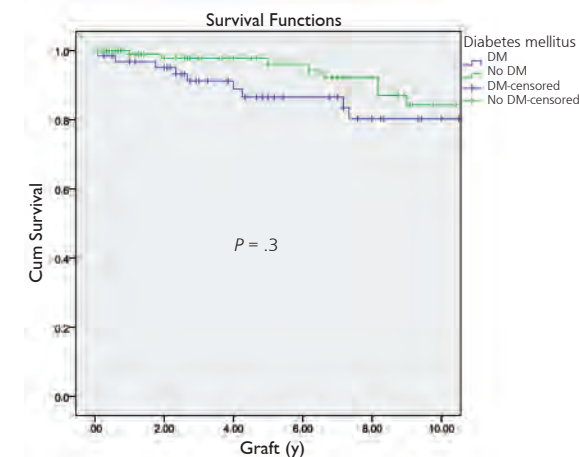
Overall patient survival at 1, 5, and 10 years after transplant was 96.4%, 89.2%, and 79.3%. Figure 1 shows patient survival rates according to diabetes status. There was a significant difference in survival with those with diabetes having the worse outcomes. Five- and 10-year patient survival was 81.1% and 69.2% for patients who developed NODAT compared with 90.3% and 79.5% for those who had no diabetes. Of patients with NODAT, 10.6% and 7.3% of the remaining patients died with a functioning transplant ($P = .9$). Overall graft survival censoring for death was 98.1%, 88.6%, and 78.1% at 1, 2, and 10 years (Figure 2). There was no

difference in graft survival between those patients with diabetes and those without diabetes. Five- and 10-year graft survival was 85.4% and 81.7% for those patients who developed NODAT and 93.6% and 84.2% for those who had no diabetes. In addition, there were no differences in renal function (serum creatinine or calculated creatinine clearance) at any time after transplant for patients who developed NODAT compared with patients who did not develop NODAT (data not shown).

With regard to the time of onset of diabetes, patients were divided into 2 subgroups: (1) early NODAT (within the first 3 mo after transplant; n=45) and (2) late NODAT (beyond 3 mo; n=28). Onset of diabetes in the early and late groups was 43 ± 24 days (range, 3-88 d) and 678 ± 813 days (range,

Figure 1. Patient Survival in Patients With NODAT and Patients Without NODAT

Abbreviations: DM, diabetes mellitus

Figure 2. Graft Survival in Patients With NODAT and Patients Without NODAT

Abbreviations: DM, diabetes mellitus

92-4215 d). When compared with the patients of early NODAT, increased BMI at the time of diabetes diagnosis and HCV infection were more frequent in late posttransplant diabetes mellitus, while Tac use was more frequently seen in early NODAT. There was no difference between early and late groups with respect to age, sex, BMI at the time of transplant, and the incidence of acute rejection (Table 4). Kaplan-Meier survival curves showed there was no difference in 5- and 10-year patient and death-censored graft survival between early and late groups. Backward stepwise logistic regression analyses was used to determine risk factors for each subtype of diabetes. According to these analyses, age was a unique risk factor for all types of diabetes. Tacrolimus use was found to be significantly associated with early diabetes, whereas HCV was a risk factor for late diabetes (Table 5).

Table 4. Clinical Data According to the Onset Time of Diabetes of Posttransplant Diabetes Mellitus

	Early (n=45)	Late (n=28)	P Value
Age	36.8 ± 10.5	35.2 ± 10.2	.2
Sex (female), n (%)	24 (46%)	20 (40%)	.3
BMI at transplant	21.6 ± 3.4	21.3 ± 2.9	.1
BMI at diagnosis of NODAT	21.6 ± 2.8	23.9 ± 4.4	.019
AR	18 (34%)	19 (39%)	.5
HCV	2 (29%)	5 (71%)	.002
Tac use	17 (32%)	6 (12%)	.012

Abbreviations: AR, acute rejection; BMI, body mass index; HCV, hepatitis C virus infection; NODAT, new-onset diabetes after transplant; Tac, tacrolimus

Table 5. Patient and Graft Survival According to the Time of NODAT

	Early	Late	Log Rank
Patient survival			
5-y (%)	84	75	0.9
10-y (%)	55	66	
Death-censored graft survival			
5-y (%)	75	61	0.08
10-y (%)	24	38	

Discussion

Our results suggest that the incidence of NODAT is high. New onset diabetes after renal transplant was found in 33.5% of our patients who received a renal transplant between 1983 and 2009. However, it is important to keep in mind that the rate of detection of NODAT may vary depending on the methods used, for example, how diabetes is defined, the duration of follow-up, the types and amounts of immunosuppression used, and the presence of

pretransplant risk factors. A meta-analysis of 19 observational studies and controlled trials that use various detection methods in diverse study populations have reported NODAT rates in the first year after transplant ranging from 2% to 50%.⁴ The largest epidemiologic studies examined NODAT incidence, using data for medicare beneficiaries from the US Renal Data System (USRDS) who were followed from 1994 to 19985 or from 1996 to 2000.⁵ Both studies demonstrated an augmented NODAT incidence (14% to 16%) in the first year after surgery, declining thereafter to an annual incidence of 4% to 6%, similar to the pretransplant baseline rate.^{5, 6} The cumulative incidence of NODAT was 24% at 3 years after transplant.⁵ Cosio and associates²¹ reported that NODAT was present in 13% of 500 kidney recipients at 1 year after transplant. The other study prospectively assessed changes in oral glucose tolerance in living-donor kidney recipients.²³

Although risk factors for developing diabetes after transplant may vary among studies, commonly reported predisposing factors include African-American and Hispanic ethnicity, obesity (defined as BMI ≥ 30 kg/m²), age older than 40 to 45 years, family history of diabetes among first-degree relatives, impaired glucose tolerance before transplant or presence of other components of the metabolic syndrome, recipients of deceased-donor kidneys, hepatitis C infection, and immunosuppressive therapy including corticosteroids, and the CNIs, Tac, and, to a lesser extent, CsA.⁴ We identified age, obesity, hepatitis C infection, family history of diabetes, and the use of Tac as risk factors for NODAT. We found that older age has long been observed an important risk factor for developing NODAT. In 1 study that included 2078 allograft recipients, Cosio and associates²¹ showed that those who were older than 45 were 2.9 times more likely to develop diabetes. Similarly, in an analysis of the USRDS, Kasiske and associates⁵ showed a strong association between older age and NODAT. Compared with a reference range of 18 to 44 years of age, transplant recipients between the age of 45 and 59 years had a relative risk for NODAT of 1.9 ($P < .0001$), whereas those who were ≥ 60 years of age had a relative risk of 2.09 ($P < .0001$).⁵ Age increased the risk for development of diabetes 1.5-fold for every 10-year increase in age.²⁴

Similar to the general population, obesity has been shown to be associated with the development of NODAT in most studies,^{5, 11, 21, 25} although some

studies have failed to demonstrate an association between obesity and the development of NODAT.^{4, 6, 7, 25} We proved that body weight at time of transplant is one of the predictors of NODAT (relative risk of 1.73; $P < .0001$). Data from the USRDS revealed that obese patients ($\text{BMI} > 30 \text{ kg/m}^2$) have an relative risk for NODAT of 1.73 (95% CI: 1.57 to 1.90; $P < .0001$), being one of the most consistent risk factors.⁵ New-onset diabetes after transplant risk increases linearly for every 1 kg above 45 kg.¹⁴ As well as obesity, overweight patients ($\text{BMI} > 25$ and $< 30 \text{ kg/m}^2$) also are at risk for developing NODAT.¹¹ Influence of weight gain over NODAT can become more evident in long-term studies than in 1-year studies.

Our results show a positive family history of diabetes was associated with a 50% increase in the risk of developing NODAT (hazard ratio, 1.43). There is conflicting evidence regarding the importance of family history of diabetes and impaired glucose tolerance before transplant.⁴ Individuals with a history of diabetes among first-degree relatives should be identified to prevent development of NODAT. Some reports have detected that a family history of diabetes increases up to 7 times the risk for NODAT.^{7, 27, 28}

In our study, hepatitis C antibody status was significant in univariate analysis ($P = .02$) and demonstrated significance in multivariate analysis ($P = .01$). Many studies have indicated that viral infections also may increase the risk for type 2 diabetes. However, this relation is more evident in the USRDS registry. One-year incidence of NODAT in HCV-positive patients at transplant was 25.6% compared with HCV-negative patients (15.4%; $P < .0001$).⁵ A meta-analysis of clinical studies involving 2502 kidney recipients concluded that the adjusted odds ratio for NODAT was 3.97 (95% CI: 1.83 to 8.61).²⁹

The risk of NODAT was greater in the patients treated with Tac compared with the patients not initially treated with Tac (hazard ratio, 1.52; $P = .007$). Data obtained from the USRDS revealed that by 1 year after transplant, the incidence of NODAT was approximately 70% greater among Tac- versus CsA-treated patients (30% vs 18%).⁵ Nonetheless, not all studies showed that Tac is more diabetogenic than CsA.²⁹⁻³¹ It has been suggested that these study inconsistencies stemmed, in part, from the difference in the definitions of NODAT and the difference in CNI

dosage and drug levels. In a single-center study consisting of 139 renal transplant recipients without known pretransplant glucose abnormalities, Maes and associates³² showed that high Tac trough levels, particularly levels greater than 15 ng/mL in the first month after transplant, were a significant risk factor for persistent, impaired fasting glucose or diabetes mellitus beyond the first year after transplant. Our results show a significantly high Tac level 2 weeks after transplant on univariate analysis ($P = .04$) and did not demonstrate significance on multivariate analysis.

We did not find a relation between maintenance or cumulative dosages of corticosteroid use and NODAT (Table 1), which may be somewhat unexpected. However, our prevalent use of corticosteroids after transplant prohibits an adequate comparison with a group of recipients not on prednisone; therefore, it is difficult to draw any major conclusions. However, the association between corticosteroids and NODAT is established clearly and is related to cumulative dosages and therapy duration in many studies.^{5, 15, 27} In the initial years of transplant, higher dosages of corticosteroids were used, and the incidence of NODAT was reported to be as high as 46%. The progressive reduction in corticosteroid dosages has led to a parallel reduction in the incidence of NODAT.²⁹ As a result of the current lower dosages, several studies did not find any influence of cumulative corticosteroid dosages on the appearance of NODAT.^{21, 27, 28, 32}

Although we did not find NODAT to worsen graft survival in our study, larger studies^{5, 7, 11} have shown a detrimental relation with graft survival. One retrospective 12-year trial reported 48% graft survival in patients with NODAT compared to 70% in controls ($P < .04$),¹¹ while a retrospective study reported only a smaller and nonsignificant difference (9.7 vs 11.3 y).¹⁰ Other authors have found no difference in graft survival between patients with NODAT and controls.^{13, 26} The majority of studies indicate that mortality is significantly higher in renal transplant recipients who develop NODAT compared with controls,^{5, 10, 21, 33} although some studies have reported no significant difference.^{11, 27} A large-scale registry analysis has indicated that mortality is increased by 87% after the onset of NODAT, independent of other variables.⁵ Baid and associates³³ evaluated 158 patients transplanted

during 1991 to 1998 and found that the onset of NODAT was associated with more than a 3-fold increase in risk of death on multivariate analysis ($P < .001$). Our study reported a 10-year patient survival of 69.2% in patients with NODAT compared with 79.5% in controls ($P < .04$).

This study shows that in a kidney transplant population, there is a significant risk of NODAT after transplant. Identifiable risk factors include age, family history of diabetes mellitus, Tac use, hepatitis C antibody status, and obesity. Given that NODAT has been shown to reduce patient survival in some data sets, it seems reasonable to consider strategies to reduce the risk of NODAT. Balancing the need for effective immunosuppression versus the desire to minimize the diabetogenicity of the regimen is a delicate issue, and must be addressed on an individual basis according to a patient's immunologic status and risk of diabetes (eg, family history and obesity).

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