Risk for new-onset diabetes mellitus after transplantation: implication of advanced age and immunosuppressive therapy

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Background: The impact of the type of calcineurin inhibitor on the development of new-onset diabetes after transplantation (NODAT) has been difficult to assess due to contradictory results in published studies using heterogeneous populations.
Aim: We attempted to assess the relative risk for development of NODAT in a population of age-stratified Afro–Caribbean and Hispanic renal-transplant recipients treated with cyclosporin A (CSA) or tacrolimus in an urban academic medical center (n = 284).
Patients & methods: Patients, based on age distribution, were divided into group 1 (20–44 years; n = 85); group 2 (45–56 years; n = 110); and group 3 (57–79 years; n = 85).
Results: In each age group, tacrolimus-treated patients had significantly higher rates of NODAT (7, 17 and 15%) compared with CSA-treated patients (2, 9 and 7%); p = 0.015. The risk of NODAT was increased in age group 2 (hazard ratio: 4.7; 95% confidence interval: 2.0–11.0; p = 0.01) and group 3 (hazard ratio :3.4; 95% confidence interval: 1.4–8.5; p = 0.01) compared with group 1 and use of tacrolimus compared with CSA (hazard ratio: 2.7; 95% confidence interval: 1.4–5.0; p = 0.01). Race, gender, acute rejection episodes and other demographic factors were insignificant factors between the age groups. **Conclusion:** We conclude that, in our population, the risk of NODAT increases with age and use of tacrolimus. Discrepancies in assigning risk to immunosuppressive regimens in previous studies may be confounded by the analysis of mixed age groups or predominantly younger patients.

Keywords: cyclosporin A, new-onset diabetes after transplantation, renal transplantation,tacrolimus

Advances in the control of immunologic events following renal transplantation have led to a substantial decline in acute rejection episodes and a significant improvement in short term graft survival, particularly during the first year post transplant. Although newer immunosuppressive medications have contributed significantly to improvements in transplantation, their use is also associated with serious side effects [1,2]. One of the most serious complications is new-onset diabetes mellitus after transplantation (NODAT), which is associated with an increased incidence of graft failure and higher patient mortality [3–5].

The incidence of NODAT ranges from 11 to 38%, with variability due to definition of diabetes as well as patient-population demographics and type of immunosuppression used [3]. Multiple risk factors contributing to the development of NODAT have been identified. Patients of Afro–Caribbean, African–American or Hispanic descent are at a clearly increased risk for NODAT compared with the Caucasian population [6–8]. In addition, older age, family history of diabetes, obesity, certain human leukocyte antigen (HLA) haplotypes and use of some immunosuppressive agents, also place patients at an increased risk [9–11].

Experimental and clinical studies have demonstrated that steroids, cyclosporin A (CSA) and tacrolimus all have an adverse impact on glucose tolerance [1,12]. NODAT is a well-recognized complication of high-dose corticosteroid therapy. However, despite a reduction in the dose of steroids used in modern era protocols, NODAT remains a significant clinical problem due to the diabetogenic effects of the calcineurin inhibitors [12,13]. In some series, especially when high-dose tacrolimus regimens are used, the risk of NODAT is higher in tacrolimus-, compared with CSA-treated patients [12,13], while others fail to find this difference [14]. In general, those studies that have failed to find a difference have involved Caucasian patients or those who are younger [14].With improvement in renal allograft survival, selection of potential recipients has widened to include older patients, a group of patients that, in the general population, has a substantially higher risk for diabetes mellitus. Owing to the adverse consequences of NODAT on patient and graft survival, differences in drug metabolism between older and younger patients, and increasing numbers of older patients undergoing renal transplantation, it becomes important to determine the effects of age and choice of

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immunosuppression on the development of NODAT. Therefore, we have examined the effect of a CSA- versus a tacrolimus-based immunosuppressive regimen on the development of NODAT in renal transplant recipients stratified by age, in our predominantly Afro–Caribbean and Hispanic patient population.

Methods

Patients

We retrospectively reviewed the records of all adult (aged > 18 years) renal allografts performed at the State University of New York (SUNY) Downstate Medical Center, Brooklyn, (NY, USA) between January 1, 1994 and December 31, 1999. A total of 284 patients with no history of pretransplant diabetes and whose allograft functioned longer than 3 months were identified. Post-transplant diabetes was defined as the need for insulin or oral hypoglycemic therapy for at least 2 consecutive months in the post-transplant period, and persisting at 1 year post transplant. The study was approved by the Institutional Review Board at SUNY Downstate Medical Center.

Data collection

The following data were collected for each patient:

- Age at transplant
- Gender
- Race
- Number of HLA mismatches
- Type of transplant
- Date of transplant
- Maintenance immunosuppression
- Development of NODAT
- Date of initiation of therapy for diabetes
- Graft failure
- Date of graft failure
- Death
- Acute rejection episodes

Laboratory data (serum creatinine, tacrolimus and CSA blood levels) were recorded at 6 weeks post transplant, by which time most transplant recipients would have achieved stability.

Immunosuppression protocols

Deceased donor renal transplant recipients received intravenous antibody induction therapy in the operating room and daily thereafter for 5 to 7 days, unless significant thrombocytopenia developed. Antibody induction for deceased donor kidney transplants was changed from horse antithymocyte globulin (ATGAM, Upjohn, Kalamazoo; 15 mg/kg) to rabbit antithymocyte globulin (Thymoglobulin, Sangtat, CA, USA; 1.5 mg/kg) in 1998. Living kidney-transplant recipients did not receive antibody induction. Intravenous methylprednisolone (250 mg) was given in the operating room and patients continued to receive 125 mg intravenously for a few more days. Oral methylprednisolone was then administered at a daily dose of 80 mg, tapered to 20 mg daily at 1 month, followed by 5 to 10 mg daily at 6 months. For maintenance therapy, patients were randomly assigned to receive CSA or tacrolimus. For the first 3 months, CSA patients received a dose of 5 to 10 mg/kg titrated to a trough level of 350 to 500 ng/ml by TDX assay or tacrolimus (0.08–0.1 mg/kg, titrated to a trough level of 10–15 ng/ml) in divided doses, azathioprine (1–2 mg/kg/day) or mycophenolate mofetil (500–1000 mg twice daily), and prednisolone as above. By 6 months post transplant, trough targets were 150 to 200 ng/ml for CSA and 5 to 10 ng/ml for tacrolimus. The CSA and tacrolimus levels reported are averaged over the first 6 weeks.

Suspected acute-rejection episodes were treated with methylprednisolone (125 mg) given intravenously every 12 h. A kidney biopsy was performed as soon as possible, and in those unresponsive to steroids. Patients with Banff histologic grade 1 or moderate grade 2 rejection were continued on methylprednisolone, whereas those with more severe rejections on biopsy or who were clinically steroid resistant were treated with monoclonal antibodies (OKT3, Ortho Biotech, Raritan, New Jersey) 5 to 10 mg daily intravenously for 5 to 10 days.

Statistical analysis

Using frequency distribution, the study population was divided into tertiles for age. The characteristics of the three age groups were compared with analysis of variance, or Chi square test, as appropriate. Cox hazard analysis was performed to determine the risk factors for the development of NODAT in our population using the three categories of age, type of calcineurin inhibitor use and other significant variables in our univariate analysis. Data were analyzed with SPSS version 10.0. A two-tailed p-value of less than 0.05 was considered significant.

Table 1. Characteristics of age-stratified patient groups.

	Group 1 (20–40 years) n = 89	Group 2 (41–55 years) n = 110	Group 3 (56–79 years) n = 85	p-value
Gender (%)				
Male	59	58	58	ns
Female	41	42	42	
Race (%)				
Black	64	64	60	ns
Caucasian	12	12	18	
Hispanic	18	18	18	
Asian	6	6	4	
Maintenance immunosuppression (%)				
Tacrolimus	65	54	46	ns
Cyclosporin	35	46	54	
Type of transplant (%)				
Deceased	66	80	88	0.02
Living	34	19	12	
HLA mismatches (%)				
Zero	2	6	7	ns
≥ 1	98	94	93	
Acute rejection (%)				
Yes	43	34	39	ns
No	57	66	61	
Graft failure (%)				
Yes	43	34	36	ns
No	57	66	64	
Death (%)				
Yes	1	16	13	ns
No	99	84	87	
Mean HLA mismatches	3.3 ± 1.4	3.6 ± 1.5	3.3 ± 1.6	ns
Mean tacrolimus level (ng/ml)	14 ± 6	16 ± 8	14 ± 7	ns
Mean CSA level (ng/mL)	487 ± 201	505 ± 203	463 ± 215	ns
Mean serum creatinine (mg/dl)	2.2 ± 1.0	2.5 ±2.3	2.3 ± 1.5	ns
Mean BMI	26.1±5.0	27.8±6.0	27.8±5.8	ns

There were significantly more living transplants and a higher rate of graft failure in the younger age group, compared with the older age groups. All means are expressed as ± standard deviation.
BMI: Body mass index; CSA: Cyclosporin; HLA: Human leucocyte antigen.

Results

Baseline characteristics

The demographics and clinical characteristics of the total population (n = 284) are shown in Table 1. The study population consisted of 58% males, 42% females, 60% Blacks and 18% Hispanics. A total of 78% of patients received a deceased donor transplant. The overall prevalence of NODAT in the study population was 20%. A total of 54% received tacrolimus, 45% received CSA while 1% received no calcineurin inhibitor. There were significantly more patients who developed NODAT in tacrolimus-treated patients, compared with those who developed NODAT in CSA-treated patients (25 vs. 15%; p = 0.031).

Table 1 demonstrates that there were no significant differences among the age groups for gender, racial composition, type of immunosuppression, number of HLA mismatches, acute rejection episodes, graft failure, death and mean levels for

Table 2. Development of NODAT in the three age groups showing significantly increased prevalence of NODAT in groups 2 and 3 compared with group 1.

	Group 1 (20–40 years) n = 89	Group 2 (41–55 years) n = 110	Group 3 (56–79 years) n = 85	p-value
Tacrolimus (%)	7	17	15	0.015
Cyclosporin (%)	2	9	7	
Total (%)	9	26	22	

Statistical significance calculated using Chi square.
NODAT: New-onset diabetes mellitus after transplantation.

tacrolimus, CSA and serum creatinine. The number of living-related kidney-transplant recipients was significantly higher in the youngest group (group 1; 34%), compared with groups 2 and 3 (19 vs. 12%; p = 0.02).

Influence of age & immunosuppression on post-transplant diabetes mellitus

The development of NODAT according to age and type of immunosuppression is shown in **Table 2**. Patients older than 40 years (groups 2 and 3) were significantly more likely to develop NODAT than those in group 1 who were younger than 40 years (group 1: 9%; group 2: 26%; group 3: 22%). Median time to development of NODAT was 3 months (range: 10 days to 70 months). There was no difference in time to presentation of diabetes or serum levels between the two calcineurin inhibitors in each age group.

Risk-factor analysis

Cox proportional hazard analysis was performed with simultaneous entry for age groups, type of calcineurin inhibitor and type of transplant since type of transplant was the only significant variable in the univariate analysis between the three groups. As shown in **Table 3**, the risk of NODAT was increased in age group 2 (hazard ratio: 4.7; 95% confidence interval [CI]: 2.0–11.0; p = 0.01) and group 3 (hazard ratio: 3.4; 95% CI: 1.4–8.5; p = 0.01) as compared with group 1. The risk of NODAT was also increased with use of tacrolimus as compared with CSA (hazard ratio: 2.7; 95% CI: 1.4–5.0; p = 0.01). There was no impact of type of transplant on development of NODAT. Type of calcineurin inhibitor use and age group independently predicted the development of diabetes. Race, gender, acute rejection episodes and other demographic factors were insignificant factors between the age groups.

Discussion

Our results demonstrate that the risk of NODAT in our study population increased significantly after the age of 40 years and following the use of tacrolimus immunosuppression. We did not find any other demographic and clinical characteristics associated with NODAT in this population. Our study is significant, in that it establishes a cut-off age at which the risk of developing NODAT escalates, and provides a basis for tailored immunosuppression to reduce NODAT in those aged over 40 years.

The overall increased incidence of NODAT in older patients agrees with previous observations in transplant recipients and also with observations in the general population that the risk of Type 2 diabetes increases with age [8,10,12,14]. The higher incidence of NODAT in older people may reflect the effects of diabetogenic immunosuppressive therapy in a susceptible population with poor insulin reserve or pre-existing glucose

Table 3: Cox proportional hazard analysis with simultaneous entry for potential risk factors for NODAT.

Covariates	Hazard ratio	95% CI	p-value
Age 20–40 years (reference age)			
Age 40-55 years	4.7	2.0–11.0	0.01*
Age 56-79 years	3.4	1.4–8.5	0.01*
Tacrolimus (versus. CSA)	2.7	1.4–5.0	0.01*
Type of transplant (deceased versus living)	1.4	0.7–3.0	ns

** Denotes significant risk factors for the development of NODAT.*
CSA: Cyclosporin; NODAT: New-onset diabetes mellitus after transplantation.

intolerance. High postprandial blood glucose level [10] and abnormal oral glucose-tolerance test [15] before transplantation have both been linked to the development of NODAT. Data from different studies demonstrate an increase in risk of NODAT for patients of African–American or Hispanic ethnicity, and those whose initial immunosuppression involved the use of tacrolimus [16,17]. African–American and Hispanic ethnicity poses the highest risk for Type 2 diabetes, hyperinsulinemia and insulin resistance in the general population [18]. Subgroup analysis of the FK506 Kidney Transplant Study showed that, after tacrolimus treatment, African–Americans were at a substantially higher risk of developing NODAT than Caucasians; NODAT was also less likely to be reversed in these patients [17]. We did not find an impact of ethnicity on development of diabetes in this study, probably since our study population was predominantly Black.

Corticosteroid-associated NODAT has been reported since the 1960s [19]. The median time to development of NODAT was 3 months, which is also the period when patients received the highest doses of corticosteroids, suggesting that high-dose corticosteroid treatment may have contributed to the development of NODAT. We did not find an increase in acute rejection episodes between the age groups to explain an increase in steroid use.

The mechanism of calcineurin inhibitor-induced NODAT is thought to involve altered insulin sensitivity, reduced insulin secretion, and pancreatic β-cell toxicity, leading to glucose intolerance [1,12,20]. Both tacrolimus and cyclosporin reduce insulin synthesis by inhibiting insulin gene transcription [21,22]. In a rat model, elevation in blood glucose preceded a change in insulin levels. In addition, glucose uptake by adipocytes isolated from cyclosporin-treated rats was shown to be reduced without any change in insulin binding [21]. These findings suggest insulin resistance as one of the mechanisms of cyclosporin-induced glucose intolerance.

Clinical studies have shown similar results. Insulin secretion was reduced by administration of tacrolimus in 18 renal failure patients for 5 days prior to transplantation [23]. Interestingly, insulin resistance did not increase, suggesting that the predominant mechanism of action of tacrolimus in inducing diabetes is through its effect on β-cell function. In another study, Filler and colleagues studied the insulin response to intravenous glucose tolerance test in 14 pediatric transplant patients treated with tacrolimus [24]. They found that tacrolimus produces a dose-dependent inhibition of insulin secretion that improved with the lowering of tacrolimus trough levels. These data suggest that both cyclosporin and tacrolimus induce diabetes primarily via a reduction in insulin secretion through their calcineurin inhibitor effects. Although unclear, the likely explanation for why patients on tacrolimus have a higher risk of diabetes than cyclosporin is that tacrolimus is more potent and perhaps exerts more efficient calcineurin inhibition than cyclosporin.

The limitations of this study include the retrospective design and single-center experience. Also most of the patients were Black. We did not find any differences in the distribution of body-mass index (BMI) and also did not have data on family history of diabetes. Romagnoli and colleagues recently reported that higher BMI and positive family history for diabetes mellitus were significant risk factors for the development of post-transplant diabetes mellitus, regardless of the immunosuppressive agent used [25]. The lack of these variables in our data limit generalizability; nonetheless this information is important when considering immunosuppression in older patients.

In conclusion, we have shown, by age stratification, that patients older than 40 years, or those receiving tacrolimus, are at a higher risk for NODAT than those younger or receiving cyclosporin. This finding may help guide physicians in their choice of immunosuppression. In young Blacks or Hispanic patients who may be at an increased risk for acute rejection and may benefit from tacrolimus therapy, fear of NODAT should not cause tacrolimus therapy to be avoided. However, the use of CSA may be preferable in the older age group, in whom the risk of NODAT with tacrolimus treatment is increased.

Highlights

- New-onset diabetes after transplantation (NODAT) is a major health problem.
- The results of this study indicates an increased risk of NODAT in minority patients older than 40 years and therapy with tacrolimus as compared with cyclosporine.
- This finding may help guide physicians in their choice of immunosuppression.
- The risk of NODAT in this high risk population may be reduced by using tacrolimus in younger and cyclosporine in older patients.

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