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Comparative Risk of Impaired Glucose Metabolism Associated with Cyclosporine Versus Tacrolimus in the Late Posttransplant Period

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New onset diabetes after transplantation (NODAT) and impaired fasting glucose (IFG) are common in kidney transplant recipients (KTRs). Calcinuerin inhibitor (CNI) therapy is a causal risk factor. NODAT is associated with increased mortality and diminished graft survival. We studied the incidence of NODAT and IFG in KTRs before and after a medically indicated switch of CNI therapy from cyclosporine (CsA) to tacrolimus (Tac). The study population consisted of 704 nondiabetic KTRs. Of them, 171 underwent conversion from CsA to Tac (group I) and 533 remained on the CsA since transplantation (Group II). Time-dependent Cox regression and generalized estimating equations were used to account for sequential CNI exposure. NODAT and IFG occurred in 15.2% and 22.1% of group I subjects and 15.6% and 25.8% of group II subjects, respectively ($p = 0.90$ for NODAT and $p = 0.38$ for IFG). Accounting for equal follow-up time since conversion from CsA to Tac, the adjusted 5-year NODAT-free survival was 87.4% and 91.4% in group I and group II, respectively ($p = 0.90$). In conclusion, conversion to Tac, compared to continuous exposure to CsA, carries quantitatively similar risk of impaired glucose metabolism in KTRs in the late posttransplant period.

Key words: Calcineurin inhibitor agents, kidney transplantation, new onset diabetes mellitus

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Introduction

New onset diabetes after transplantation (NODAT) and its precursor, impaired fasting glucose (IFG) are highly prevalent in kidney transplant recipients (KTRs). NODAT develops in up to 50% of KTRs who did not have diabetes mellitus prior to kidney transplantation and it is associated with an increased risk of posttransplant mortality, aggressive cardiovascular disease (CVD), greater health care utilization and inferior graft survival (1–7). Calcineurin inhibitor (CNI) therapy with cyclosporine (CsA) or tacrolimus (Tac) is a risk factor for posttransplant impaired glucose metabolism in the form of NODAT or IFG defined as fasting blood glucose greater than 100 mg/dL (8,9). When NODAT or IFG is defined according to standard clinical practice guidelines, the risk of posttransplant hyperglycemia is consistently higher in Tac-treated KTRs compared to CsA-treated KTRs; however, some studies have reported similar prevalence rates of NODAT in Tac- and CsA-treated KTRs when modified definitions are applied (4,10–14). In the recently published 1-year results of the Efficacy Limiting Toxicity Elimination (ELITE)-Symphony study of 1645 KTRs, the 12-month rate of NODAT was significantly higher in the Tac- compared to the CsA-treated KTRs (15).

Most studies comparing the risk of NODAT associated with Tac and CsA have considered only the early posttransplant period (typically the first year) when other diabetogenic risk factors are highly operative (e.g. high dose of glucocorticoids, increased caloric intake and weight gain). In addition, NODAT and IFG are not often separated or defined according to standardized guidelines. Finally, even though conversion from one CNI to the other is commonly undertaken in 14–45% of KTRs, the risk of NODAT and IFG associated with switching from one CNI to the other has not been determined. The latter is particularly relevant because the impetus to switch from CsA to Tac is a desire to improve cardiovascular risk factors (lipids and blood pressure) for which Tac therapy may have a salutary effect over CsA (16–18). However, it is unclear whether such CNI conversion merely substitutes one set of risk factors for an equally potent adverse CVD risk factor such as NODAT.

The current study was undertaken to (i) define the risk of NODAT and IFG according to standardized guidelines in a cohort of KTRs uniformly treated with CsA at the time of

transplantation (8,9); (ii) determine the risk of NODAT and IFG in the late posttransplant period; and (iii) estimate the rate of NODAT and IFG following conversion from CsA to Tac.

The majority of our center's renal transplant recipients are discharged on a CsA-based triple immunosuppression regimen (with mycophenolate mofetil and prednisone) according to the institutional protocol. For a variety of reasons (most commonly graft dysfunction due to rejection), treating clinicians choose to convert patients to Tac during follow-up. In this investigation, we examine the effect of conversion from CsA to Tac on the incidence of NODAT and on overall glucose metabolism in the form of fasting glucose levels.

Patients and Methods

Subjects undergoing kidney transplantation at a single academic transplant center were studied following approval by the Institutional Review Board. The study population consisted of 704 KTRs who received CsA-based triple regimen immunosuppression at the time of solitary kidney transplantation which was performed between January 1, 1999 and December 31, 2005. Demographic data, urine and blood laboratory results, relevant recipient and allograft clinical events were retrieved from the hard copies of medical records and from a relational transplant electronic database. Date and reasons for conversion from CsA to Tac were recorded. The initial immunosuppression in all study subjects was based on an institutional protocol which consisted on induction therapy with thymoglobulin for high-risk recipients, prednisone tapered to 10 mg/day by 40 days posttransplant, mycophenolate mofetil at a dose of 2–3 g daily as tolerated and stratified by race, and concentration-controlled maintenance CsA dosing with a whole blood trough level target of 100–300 ng/mL by high performance liquid chromatography (HPLC). For subjects who were converted to Tac, a triple-drug maintenance regimen was continued with prednisone and mycophenolate mofetil in the same fashion as recipients who were maintained on CsA. A concentration-controlled dosing regimen was also used in those converted to Tac to maintain a 12-h whole blood trough level of 5–8 ng/ml using HPLC-tandem mass spectrometry. The study subjects were divided into two groups: group I were recipients who received CsA as the initial CNI following kidney transplantation but were subsequently converted to Tac for a specific clinical indication and remained on Tac until the end of follow-up (n = 171) and group II are recipients who remained on CsA as the sole CNI therapy throughout the duration of the study (n = 533). All study subjects were followed until graft loss, death or December 31, 2006.

The endpoints for the study are (1) fasting serum glucose at last follow-up; (2) onset of NODAT defined as two measurements of fasting serum glucose $\geq$126 mg/dL or random serum glucose >200 mg/dl with or without symptoms of chronic hyperglycemia and on oral hypoglycemic agent or insulin therapy (9); (3) IFG defined as serum glucose $\geq$100 mg/dL following an 8-h overnight fast on three separate measurements that are at least 72 h apart (9).

Statistical analysis was performed by comparing the two study groups for the baseline characteristics and for risk factors for NODAT and IFG as primary study outcomes. Descriptive analysis of group I (KTRs who were converted from CsA to Tac) versus group II (CsA-treated KTRs) was performed with Student's *t* or chi-square testing for continuous measures and categorical variables, respectively. A covariate-adjusted regression analysis was used to adjust for the time to onset of NODAT and to determine the factors associated with the observed mean fasting glucose during CsA therapy and after conversion to Tac. To account for the effect of time until NODAT, a time-dependent Cox regression model was utilized with conversion to Tac as the time-varying factor. Thus, patients from group I contributed follow-up time and event occurrence (NODAT) to the group II while they were receiving CsA and after they were switched to Tac, the follow-up time and occurrence of NODAT was contributed to group I. A generalized estimating equations (GEE) model was employed, with fasting glucose level coded as a continuous response variable to estimate the impact of the covariates including conversion to Tac on the mean fasting glucose levels thereby accounting for correlation that would ensue between the preconversion and postconversion mean fasting glucose levels of group I subjects. The covariates adjusted for in both the Cox time-dependent and GEE regression models are recipients age, gender, race, hepatitis C infection status, primary cause of end-stage renal disease, baseline body mass index (BMI), renal allograft function defined by estimated glomerular filtration rate (GFR) (4-variable modification of diet in renal disease [MDRD] equation), antihypertensive medications, use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inihibitor, mean daily prednisone dose, and episodes of acute allograft rejection. Donor variables included in the multivariate regression model are living versus deceased, age and gender. Baseline glucose level at the time of transplantation and last serum glucose level prior to conversion to Tac were also introduced into the regression models. Hazard ratio for developing NODAT and difference in mean fasting glucose levels were estimated from the Cox and GEE regression models, respectively.

Results

Of the 704 nondiabetic KTRs who were included in the study, 171 (24.3%) were switched from CsA to Tac (Group I) at a mean posttransplant time of 17.3 $\pm$ 17.7 months (median time 11.4 months, range from 0.3 to 83.8 months). The rationale for switching from CsA to Tac was the clinical judgment of the treating transplant nephrologists. These clinical indications for conversion to Tac (entering group I) are depicted in Table 1. The most common indication for conversion to Tac was the occurrence of a biopsy-proven acute rejection episode in a recipient confirmed to have therapeutic 12-h CsA blood levels at the time of the rejection episode. This scenario accounted for 63% (n = 108) of all cases in which recipients were switched from CsA to Tac. Inability to maintain a stable 12-h trough CsA concentration accounted for nearly one-fifth (19.3%, n = 33) of conversion from CsA to Tac in this study cohort. The mean length of follow-up after conversion to Tac was 31.5 $\pm$ 21.6 months (median time of 20.8 months, range from 0.1 to 95.9 months). The overall mean

Table 1: Indications for conversion from cyclosporine to tacrolimus

	Numbers of patients	%
Biopsy-documented acute rejection	108	63.1
Biopsy-documented chronic rejection	14	8.2
Biopsy-documented CsA nephrotoxicity	16	9.4
Difficulty to maintain stable therapeutic cyclosporine levels	33	19.3

Table 2: Demographic characteristics between converters and nonconverters

	Group I [1] n = 171	Group II n = 533	p
Male (%)	50.6	57.6	0.11
Age at transplant (years)	41.4 ± 13.6	46.7 ± 13.2	<0.01
African American (%)	14.0	17.4	0.28
Deceased donor (%)	40.7	43.9	0.46
Renal diagnosis (% GN[2])	40.7	43.0	0.60
First transplant (%)	80.8	87.4	0.03
Fasting glucose prior to transplant (mg/dl)	86.9 ± 12.0	87.2 ± 10.1	0.62
Impaired fasting glucose prior to transplant (%)	4.3	5.1	0.72
Body mass index at transplant	26.0 ± 5.6	27.3 ± 5.9	0.01
Body mass index at last follow-up	28.1 ± 6.5	30.3 ± 7.3	0.001
Baseline GFR[3] (mL/min)	69.0 ± 27.9	69.7 ± 21.2	0.73
GFR at last follow-up (mL/min)	47.0 ± 19.0	51.6 ± 17.9	0.008
Acute rejection (episode per patients)	0.84 ± 0.79	0.27 ± 0.52	<0.01
Prednisone (mg/day)	8.0 ± 2.8	7.1 ± 2.7	<0.01
HCV positive serology (%)	4.7	4.9	0.90
Time to conversion (ms)	–	–	–
Mean (SD)	17.3 ± 17.7	–	–
Median (min, max)	11.4 (0.3, 83.8)	–	–
Length of follow-up (ms)	–	–	0.26
Mean (SD)	48.5 ± 24.0	46.0 ± 25.3	–
Median (min, max)	45.8 (4.8, 95.9)	43.6 (0.6, 96.0)	–

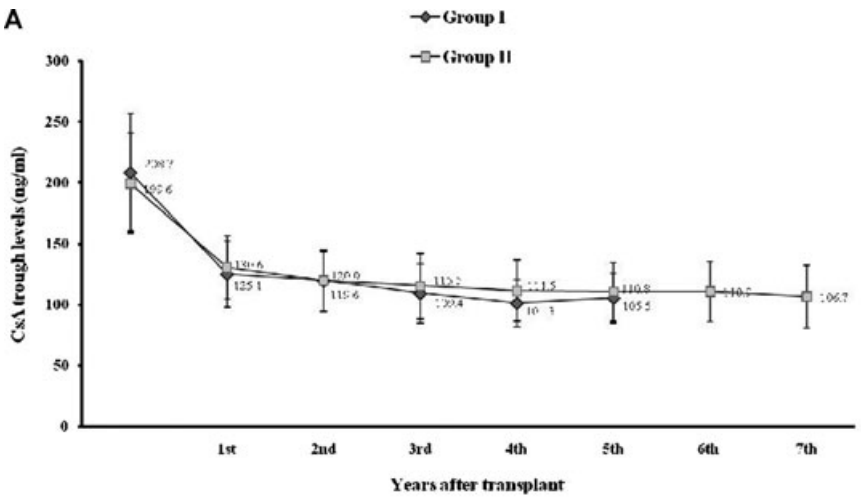
[1]Group I: KTRs who were converted from CsA (initial CNI at transplant) to Tac for medical indications.
[2]GN = glomerulonephritis.
[3]Calculated using abbreviated modification of diet in renal disease (aMDRD).

duration of follow-up for all subjects was 46.7 ± 25.0 months (median 44.3 months, range from 0.6 to 96.0 months). Demographic characteristics of the study subjects are shown in Table 2. Compared to group II, subjects who were switched from CsA to Tac (group I) were younger, had a lower BMI, had more episodes of acute rejection and received higher daily maintenance dose of prednisone.

The whole blood CsA trough levels were similar between subjects from group I prior to conversion and subjects from group II, with exception of first 3 months (208.7 ± 48.1 ng/mL in group I vs. 199.6 ± 40.9 ng/m in group II, p = 0.02) (Figure 1A). Following conversion, the whole blood Tac trough levels were higher in the first month (9.0 ± 2.8 ng/mL) and remained lower during subsequent yearly follow-up (Figure 1B).

Overall, NODAT developed in 15.2% and 15.6% of group I and II subjects, respectively (p = 0.90) and IFG in 22.1% and 25.8% of group I and II, respectively (p = 0.38). Among 171 KTRs from group I, 13 patients developed NODAT and 12 had IFG prior to conversion from CsA to Tac with respective incidence rate of 52.8 and 57.9/1000 patient-years. After switching to Tac, additional 13 patients were diagnosed with NODAT and 30 with IFG, with respective incidence rate of 30.8 and 67.2/1000 patient-years. Among 533 KTRs from group II who were never switched to Tac, a total of 83 patients was diagnosed with NODAT and 114 with IFG. The incidence rate for NODAT and IFG was 40.6 and 66.8/1000 patient years, respectively (Figure 2). At the end of study, the mean fasting glucose level in all those who did not develop NODAT was 93.4 ± 11.3 mg/dL, significantly increased compared to the baseline value prior to the transplant (87.2 ± 10.1 mg/dL, p < 0.001), but not significantly different between the groups, 92.5 ± 10.4 mg/dL in group I and 93.7 ± 11.6 mg/dL in group II (p = 0.24) (Figure 3A). Similarly, the proportion of IFG was significantly increased with the time as a whole (p < 0.001) but not between the groups (p = 0.38) (Figure 3B). Figure 4 shows the fraction of KTRs free from NODAT by CNI therapy as derived from a time-dependent analysis, which accounts for the variable contribution of different CNI exposure over time. Using multivariate time-dependent Cox regression model to account for time since conversion from CsA to Tac, the adjusted 5-year risk of NODAT-free survival after conversion from CsA to Tac was 87.4% in group I and 91.0% in group II (p = 0.90).

Significant risk factors for NODAT are depicted in Table 3. Conversion from CsA to Tac was not associated with an increased risk of NODAT (HR = 1.05, p = 0.90). Recipient age, BMI and previous serum glucose level were significant risk factors for NODAT, while African American race was near-significant (p = 0.059). Table 4 shows the results for IFG in the form of difference in mean fasting glucose. Similar to the risk factors for NODAT, significant predictors of IFG were recipient age, gender, BMI and previous glucose levels. Conversion from CsA to Tac did not have a detectable effect on the risk of IFG.



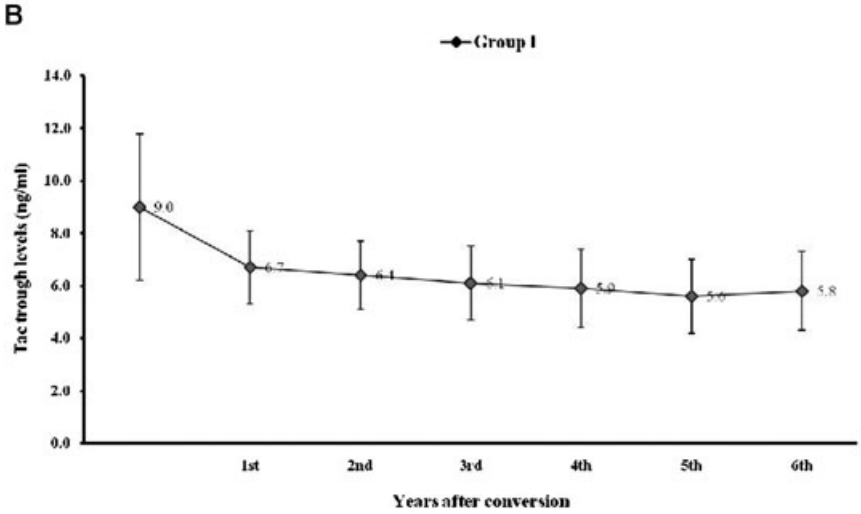


Figure 1: (A) Whole blood CsA trough levels between group I, prior to the conversion, and group II; and (B) whole blood Tac trough levels for group I following conversion.

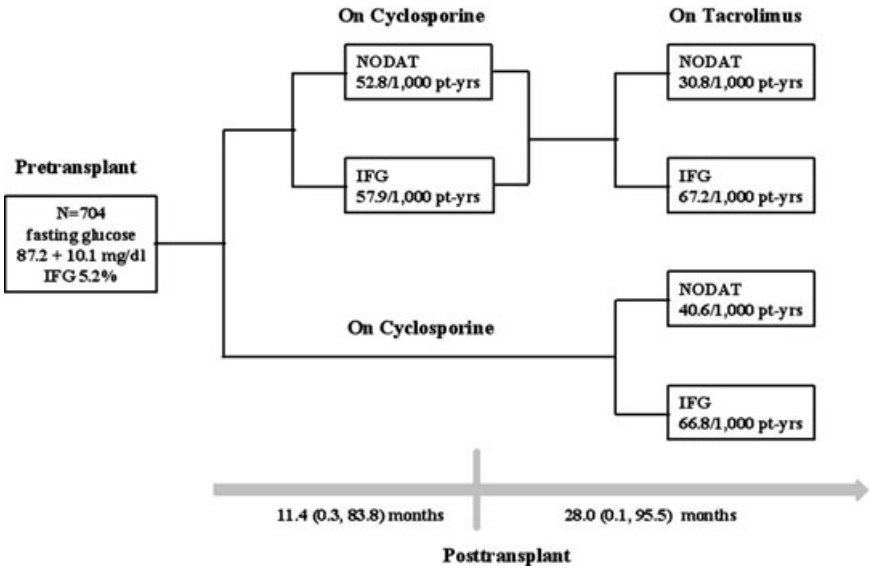


Figure 2: The risk of new onset diabetes after transplant (NODAT) and impaired fasting glucose (IGF) in kidney transplant recipients during cyclosporine therapy and after conversion to tacrolimus. pt-yrs = patient years.

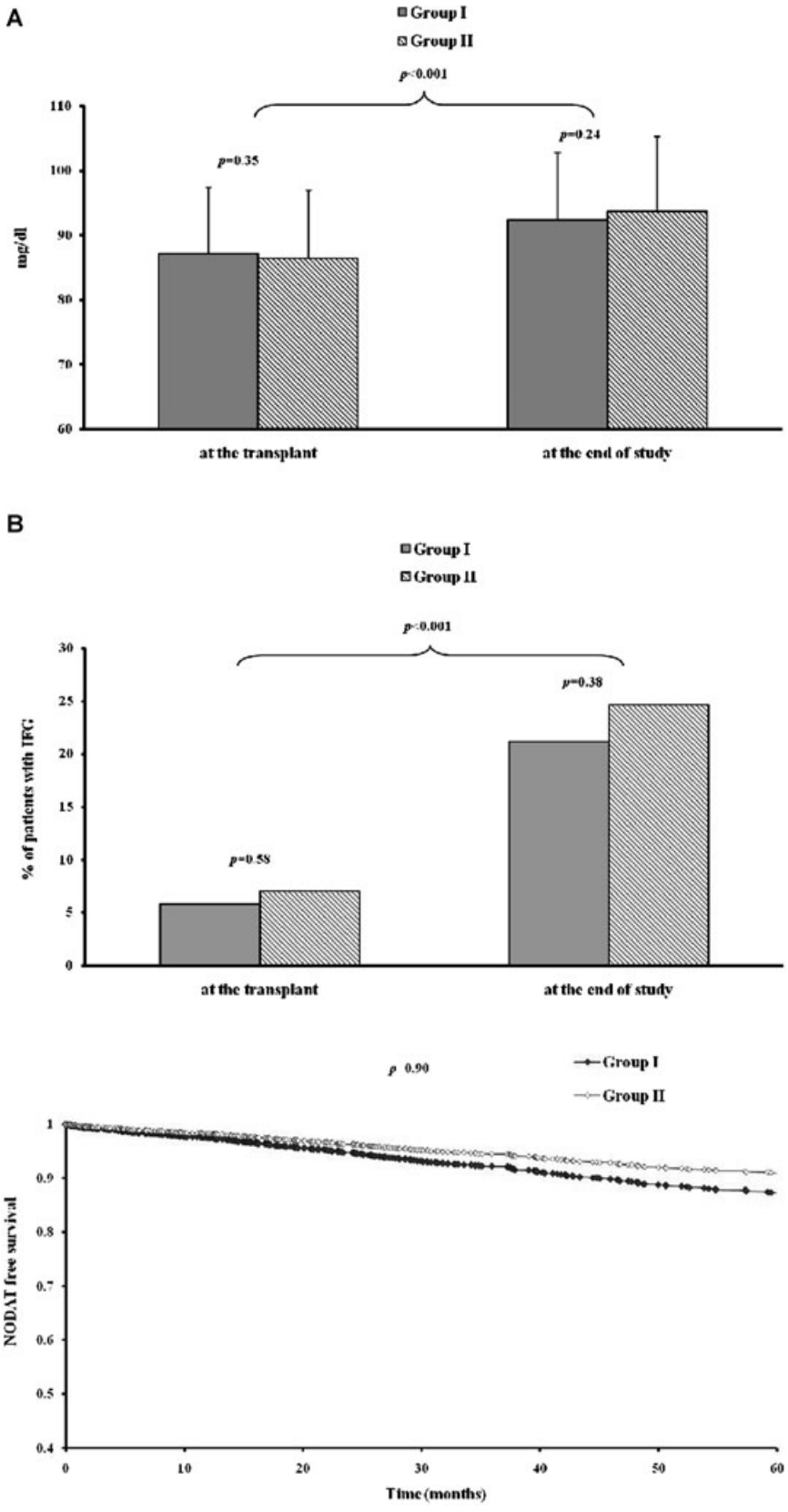


Figure 3: (A) Fasting glucose levels between the two groups and (B) distribution of impaired fasting glucose levels between the two groups.

Figure 4: NODAT-free survival curves between the two groups.

Table 3: Covariate-adjusted hazard ratios for developing NODAT

Factor	HR (95% CI)	p
Group I (converted from CsA to Tac) vs. Group II	1.05 (0.48, 2.32)	0.90
Age (per year)	1.04 (1.02, 1.06)	0.0001
AA race (ref. = all others)	1.76 (0.98, 3.17)	0.059
BMI at transplant (per unit increment)	1.09 (1.05, 1.13)	<0.0001
Previous fasting glucose level	1.06 (1.05, 1.08)	<0.0001

Discussion

This study demonstrates that the risk of NODAT and IFG appears to be similar in CsA-treated KTRs and those who were switched to Tac after an average of 17 months on CsA therapy. The design and the analytic methods employed in this study allowed for the risk of NODAT and IFG to be considered at two separate posttransplant intervals, namely the early posttransplant period when recipients with diminished beta cell reserve are more predisposed to NODAT and the late posttransplant period during which diabetogenic immunosuppressive drugs are at significantly lower levels and the remaining diabetes-free recipients had a different risk profile. This methodological partitioning of risk intervals is rarely employed in many studies of the incidence of NODAT. In the current study, partitioning of posttransplant risk intervals virtually isolate (albeit not completely) the additional diabetogenic risk engendered by switching from CsA to Tac. Thus, the result of the current study is highly relevant to clinical practice as switching from CsA to Tac is an increasingly common therapeutic maneuver. In contrast to other studies in which cumulative incidence and prevalence estimates are reported, the current study illustrates the incidence rate of NODAT and IFG in the late posttransplant period.

The CNIs, CsA and Tac, share a negative impact on CVD risks, although the magnitude may differ between them. The optimal choice of CNI for the purpose of improving CVD risk profile remains unsettled. Several studies have shown better serum lipid profile and/or blood pressure control in renal transplant patients treated with Tac than those treated with CsA, but the higher incidence of NODAT associated with Tac use, demonstrated both by epidemiological studies and clinical trials, may hamper the enthusiasm of using Tac for the purpose of CVD risk reduction (10,13,14,19–21).

Table 4: Covariate-adjusted differences in mean fasting glucose levels

Factor	Difference in mean (95% CI)	p
Converted from CsA to Tac (vs. not converted)	1.48 (−0.63, 3.59)	0.17
Age (per year)	0.18 (0.11, 0.25)	<0.0001
Gender (ref. = male)	−3.07 (−4.76, −1.38)	0.0004
BMI at transplant (per unit increment)	0.33 (0.15, 0.51)	0.0003
Hepatitis C Ab + (vs. Ab −)	4.60 (−0.83, 10.03)	0.097
Previous fasting glucose level	0.23 (0.12, 0.33)	<0.0001

Several investigators have studied the effects of conversion from CsA to Tac on cardiovascular risk factors in renal transplant patients (16–18,22–24). All those studies have documented beneficial effects of such approach in improving blood pressure control and lipid metabolism. However, none of these studies provided sufficient information regarding risk of developing NODAT and IFG with conversion.

NODAT is associated with poor renal allograft and patient outcome (4). New onset of hyperglycemia and early diagnosed NODAT are associated with elevated CVD events (3,7). Reducing the incidence of NODAT and improving glycemic control, even within no diabetic range, should be part of any strategy aimed to curtail the CVD risks in renal transplant patient population. Our study provides the needed information on the risk of developing abnormal glucose metabolism when changing CNIs, a common practice among the transplant physicians, is contemplated.

The strength of the current study includes the relatively large sample size, the use of standard definition of NODAT and adjustment for baseline fasting glucose levels. Multivariate analysis using generalized estimating equation and a time to event analysis allowed us to clearly describe the risk of Tac conversion on impaired glucose metabolism and, in particular, the development of NODAT as well as proportion of subjects with impaired fasting glycemia. Our findings of lack of association between Tac conversion and worsening impaired glucose metabolism suggest that conversion from CsA to Tac in the late posttransplant period does not necessarily incur an increased risk of disturbed glucose metabolism in select cohort of clinically stable KTRs. It is possible that this study did not find increased risk of NODAT with conversion from CsA to Tac because of differences in drug exposure to Tac during early versus late posttransplant period. In fact, the mean Tac trough level within the first months following conversion in this cohort was 9.0 ng/mL, a level that is lower than the typical trough concentration when Tac is used conventionally as the *de novo* CNI in kidney transplantation. Lack of increased risk of NODAT with conversion from CsA to Tac is consistent with other recent studies (25,26).

The findings in this study are tempered by several limitations related to its retrospective design. Patients who were switched to Tac were younger and had lower BMI, both of which are known risk factors for the development of NODAT. It's likely that those patients were more carefully scrutinized when clinically indicated conversion was contemplated by individual physicians. Thus those patients

could represent a selected group with less predisposition to develop impaired glucose metabolism and possibly even better informed and educated for the stronger pro-diabetic potential associated with Tac use. Appropriate use of statistical methodology with multivariate analysis adjusting for age and BMI, among others, helped us to lessen but not completely eliminate concern of such selection bias. Thus caution is required in interpreting our findings. A prospective randomized trial with conversion in both directions may help to give a definite answer. Finally, insufficient information from our retrospective ascertainment of clinical data prevented us from evaluating the impact of CNI conversion therapy on cardiovascular event rates.

In conclusion, conversion of maintenance CNI from CsA to Tac beyond the first years after transplantation in selected renal transplant recipients does not appear associated with either worsening abnormal glucose metabolism or statistically significant increase in the risk of NODAT.

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