

# POSTTRANSPLANT DIABETES MELLITUS IN KIDNEY ALLOGRAFT RECIPIENTS: INCIDENCE, RISK FACTORS, AND MANAGEMENT<sup>1</sup>

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**Background.** Posttransplant diabetes mellitus (PTDM), associated with the use of immunosuppressants, occurs at varying rates in kidney transplant recipients.

**Methods.** Five transplant centers conducted a retrospective review of 435 kidney recipients completing at least 6 months of follow-up to determine risk factors, incidence, and management strategies for posttransplant glucose intolerance. A distinction was made between hyperglycemia and diabetes.

**Results.** The incidence of PTDM was found to be 4.9%. Among tacrolimus-treated patients it was 5.7%, compared with 3.3% among cyclosporine-treated patients ( $P=0.453$ ). Mean daily maintenance doses of prednisone and mycophenolate mofetil (MMF) were significantly lower in tacrolimus-treated patients. Significantly more tacrolimus-treated patients were prednisone-free (9.0%/0%;  $P<0.001$ ). Logistic regression analysis revealed that the absence of an antiproliferative agent correlated with the development of PTDM (odds ratio=3.56;  $P=0.01$ ).

**Conclusions.** Based on this study, we propose management guidelines specifically for glucose intolerance developing after renal transplantation. Maintenance of blood glucose levels within strict limits is recommended, and the contribution of immunosuppressive agents to the development of PTDM is accounted for. Gradual tapering of prednisone and tacrolimus is proposed for patients who develop PTDM but also bear minimal risk of rejection. Tapering and eventual withdrawal of insulin should be attempted once blood glucose levels normalize. Switching to the alternative calcineurin inhibitor should only be considered as a late intervention. Tacrolimus therapy should be considered even in patients at high risk for diabetes, because the benefit of reduced acute rejection

incidence and severity, as demonstrated in other studies, outweighs the risk of PTDM.

## INTRODUCTION

Reports of the incidence of posttransplant diabetes mellitus (PTDM) historically, and more recently as the result of adopting newer agents into immunosuppressive regimens, prompted the present review of PTDM at five U.S. kidney transplant centers. Institutions experienced in the use of tacrolimus-based immunosuppression participated in the roundtable conference to evaluate the onset of PTDM as it occurs in routine clinical practice. An additional aim of the conference was to develop guidelines for the management of PTDM.

PTDM is recognized as an adverse event associated with the use of corticosteroids, cyclosporine, or tacrolimus. Historically, immunosuppressive regimens consisting of corticosteroids and azathioprine have been associated with an incidence of PTDM as high as 46% (1, 2). More recently, the incidence of PTDM related to cyclosporine- and corticosteroid-based regimens has been reported to be as high as 20% among kidney allograft recipients (3–5). Most cases of PTDM occur during the first 3 months after transplantation or after treatment for rejection. Decreases in the release of insulin and peripheral insulin resistance have been identified as possible mechanisms of immunosuppression-associated PTDM (6–10).

The U.S. Multicenter Phase III Trial of tacrolimus therapy in kidney transplantation revealed an increased incidence of PTDM among patients receiving tacrolimus (FK506, Prograf, Fujisawa Healthcare, Inc., Deerfield, IL) compared with cyclosporine (CsA) (Sandimmune, cyclosporine, Novartis, East Hanover, NJ) at 1 year of follow-up (19.9% vs. 4.0%, respectively,  $P<0.001$  (11)). The incidence of PTDM among tacrolimus-treated, African-American patients was higher (36.6% vs. 12.2% among CsA-treated African-American patients; significance not reported (12)). On the other hand, the analysis also revealed that significantly fewer African-American patients treated with tacrolimus required antilymphocyte antibody therapy to resolve acute rejection episodes (5.5% vs. 26.9% CsA-treated, African-American patients,  $P<0.01$  (12)). A multivariate analysis identified African-American recipient race, high corticosteroid dose, and high tacrolimus trough levels as risk factors for the development of PTDM in this clinical trial (11).

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Follow-up of this multicenter trial at 5 years revealed that overall 47% of tacrolimus-treated patients who developed PTDM over the first year discontinued insulin and remained on tacrolimus therapy (13). The reduced mean daily dose and whole blood trough levels of tacrolimus at 5 years (0.12 mg/kg/day and 8.4 ng/mL, respectively) compared to those initially targeted (0.2 mg/kg/day and 10–25 ng/mL, respectively) may have contributed to the reversal of insulin dependence over time (11).

Most kidney transplant centers in the United States now incorporate mycophenolate mofetil (MMF) (CellCept, Hoffmann-LaRoche Inc., Nutley, NJ) into immunosuppressive regimens. A recent report compared the use of tacrolimus or CsA (Neoral, cyclosporine, Novartis) combined with MMF in kidney transplant patients. The study revealed a low incidence of insulin use at 1 year of follow-up (2.2% among tacrolimus-treated patients vs. 6.5% among Neoral-treated patients (14)) and at 2 years (tacrolimus: 5.6%; Neoral: 4.0% (15)).

Findings from another recent study corroborate these results. In this dose-finding study of MMF in combination with tacrolimus (16), the incidence of PTDM was 4.8% among patients treated with tacrolimus plus a daily dose of 2 g of MMF.

## MATERIALS AND METHODS

### Center Participation and Patient Inclusion Criteria

The purpose of the retrospective chart review was to collect data on individual patients that reflects the most current clinical practice at kidney transplant centers experienced in the use of tacrolimus as primary immunosuppressive therapy. Five centers conducted a retrospective analysis of the last 100 patients receiving kidney allografts between January 1997 and July 1999 who had been followed for at least 6 months after transplantation. Chart review was conducted according to institutional ethical guidelines.

A total of 435 patients met the inclusion criteria for the review and were included in the analysis presented in this report. The participating institutions were the University of Cincinnati Medical Center, University of North Carolina at Chapel Hill, Medical College of Wisconsin, Northwestern University Medical School, and the Thomas E. Starzl Transplantation Institute, University of Pittsburgh Medical Center. Demographic profiles and relevant recipient factors are presented in Table 1. Mean follow-up was 561 days ( $\pm 201$ , range 201–1336 days). After transplantation, patients were treated according to center-specific immunosuppressive protocols. A summary of treatment regimens is presented in Table 2.

### Data Collection and Analysis

**Patient chart review.** We collected data on the immunosuppressive regimen (agents, doses, calcineurin inhibitor trough levels), incidence of PTDM, and management strategies at 1 week, 1 month, 3 months, 6 months, and 12 months after transplantation. For patients who developed PTDM while receiving tacrolimus therapy, we also analyzed the mean tacrolimus dose, trough blood levels, and corticosteroid doses at the time of development of insulin dependence. Management strategies were summarized as the basis of the reported guidelines.

**Data and statistical analysis.** Data were entered into an Excel (Microsoft) database and queried as appropriate for median or mean  $\pm$  SD (recipient demographic factors, doses of immunosuppressive agents, serum creatinine levels, serum glucose levels) and the incidence of PTDM.

Groups of patients maintained on tacrolimus- or CsA-based therapy were compared for the incidence of PTDM, MMF dosing (median

**TABLE 1. Patient demographics and recipient characteristics<sup>a</sup>**

Total number (n)	435
Mean age (years)	45 $\pm$ 14 (5–78)
Gender	
Male	234 (53.9%)
Female	200 (46.1%)
Race	
Caucasian	278 (64.5%)
African-American	122 (28.3%)
Hispanic	12 (2.8%)
Other	19 (4.4%)
Mean weight (kg)	74.6 $\pm$ 18.8 (19.4–126.4)
Transplant type	
Cadaveric	269 (61.8%)
LRD <sup>b</sup>	128 (29.4%)
LURD <sup>c</sup>	38 (8.7%)
Number of transplants	
1	361 (83.1%)
2	60 (13.8%)
$\geq 3$	13 (3.0%)
Primary diagnosis	
Hypertension	91 (20.9%)
Glomerulonephritis	68 (15.6%)
Diabetes	66 (15.2%)
Focal glomerulosclerosis	41 (9.4%)
Polycystic kidney disease	33 (7.6%)
Nephritis	24 (5.5%)
IgA nephropathy	14 (3.2%)
Systemic lupus	9 (2.1%)
Other	69 (15.9%)
Unknown	20 (4.6%)

<sup>a</sup> One, four, and one patient not accounted for with respect to gender, race, and number of transplants, respectively.

<sup>b</sup> LRD, living-related donor.

<sup>c</sup> LURD, living-unrelated donor.

**TABLE 2. Immunosuppressive regimens**

Maintenance immunosuppressive agents	
Calcineurin inhibitors <sup>a</sup>	n (%)
Tacrolimus	283 (65.1)
CsA	149 (34.2)
Secondary agents	n (%)
MMF	339 (77.9)
Prednisone	400 (92.0)
Azathioprine	5 (1.1)
Sirolimus	19 (4.4)
SDZ-RAD/everolimus	13 (3.0)

<sup>a</sup> Three patients received neither tacrolimus nor CsA.

and mean), oral prednisone dosing (median and mean), and serum creatinine levels (median). Differences between measurements with  $P \leq 0.05$ , as determined by chi-square, Fisher's exact, or Mann-Whitney *U* tests, as appropriate, were considered significant.

A distinction was made between PTDM and hyperglycemia. PTDM was defined as the requirement for insulin to normalize blood glucose levels in patients with no previous history of diabetes. Patients who required oral antidiabetic agents to normalize blood glucose levels were described as being hyperglycemic.

A multivariate analysis of the risk of developing PTDM was performed using logistic regression analysis. The dependent variable (PTDM) was analyzed against a series of eight independent recipient variables: age, gender, race, weight at time of transplantation, transplant number, type of calcineurin inhibitor used, use of an antiproliferative agent (MMF, azathioprine, rapamycin, SDZ-RAD/everolimus

mus, or none), and use of prednisone. Subsequently, repeated, weighted analyses were performed in which the effect of the least significant independent variable was determined sequentially. A second analysis was conducted, including only patients who were maintained on tacrolimus-based therapy, to evaluate risk factors.

RESULTS

Patient Demographics and Recipient Characteristics

Included in the database were 435 patients from five centers (Table 1). The majority of patients were male, Caucasian adults who had received primary cadaveric allografts. Hypertension was the primary diagnosis leading to transplantation in approximately 21% of patients. Approximately 15% of patients were diabetic at the time of transplantation.

Maintenance Immunosuppression

Tacrolimus-based immunosuppression was the primary therapy in 65.1% of patients (Table 2). Over the course of the follow-up period, 60 patients were switched from CsA-based immunosuppression to tacrolimus. The mean time of conversion was 157 days ( $\pm 113$ ; 31–365) after transplantation. Conversely, six patients were switched to a CsA-based regimen from tacrolimus at a mean time of 147 days ( $\pm 115$ ; 15–396) after transplantation. With respect to PTDM, patients were categorized according to the immunosuppressive therapy that they received at the time of diagnosis.

MMF was combined with calcineurin inhibitors in approximately 78% of patients. As part of the maintenance regimen, 400 patients (92.0%) received prednisone. Five patients (1.1%) received azathioprine. Sirolimus was used in 19 patients (4.4%), and 13 patients at one center (3.0% of the population overall) were enrolled in a clinical trial of SDZ-RAD/everolimus (vs. MMF) in kidney transplantation. All patients enrolled in the SDZ-RAD/everolimus study received CsA; one patient was switched to a regimen of tacrolimus + MMF.

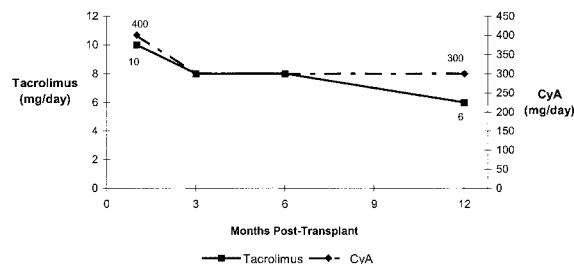
Median values for calcineurin inhibitor daily doses, trough blood levels, MMF and prednisone daily doses, and serum creatinine levels are presented in Figures 1–3, respectively. Corresponding mean values at the time of latest follow-up are described in the text that follows.

Dosing and Blood Levels of Immunosuppressants

The median daily doses and median whole blood trough levels of tacrolimus and CsA are presented in Figure 1. Mean daily doses of both calcineurin inhibitors decreased over the follow-up period (12.8–7.6 mg/day and 492–307 mg/day for tacrolimus and CsA, respectively). Mean trough blood levels of tacrolimus and CsA at latest follow-up were  $10.1 \pm 10.5$  ng/mL and  $221 \pm 86$  ng/mL, respectively.

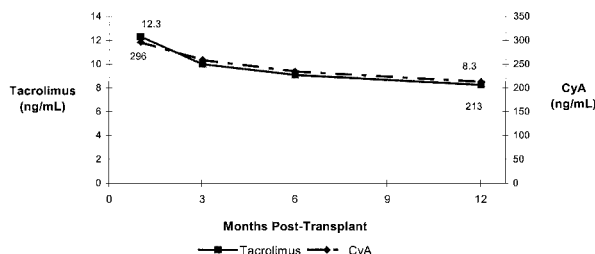
The median daily doses of MMF and prednisone are presented in Figure 2. The mean daily dose of MMF over the entire follow-up period was  $1982 \pm 756$  mg in patients maintained on tacrolimus and  $2084 \pm 589$  mg in patients receiving CsA ( $P=0.012$ ). Mean dosing of MMF at the time of latest follow-up was  $1640 \pm 693$  and  $1831 \pm 565$  mg in patients receiving tacrolimus or CsA, respectively ( $P<0.001$ ). The mean daily oral prednisone dose over the entire follow-up period was  $14.7 \pm 11.2$  mg for tacrolimus-treated patients and  $20.0 \pm 18$  mg for CsA-treated patients. Corresponding mean doses at the time of latest follow-up were  $7.8 \pm 3.5$  mg and

A.



N	1 Week	1 Month	3 Months	6 Months	1 Year
Tacrolimus	271	287	315	320	228
CyA	139	138	114	104	79

B.



N	1 Week	1 Month	3 Months	6 Months	1 Year
Tacrolimus	268	286	310	304	213
CyA	138	138	113	103	78

FIGURE 1. Median daily doses (A) and whole blood trough levels (B) of calcineurin inhibitors, with N values at each time point appearing in the tables.

$7.8 \pm 2.9$  mg, respectively ( $P=0.428$ ). All patients receiving CsA were maintained on prednisone throughout the follow-up period. In contrast, 25 patients (9.0%) receiving tacrolimus therapy were prednisone-free at 1 year ( $P<0.001$ ).

Renal Function

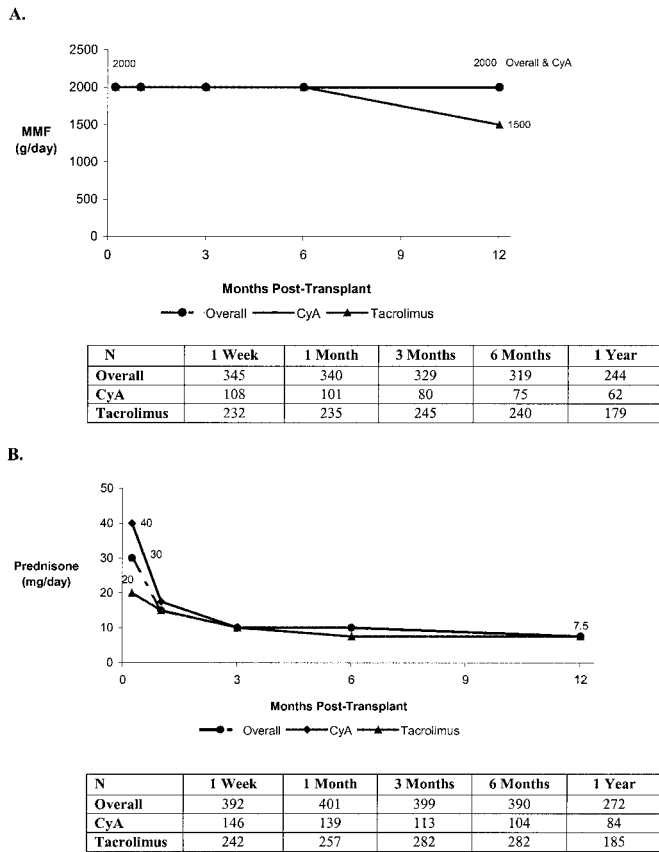
In the entire population, median serum creatinine levels decreased from 1.95 mg/dL at 1 week after transplantation to 1.35 mg/dL at the time of latest follow-up (Fig. 3). Mean values at the time of latest follow-up were  $1.5 \pm 0.6$  mg/dL for tacrolimus-treated patients and  $1.5 \pm 0.7$  mg/dL for patients maintained on CsA ( $P=0.407$ ; range 0.5–5.2 mg/dL in the population overall).

Incidence of Dysregulated Glucose Metabolism

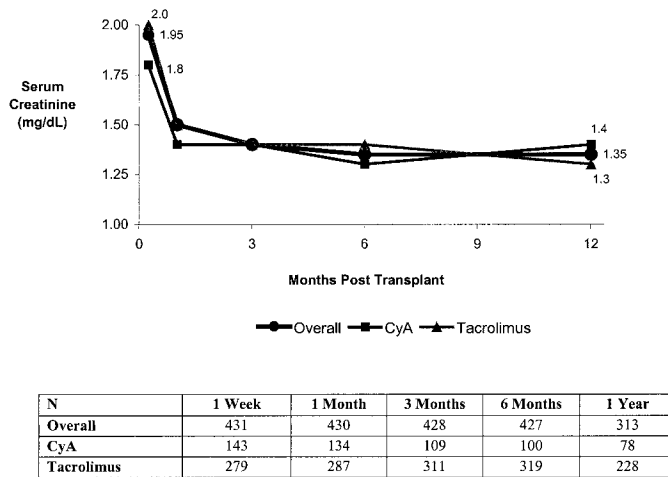
PTDM was defined as the requirement for insulin to normalize blood glucose levels in patients with no previous history of diabetes. Patients who required oral antidiabetic agents to normalize blood glucose levels were distinguished as being hyperglycemic.

A summary of the development of PTDM and hyperglycemia appears in Table 3. Overall, 18 patients without a previous history of diabetes developed PTDM over the course of follow-up (18/369=4.9%). After transplantation, 23 additional patients developed hyperglycemia (23/369=6.2%).

Of the 369 patients with no history of diabetes at transplantation, 245 received tacrolimus and 121 received CsA. Three patients included in the chart review who had no history of PTDM received neither calcineurin inhibitor. Four patients receiving CsA (4/121=3.3%) and 14 receiving ta-



**FIGURE 2. Median daily doses of MMF (A) and Prednisone (B), with N values at each time point appearing in the tables.**



**FIGURE 3. Median serum creatinine, with N values at each time point appearing in the table.**

rolimus (14/245=5.7%) developed PTDM ( $P=0.453$ ; Table 3). In addition, 15 tacrolimus- and 8 CsA-treated patients developed hyperglycemia (6.1% and 6.6%, respectively;  $P=0.999$ ; Table 3). There seemed to be differences among centers with respect to the incidence of PTDM (range 0–9.6%) and hyperglycemia (range 1.3–9.5%).

**TABLE 3. Analysis of patients developing PTDM<sup>a</sup> or new onset hyperglycemia<sup>b</sup>**

Patients without previous history of diabetes	n	369
Tacrolimus	n	245
CsA	n	121
PTDM	n (%)	18/369 <sup>c</sup> (4.9)
Tacrolimus	n (%)	14/245 (5.7)
CsA	n (%)	4/121 (3.3) $P=0.453$
Hyperglycemia	n (%)	23/369 <sup>c</sup> (6.2)
Tacrolimus	n (%)	15/245 (6.1)
CsA	n (%)	8/121 (6.6) $P=0.999$
Mean time to development of PTDM	Days	87.8
Profile of patients developing PTDM		
Mean age	Years	50.32±18.27
Gender	n (%)	
Male		9/18 (50.0)
Female		9/18 (50.0)
Race		
Caucasian	n (%)	9/242 (3.7)
Receiving tacrolimus	n	6
Receiving CsA	n	3
African-American	n (%)	9/100 (9.0) $P=0.549$
Receiving tacrolimus	n	8
Receiving CsA	n	1

<sup>a</sup> Defined as the requirement for insulin among patients without a pretransplant history of diabetes.

<sup>b</sup> Defined as the requirement for treatment with (an) oral antidiabetic agent(s) among patients without a pretransplant history of diabetes.

<sup>c</sup> Three patients with no history of diabetes did not receive either calcineurin inhibitor.

The incidence of PTDM was higher among African-American compared with Caucasian patients (9.0% vs. 3.7%), but the difference was not statistically significant ( $P=0.549$ ). There was no statistically significant effect of primary diagnosis on the incidence of PTDM ( $P=0.599$ ).

For tacrolimus-treated patients who developed PTDM, we collected data on tacrolimus dosing and whole blood trough levels as well as prednisone dosing. The median daily dose of tacrolimus and the median whole blood trough level at the time of diagnosis were 12.0 mg and 12.4 ng/mL, respectively. Corresponding values at the time of latest follow-up before diagnosis were 14.0 mg and 12.7 ng/mL. The median daily prednisone dose was 13.8 mg at the time of latest follow-up before diagnosis. The median dose was 12.5 mg at the time of diagnosis of PTDM.

*Multivariate Analysis of Risk Factors for the Development of PTDM*

We conducted a multivariate analysis of the potential risk factors for the development of PTDM. Eight recipient demographic and maintenance immunosuppression factors were chosen as independent variables: age, gender, race, weight at transplantation, number of transplants, type of calcineurin inhibitor (tacrolimus or CsA), use of an antiproliferative agent (MMF, azathioprine, rapamycin, SDZ-RAD/everolimus, or none), or use of prednisone. Only the absence of an antiproliferative agent resulted in a significant, positive odds ratio (3.56;  $P<0.01$ ).

These findings prompted additional, weighted analyses in which the least significant independent variable was removed, and the data were re-analyzed. The order of removal of variables was: use of prednisone (yes/no), age, gender, number of transplants, race, calcineurin inhibitor, weight at transplantation, and use of an antiproliferative agent (yes/no). Again, only the use of an antiproliferative agent retained statistical significance throughout the analysis.

In a subsequent univariate analysis, tacrolimus dosing and blood trough levels were significantly higher among patients who did not receive antiproliferative agent combination therapy (n=30) compared with those who did (n=215; Fig. 4; *P* values: tacrolimus dosing *P*<0.001; tacrolimus blood trough levels *P*<0.001). There was a trend toward higher tacrolimus doses in patients who developed PTDM compared with those who did not (*P*=0.096).

The entire analysis was repeated, including only patients who received tacrolimus therapy. Once again, the analysis revealed that the absence of antiproliferative agents is related to the development of PTDM (odds ratio 6.42; *P*=0.008).

DISCUSSION

Clinical focus on the improvement of long-term outcomes in renal transplantation has attracted attention to factors impacting the development of diabetes after renal transplan-

tation (see 17). However, the diagnostic criteria and proposed management strategies are based entirely on guidelines developed for the general population. The aims of this study were to evaluate the incidence of posttransplant diabetes (PTDM) in current practice and to develop diagnostic and management guidelines specifically for renal allograft recipients.

Dysregulated glucose metabolism has been recognized as a complication after kidney transplantation since the 1970s, but inconsistent definitions of diabetes in the literature have complicated the interpretation of reports of immunosuppression-related glucose intolerance. Definitions have ranged from the requirement for de novo insulin therapy for greater than two consecutive weeks to the determination of three consecutive elevated blood glucose levels (>140 mg/dL or >150 mg/dL) (1, 3-5).

American Diabetes Association (ADA) guidelines do not account for the occurrence of diabetes among recipients of organ allografts (18). According to a recent review of the impact and management of PTDM among kidney allograft recipients, the diagnosis of diabetes after kidney transplantation should coincide with the diagnosis in the general population (19). The authors suggest that the diagnosis should be made in any one of three sets of circumstances. In the first, PTDM is diagnosed when random blood glucose levels exceed 200 mg/dL and are accompanied by the clinical symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss). Another alternative for diagnosing PTDM is a fasting plasma glucose of ≥126 mg/dL. The third indication is 2-hr plasma glucose levels of ≥200 mg/dL in a standard oral glucose tolerance test (OGTT).

The Clinical Practice Guidelines Committee of the American Society of Transplantation (AST) has published recommendations for outpatient surveillance of recipients of renal allografts (17). Blood glucose management is cited as a critical focus of long-term patient management. The committee acknowledges the variation in definition of PTDM in the literature and suggests that a fasting plasma glucose level of >126 mg/dL is an indication for oral glucose tolerance testing to establish the diagnosis of PTDM. These guidelines will prove instrumental to the prospective optimization of long-term kidney function and management of cardiovascular risk among recipients of kidney allografts.

In this study, we have defined PTDM as the requirement for insulin to normalize blood glucose levels in patients with no pretransplant history of diabetes. Although the rationale for our definition is based on the principles of diabetes diagnosis and management described for the general population (18), we believe that kidney allograft recipients who develop diabetes after transplantation constitute a unique population. Therefore, PTDM warrants unique evaluation and management strategies. This realization, supported by the data retrieved from our clinical review, has prompted the distinction between hyperglycemia and diabetes proposed in Figure 5.

PTDM occurred at relatively low frequency in the population of patients surveyed in this study (4.9%). In contrast to the results of the Phase III Trial of tacrolimus in kidney transplantation, there was no significant difference in the incidence of PTDM among patients treated with tacrolimus or CsA. The majority of patients were followed for a period of at least 1 year (mean follow-up 561±201 days). Furthermore,

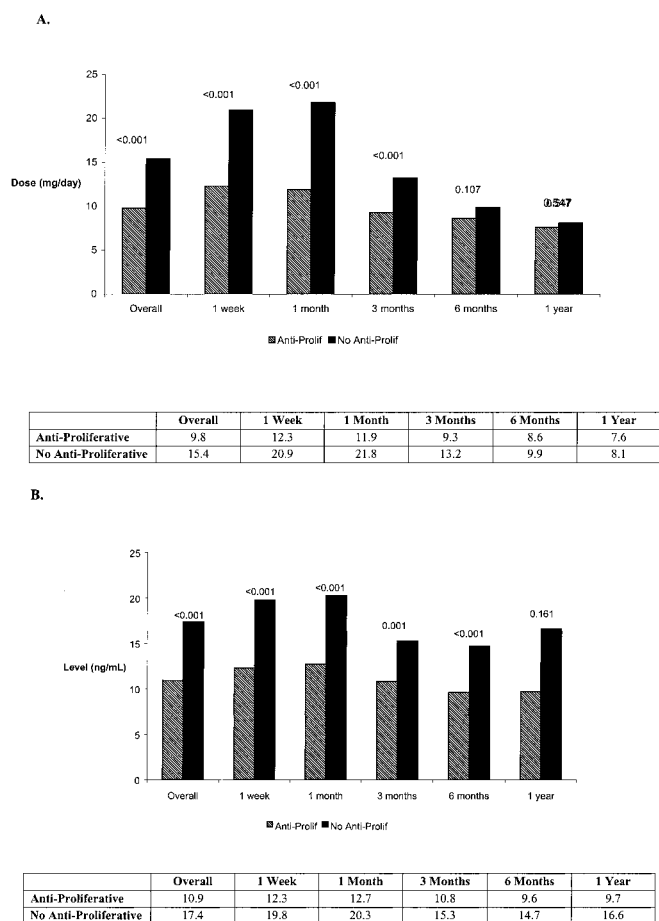
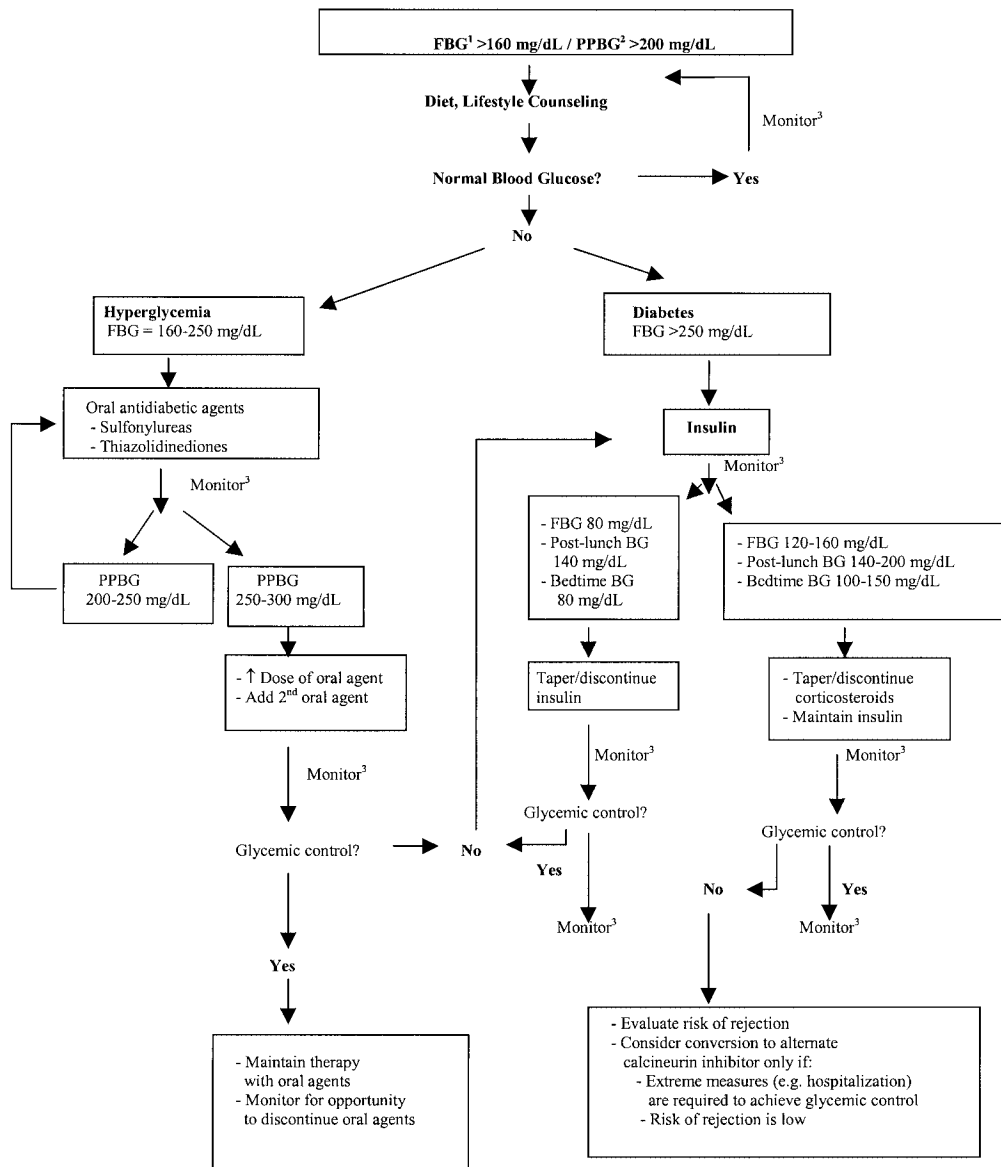


FIGURE 4. Tacrolimus doses (A) and tacrolimus whole blood trough levels (B) in patients who were maintained with and without antiproliferative agent(s).



**FIGURE 5. Guidelines for the management of PTDM.**

<sup>1</sup>Fasting blood glucose.  
<sup>2</sup>Postprandial blood glucose.  
<sup>3</sup>Self-monitor blood glucose 2-4 times daily.  
 Laboratory monitoring concomitant with monitoring of renal function at regular clinic visits.

this retrospective review focused on issues concerning the development of PTDM and did not consider the incidence of acute rejection. Longer follow-up among a larger population of patients would be required to determine the rate of reversal of insulin dependence among patients who develop PTDM under current clinical practice conditions.

Interestingly, the absence of an antiproliferative agent (MMF, azathioprine, sirolimus, or SDZ-RAD/everolimus) was the only significant positive factor identified in a multivariate analysis of risk of developing PTDM. That is, patients who did not receive an antiproliferative agent experienced an increased incidence of PTDM. A high tacrolimus trough level did not emerge as a risk factor for PTDM, as it did in the multivariate analysis of risk conducted over the course of the Phase III Trial of tacrolimus in kidney transplantation (11). However, in the present analysis, it was noted that higher tacrolimus blood levels in patients not receiving antiprolif-

erative agents were associated with the development of PTDM. Additional, prospective study would be required to determine the reproducibility of this result and the contribution of additional factors to the occurrence of PTDM under maintenance on current immunosuppressive regimens.

Our proposed diagnostic and management strategies support the AST Committee's opinion on the stringent management of blood glucose levels (Fig. 5). Our strategies also account for the contribution of immunosuppressive agents to the development of glucose intolerance. Finally, the scheme represented in Figure 5 recognizes that immunosuppression-related hyperglycemia and PTDM are reversible in some patients. In further agreement with the AST Committee guidelines, we recommend that blood glucose be monitored at frequent, regular intervals.

In recipients of kidney allografts, blood glucose should be monitored daily during the initial hospital stay. After dis-

charge from hospital, patients with elevated blood glucose levels should self-monitor at least twice daily (2–4 times/day is recommended). In addition, blood glucose levels should be verified at each regular outpatient clinic visit. Patients with fasting blood glucose of >160 mg/dL or postprandial blood glucose of >200 mg/dL should be investigated for dysregulated glucose metabolism.

Hyperglycemia, defined as fasting blood glucose of 160–250 mg/dL, should be managed initially by administration of oral antidiabetic agents. The individual medical profile of the patient and the relative benefit/toxicity profile of each drug are definitive guides to choosing an appropriate oral agent. Sulfonylureas or thiazolidinediones, a new class of antidiabetic oral agent (20–22), should be considered first.

Persistent elevation of blood glucose levels within this range (160–250 mg/dL) might respond to an increased dose of a single agent or to an additional oral agent. Glycemic control may provide the opportunity to discontinue oral agents, because the doses of immunosuppressive agents are naturally tapered over time after transplantation.

Insulin may be required to normalize blood glucose levels in patients whose fasting blood glucose exceeds 250 mg/dL. Insulin tapering or discontinuation should be considered in patients whose fasting and bedtime blood glucose measure  $\leq 80$  mg/dL and whose postprandial blood glucose is  $\leq 140$  mg/dL. Insulin should be withdrawn or tapered over an extended period to ensure adequate glycemic control. During this time, oral agents may be used to control blood glucose levels.

Modifying the immunosuppressive regimen should be considered only in patients whose blood glucose levels remain difficult to control. Tapering corticosteroid dose or discontinuing corticosteroid therapy should be considered before making adjustments to primary immunosuppressive agents.

Published evidence suggests that safe and effective corticosteroid withdrawal may be achieved in kidney allograft recipients maintained on a tacrolimus-based regimen (23–27). However, we caution that surveillance biopsies were not performed in the present patient population, and the follow-up period is relatively short. The possibility of indolent rejection should be considered when corticosteroids are discontinued.

When corticosteroid tapering is indicated, it should be achieved gradually, with concomitant monitoring for signs of acute rejection, including attention to clinical signs, measurement of serum creatinine levels, and kidney allograft biopsy, if necessary. The relative merits of tapering insulin versus corticosteroids should be decided on an individual basis.

The early use of tacrolimus was associated with increased risk of developing PTDM (11). However, the incidence and severity of acute rejection episodes have been shown to be significantly reduced among tacrolimus-treated patients (11, 12, 14, 16, 28). In addition, the results of recent clinical trials, particularly those evaluating the combination of tacrolimus with MMF, suggest that the incidence of PTDM is equivalent in patients receiving tacrolimus- or CsA-based immunosuppressive therapy (2.2–7%) (14, 16, 24, 28).

For patients who develop PTDM while receiving tacrolimus therapy, conversion to CsA should be considered in cases of severe manifestations of diabetes. Patients with severe manifestations include those who require hospitalization to

normalize blood glucose levels, those who experience serious secondary complications of PTDM, or those in whom blood glucose levels remain unstable. The risk of rejection should be carefully evaluated before conversion, and patients should be monitored for rejection if conversion becomes necessary.

Immunosuppressive agents, including corticosteroids, CsA, and tacrolimus, have all been implicated in the development of PTDM. Results of the present review suggest that the incidence of PTDM is low under current immunosuppressive protocols, prompting reconsideration of previously identified risk factors for developing dysregulated glucose metabolism after transplantation. Tacrolimus therapy should be considered even in patients at high risk for the development of PTDM, because the benefits of reduced acute rejection incidence and severity, as demonstrated in other studies (11, 12, 14, 16, 28), outweigh the risk of developing PTDM.

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## Ki67, E-CADHERIN, AND p53 AS PROGNOSTIC INDICATORS OF LONG-TERM OUTCOME AFTER LIVER TRANSPLANTATION FOR METASTATIC NEUROENDOCRINE TUMORS

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**Background.** Patients suffering from hepatic metastases of neuroendocrine tumors (NET) are potential candidates for orthotopic liver transplantation. Because recurrence rates are high and outcome is vari-

able, prognostic indicators are required. The aim of our study was to identify predictors of long-term survival with a focus on the impact of tumor biology.

**Methods.** We retrospectively analyzed 19 patients who received an orthotopic liver graft for metastatic NET at the Medizinische Hochschule Hannover. Expression of Ki67, E-cadherin, and p53 was studied immunohistochemically in metastases of neuroendocrine tumors of the explanted livers.

**Results.** Patients were followed up to 146 months after liver transplantation. Six patients died during follow-up. The resulting 1-, 5-, and 10-year survival rates are 89%, 80%, and 50%, respectively. All deaths during long-term follow-up were tumor-associated. Recurrence was diagnosed in 12 patients between 2 weeks and 48 months after liver transplantation. Three patients are without tumor recurrence more than 8 years after liver transplantation. Survival in the 5 patients with low Ki67 and regular E-cadherin staining was significantly better than in the 12 patients with high Ki67 or aberrant E-cadherin expres-

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