Home Glucometer Monitoring Markedly Improves Diagnosis of Post Renal Transplant Diabetes Mellitus in Renal Transplant Recipients

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Background. Definitions of de novo posttransplant diabetes mellitus (PTDM) have varied widely in the renal transplant literature, and most have not used the American Diabetes Association (ADA) definition of diabetes (fasting plasma glucose [FPG] ≥126 mg/dl on two occasions, or a casual plasma glucose level >200 mg/dl). Most patients are monitored for PTDM by 12-hour FPG levels drawn for clinic visits. In contrast, we describe the diagnosis of PTDM by home glucometer monitoring

Methods. We screened 89 consecutive nondiabetic renal transplant recipients for PTDM by ADA criteria and home glucometer monitoring during the first 3 months posttransplant

Results. Of 23 patients with impaired fasting glucose levels of 111–126 mg/dl, 14 (61%) met ADA criteria for diabetes mellitus of based on home glucometer monitoring. The incidence of de novo PTDM was 31% during this period. Predictors of PTDM in a Cox proportional hazards model were race and acute rejection, with a trend towards BMI. Clinic visit FPG levels did not differ between PTDM and non-PTDM patients. All diagnoses were made based on prelunch or supper FPG >200 mg/dl

Conclusions. Overnight FPG are inadequate for diagnosis of PTDM. All renal transplant recipients with impaired FPG should, at minimum, have home FPG testing.

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De novo posttransplant diabetes mellitus (PTDM) occurs in 7–30% of renal transplant recipients, with the incidence increasing over time after transplantation (*1*). The pathogenesis of PTDM is multifactorial, with corticosteroid administration (*2*), calcineurin inhibitors (*3*, *4*), sirolimus (*5*), obesity (*1*, *6*, *7*), race (*8*), hepatitis C infection (*9*) and age (*6*) all implicated as causative factors. The pathophysiology of PTDM involves both islet cell dysfunction (*10*) and insulin resistance (*6*, *11*, *12*). Compared with normoglycemic transplant recipients, patients with PTDM have an increased risk of graft loss, cardiovascular morbidity, and premature death with a functioning allograft (*1*, *13*).

Timely diagnosis and accurate assessment of the prevalence of PTDM have been confounded by narrow definitions of posttransplant diabetes mellitus including "a new requirement for insulin therapy for more than 30 days" (*14–18*), and "a new requirement for insulin or oral hypoglycemic agents" (*19*). Few reports in transplant recipients have used the ADA-accepted definition of diabetes (fasting plasma glucose [FPG] ≥126 mg/dl on two occasions, or a single random blood glucose level >200 mg/dl), and only a handful have addressed the presence of impaired glucose tolerance (FPG 111–125 mg/dl) (*4*, *12*, *20*, *21*). Indeed, it is only recently that the transplant community has endorsed the standard clinical criteria for diagnosis of diabetes mellitus (*22*) established by the World Health Organization (*23*) and the American Diabetes Association (*24*).

Most renal transplant patients are monitored for PTDM based on 12-hour FPG levels drawn concurrently with their tacrolimus, sirolimus, or cyclosporine trough or C-2 levels, although these levels may not accurately reflect overall glycemic control. In patients with Type 2 diabetes, some reports suggest that overnight FPG levels correlate poorly with HbA1c levels, whereas postprandial and suppertime glucose levels are a better indicator of glycemic control (*25*). In this report, we describe the results of home FPG monitoring in conjunction with the ADA criteria for diagnosis of posttransplant diabetes in a cohort of renal transplant recipients.

METHODS

Human Subjects' Protection

This study was approved by the Research Subjects Review Board at the University of Rochester Medical Center.

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Research data were coded such that subjects could not be identified, directly or through linked identifiers, in compliance with the Department of Health and Human Services Regulations for the Protection of Human Subjects (45 CFR 46.101(b) (*4*)).

Data Collection

From November 2000 through February 2003, all adult (age >18 years) kidney and kidney pancreas transplant recipients with morning clinic fasting plasma glucose levels of 110–125 mg/dl after the second week posttransplant were given home glucometers (One-Touch; Lifescan, Milpitas, CA), test strips, and lancets. Patients were instructed in clinic on proper use of the glucometer, calibration, timing of testing, and recording of results. Glucometer calibration was verified in clinic by manufacturer's instructions, and validated by comparison with plasma glucose levels from the clinical laboratory on their next return visit.

Preprandial (breakfast, lunch, and supper) and bedtime glucose levels were recorded for 3 days. A diagnosis of diabetes mellitus was made by the American Diabetes Association criteria, as recommended by the American Society of Transplantation from 1997–2004 (*22*, *24*, *26*): FPG ≥126 mg/dl on two occasions or a single random blood glucose level >200 mg/dl. Impaired plasma glucose was defined as a 12-hour FPG level of 111–125 mg/dl. During the 14 days following any steroid treatment for acute rejection, diagnosis of diabetes was suspended.

To determine the total incidence of PTDM during the same time period, we also performed a retrospective review of all kidney and kidney pancreas transplants (n=117). Demographic data collected included the age, gender, ethnicity, type of transplant, pretransplant diagnosis of diabetes, hepatitis C serology, weight, body mass index, family history of diabetes, time to diagnosis after transplantation, presence of delayed graft function, mean and cumulative tacrolimus doses, mean and cumulative steroid doses, use of antibody induction therapy, and modality and duration of dialysis prior to transplantation. A family history of diabetes was defined as the presence of diabetes mellitus in a first degree relative. Delayed graft function was defined as the need for dialysis within the first seven days posttransplant.

Immunosuppression Regimen

During the period covered by this study, all patients received tacrolimus, mycophenolate mofetil, and prednisone based immunosuppression, with the exception of one patient receiving modified cyclosporine. Patients were discharged from the hospital on 20 mg/day of prednisone, which was tapered to 15 mg/day after 4 weeks, 10 mg/day after 12 weeks, and then down to 5 mg/day at week 26 posttransplant. Goal serum tacrolimus levels were 12–15 ng/ml (IMX assay) during the first 4 weeks, 11–13 ng/ml during weeks 5–12, 10–11 ng/ml during weeks 13–26, and 7–10 ng/ml thereafter. Only 9 patients received antibody induction therapy.

Statistical Analysis

Statistical analysis was performed using the Statistica software package (StatSoft 2000; STATISTICA for Windows, Tulsa, OK). Mean tacrolimus levels during the first 90 days posttransplant were derived by multiplying the number of days between the previous tacrolimus level by the next tacrolimus level. The mean level was then calculated by adding all interval weighted values and then dividing by the total number of days. Demographic data was compared using Fisher's exact *t* test (2 tailed) for categorical variables, and the Mann-Whitney *U* test for continuous variables. A Cox proportional hazards analysis was conducted to determine the relative risk of developing posttransplant diabetes mellitus. The proportion of patients diagnosed with PTDM by the ADA criteria versus the alternative definition of a de novo need for insulin greater than 30 days were compared using the McNemar test for paired proportions. The study was powered to detect a 40% difference in these proportions (β=0.8, α=0.05, n=25).

RESULTS

Diagnosis of Posttransplant Diabetes Mellitus

In all, 117 consecutive renal transplant recipients were screened for impaired glucose tolerance 14–90 days posttransplant (Fig. 1). Renal transplant recipients without a pretransplant history of diabetes mellitus (76%) who presented to the outpatient clinic were classified according to the 2003 ADA diagnostic criteria: normoglycemic (FPG < 110 mg/dl), impaired (FPG 111–125 mg/dl) and diabetic (FPG ≥ 126 mg/dl). Five patients (5%) presented with overt PTDM, whereas another 29 (32%) had FPG levels within the impaired range. All of patients with impaired FPG were prescribed glucometers and asked to check their preprandial breakfast, lunch, supper and prebedtime plasma glucose levels at home for 3 consecutive days. Patients were trained in clinic on proper glucometer use and calibration.

Twenty-three patients with impaired glucose tolerance had three days of complete home glucometer readings, and were used for statistical analysis of blood glucose patterns. Figure 1B shows the mean preprandial plasma glucose levels in the 23 patients. PTDM was diagnosed in 14 (61%) patients with IPG by at least two preprandial plasma glucose levels of 200 mg/dl or greater. Almost uniformly, the diagnoses were based on preprandial lunch and suppertime levels. Only one patient was a simultaneous kidney-pancreas recipient, while the remaining 13 received kidney transplants. Six patients had fewer than 3 full days of glucometer readings, and five of these were also diagnosed with PTDM and severe hyperglycemia within 48 hr. These individuals had presuppertime PG levels of 480±74 mg/dl and were immediately started on therapy. All patients with IPG had symptoms of diabetes by interview, defined as polyuria, polydipsia, and unexplained weight loss. However, the nondiabetic cohort frequently reported polyuria (100%), polydipsia (93%), and weight loss (67%). Thus, attributing these symptoms to diabetes mellitus in the early posttransplant period was problematic.

Risk Factors for PTDM in Patients with Glucose Intolerance

Factors which might predict differences between the impaired plasma glucose (IPG), euglycemic and PTDM subgroups were studied in the 23 patients for whom we had 3 days of complete preprandial FPG levels. Table 1 shows the demographics for both groups, and univariate analysis indicated that IPG patients who developed PTDM tended to be

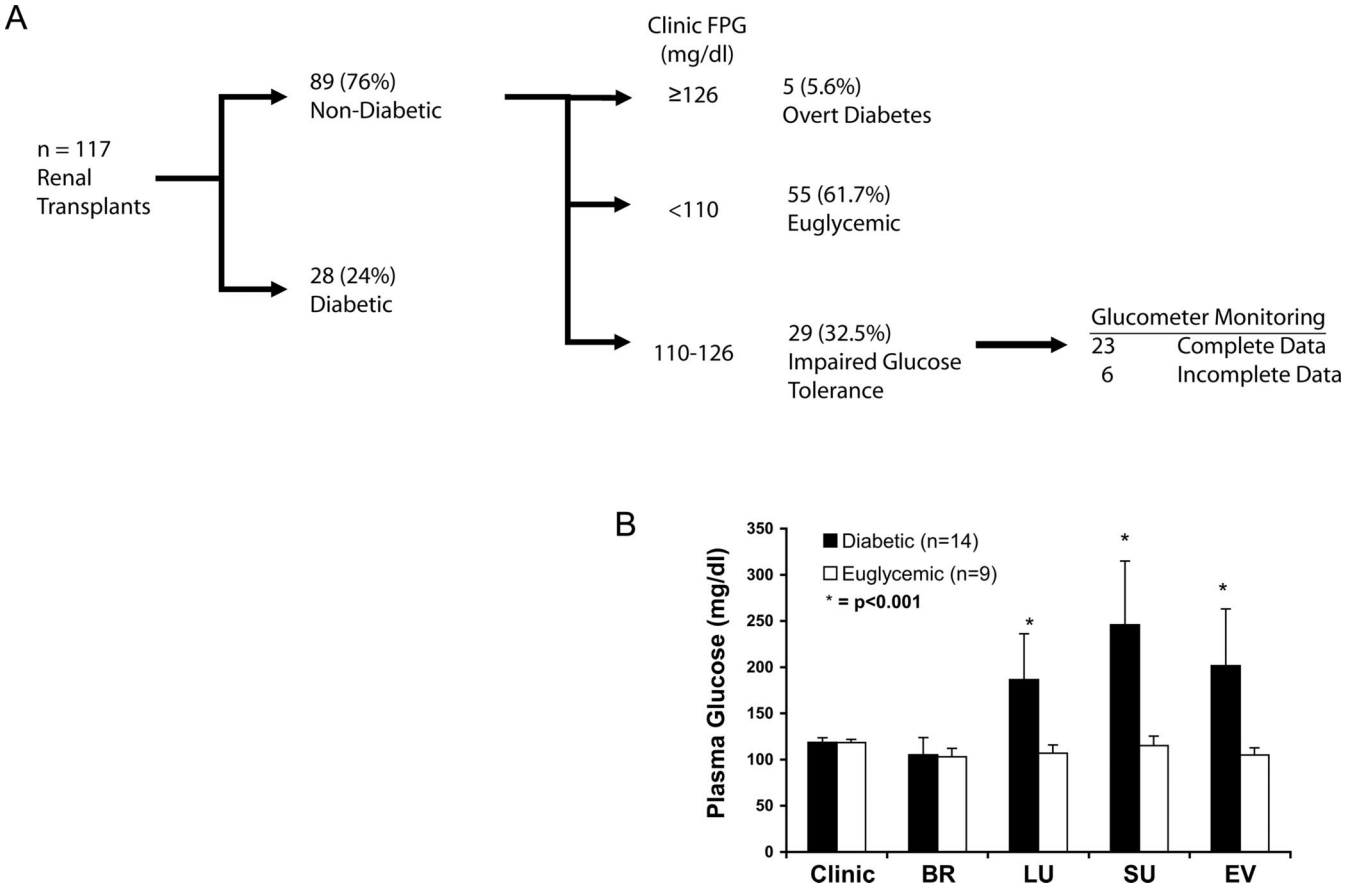

FIGURE 1. (A) Classification of renal transplant study cohort based on American Diabetes Association criteria for diagnosis of diabetes and glucose intolerance. Patients in this cohort were screened within 14-90 days posttransplant. (B) Results of home glucometer testing in the glucose intolerant cohort (clinic FPG 110-125 mg/dl). Clinic, preprandial breakfast (BR), lunch (LU), supper (SU) and bedtime (EV) reflect three measurements on 3 consecutive days for each patient. Clinic FPGs reflect two measurements on two separate clinic visits within 14 days. Results are mean ± standard deviation.

TABLE 1. Characteristics of patients with fasting plasma glucose levels 116-125 mg/dl within 90 days posttransplant

	Non-PTDM	PTDM	P value
n	9	14	
Non-Caucasian	0%	17%	0.0282
Age	42.3 ± 9.6	50.6 ± 13	0.0451
Male	52.3%	53.5%	NS
Body mass index (kg/m^2)	25.3 ± 5.4	26.8 ± 6.7	NS
Family history of diabetes	39.1	60.9%	0.0517
Mean tacrolimus level (ng/ml)	12.8 ± 2.1	12.7 ± 2.3	NS
Mean steroid dose (mg/d) – 90 days	33.9 ± 9	34.9 ± 7.2	NS
Acute rejection	17.4%	39.2%	0.0348
Delayed graft function	22.2%	7.1%	NS
Antibody induction	0.0%	35.7%	0.0427
Hepatitis C virus	0.0%	7.1%	NS
Cadaveric organ	71.4%	44.4%	0.0413
Duration of dialysis (months)	25.4 ± 16.8	25.6 ± 22.2	NS

PTDM, posttransplant diabetes mellitus.

older, received antibody induction therapy, and have had a rejection episode. There was a trend towards having a positive family history of diabetes, which did not reach statistical significance. A Cox proportional hazards analysis confirmed these risk factors, as well as identifying family history of diabetes and body mass index (BMI) > 35 kg/m^2 (Table 2). Duration of hemodialysis for longer than 36 months prior to renal transplantation was associated with a decreased risk of PTDM. In neither analysis did the mean steroid dose, mean tacrolimus level, or delayed graft function correlate with the

TABLE 2. Cox proportional hazards model for development of PTDM in patients with fasting plasma glucose 110-125 mg/dl

Factor	Odds ratio	Range	*P* value
Induction	36.4	(5–264)	0.0004
Body mass index > 35	28.8	(2–340)	0.0076
Non-Caucasian	20.3	(3–145)	0.0026
Rejection	6.3	(1–28)	0.0163
Dialysis > 36 months	0.1	(0.5–0)	0.0073
Family history			NS
Delayed graft function			NS
Hepatitis C virus			NS
Prednisone >3 g			NS
Tacrolimus >13 ng/ml			NS
Age >60 years			NS
Peritoneal dialysis			NS
Cadaveric graft			NS

PTDM, posttransplant diabetes mellitus.

development of PTDM in the IPG group. The presence of hepatitis C infection was not associated with development of PTDM, although the number of such patients was quite small and the analysis lacked power to detect significant differences. Unfortunately, pretransplant hemoglobin A_{1c} levels were not uniformly available for this cohort and thus not included in the analysis.

Prevalence of and Risk Factors for PTDM in the Entire Study Cohort

We next examined differences in the entire 117 patients between all patients who developed PTDM (n=28), and those who did not. This cohort included the five patients with overt PTDM on fasting clinic labs (Fig. 1), the 19 patients diagnosed within the first 90 days posttransplant (14 patients with complete 3-day glucometer readings and the five patients with incomplete glucometer data; Figure 1), and an additional group of four patients who were diagnosed with PTDM after the 90 day posttransplant glucometer study period. Figure 2B shows the Kaplan-Meier plot of the percentage of patients without a pretransplant diagnosis of diabetes who remained free of PTDM over the 0–90 days of the glucometer study, and from 90–600 days posttransplant. The majority of patients in this series presented within the first 6 months posttransplant. Of the 28 patients who met ADA criteria for PTDM during the first 2 years posttransplant, only five (18%) would have been diagnosed with PTDM by the oft used criteria of "a de novo requirement for insulin lasting greater than 30 days" (P=0.0269). Univariate analysis of the PTDM versus euglycemic subgroups revealed statistically significant differences between the two groups in non-Caucasian race, BMI, acute rejection, and induction therapy (Table 3). A Cox proportional hazards model showed that nonwhite ethnicity/race, BMI>35, age>60 years, induction therapy, rejection episodes, and family history were all associated

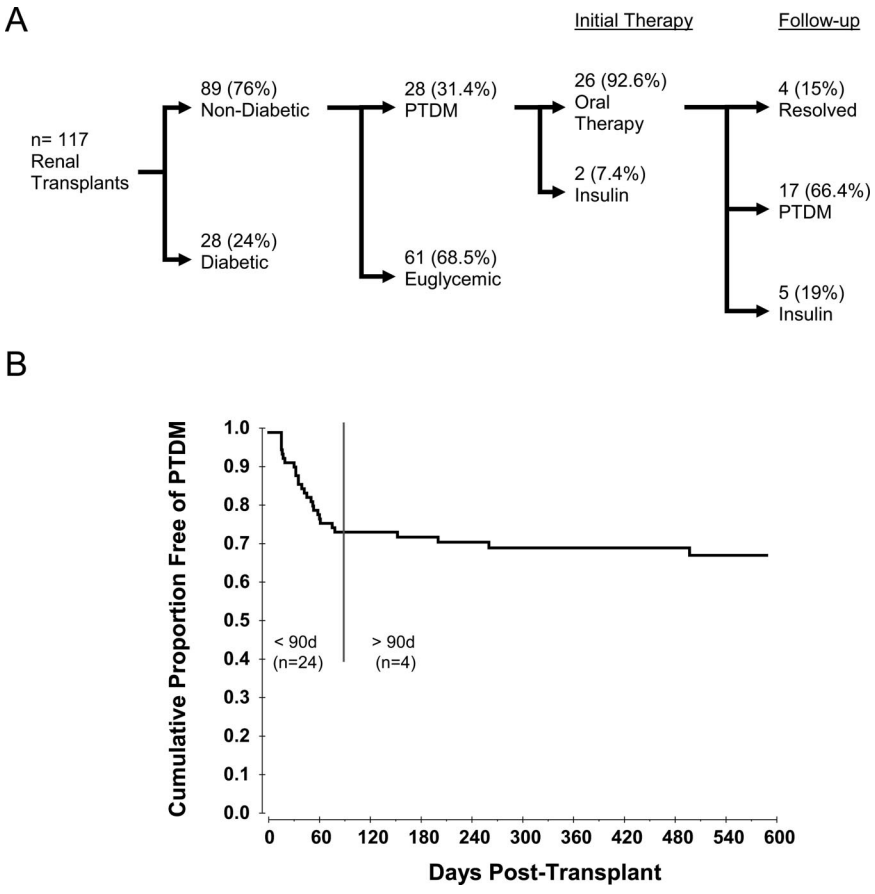

FIGURE 2. (A) Follow-up of posttransplant diabetes regimens. This cohort of patients included patients with PTDM diagnosed within the first 90 days posttransplant (n=24) of glucometer monitoring, as well as an additional 4 patients who were diagnosed with PTDM after 90 days posttransplant. Although some patients came off insulin therapy, the majority of patients required ongoing oral or insulin therapy for glycemic control. (B) Kaplan-Meier graph showing the proportion of patients without diabetes pretransplant that remained diabetes-free after kidney or kidney-pancreas transplantation.

TABLE 3. Demographics of all patients without a pretransplant diagnosis of diabetes

	Non-PTDM	PTDM	*P* value
n	61	28	
Non-Caucasian	9.6%	32.2%	0.0124
Age	45.8 ± 12.6	50.2 ± 13.6	NS
Male	52.3%	53.5%	NS
BMI (kg/m^2)	25.2 ± 4.8	28.1 ± 6.5	0.0419
Family history of diabetes	45.5%	64.3%	NS
Mean tacrolimus level (ng/ml)	12.8 ± 2.1	12.7 ± 2.3	NS
Mean steroid dose (mg/d) – 90 days	33.9 ± 9.0	34.9 ± 7.2	NS
Acute rejection	22.9%	46.3%	0.0042
Delayed graft function	5.6%	12.4%	NS
Antibody induction	11.2%	18.0%	0.0427
Hepatitis C virus	4.5%	3.4%	NS
Cadaveric organ	62.2%	39.2%	NS
Duration of dialysis (months)	30.6 ± 25.2	27.1 ± 22.5	NS

PTDM, posttransplant diabetes mellitus.

with an increased odds of developing PTDM. Again, pretransplant duration of dialysis > 36 months lowered the odds of developing PTDM (Table 4).

Resolution of PTDM

All patients who were diagnosed with PTDM by home glucometer monitoring were started on hypoglycemic therapy at the time of diagnosis, either oral hypoglycemic agents or insulin. This was done as part of the standard of care for management of PTDM, and not as a study intervention. Previous reports in the literature have noted the resolution of PTDM, as defined by loss of the need for insulin therapy (*15*). We were thus interested in whether PTDM resolved in this cohort, as more appropriately defined by loss of the need for both oral agents and insulin to maintain euglycemia. While 5 patients who initially required insulin therapy were eventually weaned to oral hypoglycemic agents, only one patient became euglycemic as assessed by both preprandial glucometer monitoring and HgA1c level of 5.5; all other patients continued to require oral hypoglycemic therapy.

TABLE 4. Cox proportional hazards model for development of posttransplant diabetes mellitus in the entire cohort

Factor	Odds ratio	Range	*P* value
Non-Caucasian	3.2	(1.3–7.4)	0.0080
Age > 60	3.2	(1.1–9.1)	0.0129
Induction	2.9	(1.2–7.4)	0.0214
Rejection	2.7	(1.2–5.9)	0.0316
Family history	2.5	(2.5–5.7)	0.0279
Body mass index > 35	2.5	(1.1–5.8)	0.0317
Dialysis > 36 months	0.2	(0.1–0.7)	0.0069
Delayed graft function			NS
Hepatitis C virus			NS
Prednisone > 3g			NS
Tacrolimus >13 ng/ml			NS
Peritoneal dialysis			NS
Cadaveric graft			NS

DISCUSSION

This study challenges the previously published conclusions that PTDM is a condition of limited frequency, is most appropriately diagnosed by the de novo requirement for over 30 days of insulin therapy, and resolves once euglycemia can be maintained off insulin. Only recently has the renal transplant community endorsed the international standards for diagnosis of diabetes mellitus. Prior to this, the presence of numerous definitions for PTDM in the literature has, unfortunately, prevented an accurate assessment of the true magnitude of posttransplant diabetes mellitus (*1*, *27*). We believe that the use of such non-standard definitions of diabetes in renal transplantation has likely led to the under-diagnosis and under-treatment of PTDM throughout the transplant community. Similarly dubious criteria for "resolution" of PTDM, irrespective of clinical measures of hyperglycemia or the need for oral hypoglycemic agents, have led to a false sense that PTDM is a short-lived condition limited to the peri-transplant period.

Our findings support the utility of preprandial glucose screening when monitoring renal transplant recipients for PTDM. When 12 hr fasting glucose levels are within the "impaired glucose tolerance" range of the ADA criteria, a substantial number of these patients will have prelunch and presuppertime levels greater than 200 mg/dl that are diagnostic of diabetes mellitus. This pattern of hyperglycemia, characterized by a rising glycemic levels throughout the day, but 8–12 hr fasting euglycemia, was seen in all subjects with PTDM. It is interesting that some studies in non-transplant Type 2 diabetics have not shown a similar pattern (*28*). One possible explanation for this difference may be the effect of prednisone which, when taken in the morning, causes an increase in insulin resistance which peaks between lunch an suppertime. Alternatively, the morning dose of tacrolimus may have impaired insulin secretion at times which coincide with peak oral carbohydrate intake. Further study of glycemic patterns in patients on steroid free, tacrolimus based immunosuppression regimens will be necessary to separate these effects.

It is likely that a significant number of dialysis patients

have occult Type 2 diabetes, which is then unmasked after renal transplantation. While the primary pathophysiology of type 2 diabetes is insulin resistance, β-cell insulin secretion also declines over time (*29–31*). The clinical appearance of overt diabetes is often delayed as end stage renal disease increases the half-life of plasma insulin by 30% (*32*). Thus, ESRD patients may progressively lose islet cells, but maintain euglycemia for some time. This may account for our finding that a duration of dialysis greater than 36 months lowered the odds of developing PTDM. We hypothesize that this group may have lost enough additional β-cell mass during the 3 years on dialysis to become overtly diabetic despite an increase in insulin half life. After kidney transplantation, however, the restoration of renal insulin metabolism, coupled with steroid induced insulin resistance (*33*) and calcineurin inhibitor impairment of insulin secretion (*34*) all combine to reveal previously undiagnosed diabetes.

Although we found that home glucose monitoring markedly improves diagnosis of PTDM, our study cohort was restricted to patients with impaired fasting glucose levels and had a modest sample size. The former approach may miss patients with early type 2 diabetes, who may have quite normal fasting glucose levels, but postprandial hyperglycemia (*35*, *36*). Indeed, several investigators have noted that when only fasting blood glucose is measured, impaired glucose tolerance may remain undetected in some subjects (*37*). The latter issue of modest sample size makes the risk of a Type I error somewhat more likely. Thus, our results suggest that a larger prospective study of pre- and postprandial glucose levels, with appropriate statistical power, should be undertaken.

Within the endocrinology community, the definitions of diabetes mellitus and impaired glucose tolerance, as well as the recommended methods for diagnosis, have been evolving. Indeed, after this study had been completed, the ADA changed their definition of impaired glucose tolerance to an 8-hour fasting plasma glucose level of between 100-125 mg/dl (*38*). This change was made to bring the definitions of impaired fasting glucose (IFG; 8-hour fasting plasma glucose reading) and impaired glucose tolerance (IGT; using oral glucose tolerance testing) closer in line in diagnosis of Type 2 diabetes (*39*). One caveat to our study is that we were not able to capture patients who would meet the newer ADA criteria for IFG. In addition, the WHO and ADA criteria differ with respect to the need for an abnormal oral glucose tolerance test to diagnose diabetes. The WHO criteria focus on an abnormal OGTT, while the ADA criteria do not recommend OGTT for routine clinical use. While our study did not perform OGTTs, all of our patients met ADA criteria for diagnosis of diabetes based on random blood glucose levels $>$ 200 mg/dl. Both OGTT and FPG monitoring capture the vast majority of patients with Type 2 diabetes, and combined testing has a higher sensitivity and specificity (*37*). With respect to screening for PTDM, the addition of OGTT or combined pre- and postprandial plasma glucose testing to home glucometer monitoring would likely detect more cases of PTDM. Further study will be necessary to determine the sensitivity and specificity of home monitoring with respect to the OGTT.

Almost all patients diagnosed with PTDM in this study continued to require either insulin or oral hypoglycemic therapy, suggesting that the diagnosis of PTDM was not an artifact of early peritransplant steroid induction therapy. Several recent studies have defined the resolution of PTDM as reverting to a state of noninsulin dependence (*14–16*). This definition obscures the true issue of whether the physiologic state of diabetes mellitus persists in these patients, but can be managed with oral hypoglycemic agents. Consistent with our results is the finding that the incidence of PTDM continues to increase for years after renal transplantation (*1*, *40*). If PTDM truly regressed, one should see an improvement in the prevalence of PTDM over time in a cohort of posttransplant patients.

This work does not address the use of home glucose monitoring to optimize glycemic control in renal transplant recipients. Although preprandial glucose testing has been the standard for self-management of glycemic control in diabetes mellitus, there is increasing evidence to support the use of postprandial monitoring to adjust oral hypoglycemic and insulin therapy (*41*, *42*). Our results and those of others (*6*, *21*) suggest that preprandial glycemic patterns in steroid treated transplant recipients on tacrolimus may differ from those seen in diabetic patients not taking these medications. Further study will be necessary to determine whether postprandial glycemic monitoring is a useful adjunct in this population.

Based on our findings, we conclude that renal transplant recipients with 12-hr fasting plasma glucose levels in the impaired glucose tolerance range (111–125 mg/dl) should, at minimum, undergo preprandial home glucose monitoring.

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