

Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years

FERNANDO G. COSIO, TODD E. PESAVENTO, KWAME OSEI, MITCHELL L. HENRY, and RONALD M. FERGUSON

Departments of Internal Medicine and Surgery, The Ohio State University, Columbus, Ohio, USA

Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years.

Background. Post-transplant diabetes mellitus (PTDM) is a serious complication of transplantation caused by immunosuppressive drugs. In this study, we assessed the incidence of PTDM and the factors that are associated with the development of this complication.

Methods. The study population included 2078 non-DM renal allograft recipients, transplanted since 1983 in one institution. PTDM was diagnosed by the requirement of hypoglycemic medications, starting more than 30 days after transplantation. Post-transplant, all patients received cyclosporine (CsA) and prednisone, but none of these patients received tacrolimus.

Results. At 1, 3, 5, and 10 years after transplantation, 7, 10, 13, and 21% of patients developed PTDM. By multivariate Cox, the following variables correlated with a more rapid increase in the number of PTDM cases: (1) older age (RR = 2.2 comparing patients younger or older than 45 years, $P < 0.0001$), (2) transplant done after 1995 (RR = 1.7, $P = 0.003$), (3) African American race (RR = 1.6, $P = 0.003$), and (4) higher body weight at transplant (RR = 1.4, $P < 0.0001$). Compared with before 1995, since 1995, the percentage of patients with PTDM has increased from 5.9 to 10.5% at one year and from 8.8 to 16.9% at three years. This increase was statistically independent from all other variables tested. However, since 1995, recipients have become significantly heavier ($P < 0.0001$) and older ($P < 0.0001$), and the average CsA level has increased significantly ($P < 0.0001$). Also, since 1995, the cumulative dose of corticosteroids has declined ($P < 0.0001$); patients received a newer, better absorbed preparation of CsA and received mycophenolate mofetil.

Conclusions. The risk of PTDM increases continuously with time post-transplant. There has been an increase in the incidence of PTDM in patients transplanted recently, and that increase can be explained only partially by changes in the recipients' characteristics. We postulate that this increase may be due to the introduction of better absorbed CsA formulations that result in higher blood levels and higher cumulative exposure to this diabetogenic drug.

Key words: kidney transplantation, diabetes, cardiovascular risk, immunosuppression, cyclosporine A, mycophenolate mofetil.

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During the last two decades, there have been impressive improvements in the control of immunologic events that follow renal transplantation. Consequently, the number of acute rejection episodes early post-transplant has declined dramatically and graft survival, particularly during the first year post-transplant, has improved substantially [1, 2]. It is clear that in large part, these improvements are the consequence of the use of better immunosuppressive protocols employing newer, more potent immunosuppressive drugs.

Improvements in the control of immunologic phenomena post-transplant have been accompanied by significant improvements in graft survival [3]. However, high patient mortality continues to be the major threat to the success of renal transplantation [4, 5]. Because the excess mortality of transplant recipients is largely due to cardiovascular causes [6], searching for variables associated with increased cardiovascular risk and correcting those variables are critically important. Previous studies have identified several cardiovascular risk factors in patients with end-stage renal disease and in transplant patients [7, 8]. However, it has also been pointed out that the cardiovascular mortality of patients with kidney disease is much higher than that of patients without kidney problems who have a similar risk profile [9]. These results suggest that other cardiovascular risk factors need to be considered in patients with kidney disease. One of those factors is likely to be insulin resistance that occurs commonly in patients receiving immunosuppressive medications and is clearly associated with increased cardiovascular risk [10, 11].

The ultimate manifestation of insulin resistance in transplant patients is the development of post-transplant diabetes mellitus (PTDM). The issue of PTDM has been recently reviewed in the literature [12]. However, important information is lacking about this serious complication of transplantation. In this study, we evaluated the development of PTDM in a large population of renal transplant recipients treated in one institution with uniform immunosuppressive protocols. In particular, we as-

Table 1. Characteristics of the patient population

Patient characteristic	Value
Age years	40.9 ± 14
Gender % males	60%
Race % African American	11%
Weight at transplant kg	74.4 ± 18
Donor type % CAD	70.7%

sessed the timing of the development of DM after transplantation, the influence of different variables on that timing, and whether the introduction of newer immunosuppressive medications has had effects on the overall incidence of PTDM and its pattern of presentation. The latter is an important consideration because in addition to corticosteroids, newer immunosuppressive medications, which have clearly contributed significantly to improvements in transplantation, are diabetogenic [reviewed in 12]. It is our hope that a better characterization of PTDM, first on clinical grounds, will facilitate its early detection and treatment as well as help in the design of future trials to prevent the development of this devastating complication of transplantation.

METHODS

Patient population

This study includes an analysis of 2078 patients transplanted in a single institution from August of 1982 to February of 1999. This population included 606 patients who received kidneys from living donors (LRDs) and 1464 patients who received kidneys from cadaveric donors (CADs). The demographic characteristics of the patient populations are shown in Table 1. None of these patients had a history of DM prior to transplantation. In addition, all of the patients who required hypoglycemic medications during the first month post-transplant were not included in this cohort of patients because it was considered that these patient most likely were diabetic prior to transplantation. No precise information about the recipients' family histories of DM was available; thus, this variable was not considered in these studies. The diagnosis of PTDM was made when the patient started to require hypoglycemic medications, including either oral hypoglycemic drugs and/or insulin.

All CAD kidneys were preserved by pulsatile perfusion. In the immediate post-transplant period, patients received induction immunosuppression consisting of polyclonal (Minnesota ALG or ATG) or monoclonal anti-lymphocyte antibodies (OKT3; Ortho Biotech, Raritan, NJ, USA) until the serum creatinine was ≤ 2.5 mg/dL when CsA was initiated. Since May of 1998, induction has been done with two doses of anti-interleukin-2 (IL-2) receptor monoclonal antibodies (Basiliximab, Simulect, Novartis) instead of anti-lymphocyte antibodies. In most

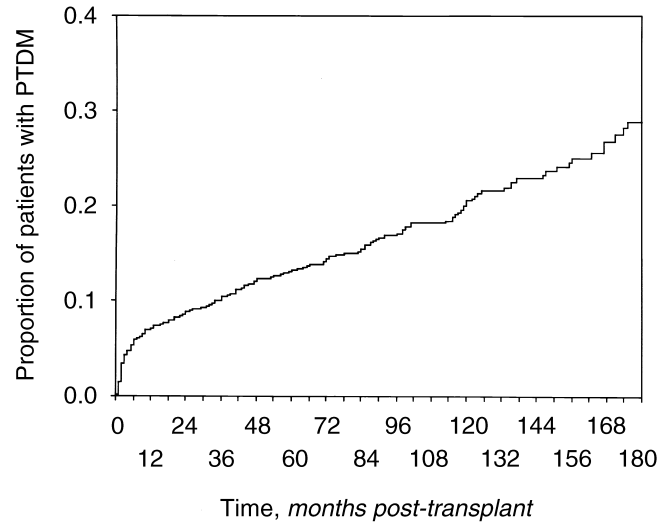


Fig. 1. Incidence of post-transplant diabetes mellitus (PTDM) with time post-transplant (Kaplan–Meier plots).

patients, of triple therapy with prednisone, azathioprine, maintenance immunosuppression consisted and cyclosporine (CsA) until the mid-1995 when azathioprine was replaced by mycophenolate mofetil (CellCept) and Sandimmune was substituted for Neoral. Based on these changes in immunosuppressive protocols, patients were divided by the date of transplantation into those transplanted prior to July 1, 1995 ($N = 1551$), and those transplanted after that date ($N = 527$).

Analysis of the data

The data are expressed as means \pm SD. Means were compared by Student *t* test or by the nonparametric test if the variable was not normally distributed. The incidence of PTDM over time post-transplant was analyzed by Cox regression (univariate and multivariate) and also by Kaplan–Meier plots after censoring patients for patient death and for graft loss.

RESULTS

Incidence of PTDM

Figure 1 displays the cumulative incidence of PTDM with time post-transplant. During the first six-months post-transplant, 5.9% of patients developed this complication. Thereafter, the percentage of cases of PTDM increased linearly with time post-transplant. The cumulative percentage of PTDM at 1, 3, 5, 10, and 15 years was 7.1, 10.4, 13.2, 20.5, and 29.8%, respectively.

Table 2 displays the results of univariate and multivariate Cox regression analysis and shows the variables that correlate significantly with the development of PTDM. Statistically, the strongest correlation found was between the age of the patient at the time of transplantation and

Table 2. Variables that correlate significantly with the development of post-transplant diabetes mellitus (PTDM) in the study population

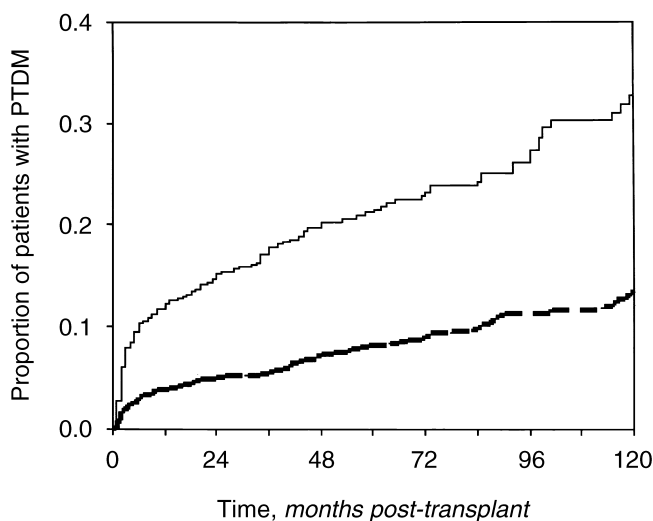
Variable	Univariate analysis	Multivariate analysis
Age ^b	2.9 ^a	2.2, ^a $P < 0.0001$
Race	1.5	1.6, $P = 0.003$
Weight at transplantation ^c	1.5	1.4, $P < 0.0001$
Transplant year (< > 1995)	1.9	1.7, $P = 0.003$
Gender	0.7	NS
Donor origin	1.7	NS

The data represent the results of univariate and multivariate Cox analysis.

^a Values represent relative risk calculated by Cox regression

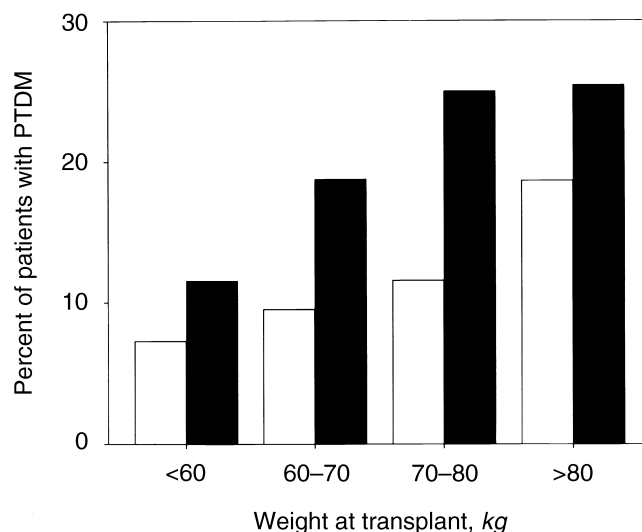
^b Relative risk calculated for patients who were younger than or older than 45 years old

^c Relative risk calculated for patients in the following weight groups, in kg: <60, 60–70, 70–80, and >80

**Fig. 2.** Incidence of PTDM with time post-transplant in recipients who were younger than 45 years old at transplant (heavy dashed line) or older than 45 (thin solid line; Kaplan-Meier plots).

PTDM. Thus, recipients older than 45 years old were 2.9 times more likely to become diabetic post-transplant than younger recipients. Figure 2 displays Kaplan-Meier plots of the proportion of patients with PTDM in recipients who were younger than 45 or more than 45 years old at the time of transplantation. As can be seen, the risk of PTDM is significantly higher in older recipients both during the six months post-transplant and beyond. It should be noted in Figure 2 that the rate of increase in PTDM cases after the first six months is significantly faster in older than in younger individuals. As demonstrated in Table 2, the relationship between PTDM and the age of the recipient is statistically independent from all other variables tested.

Race is also an independent predictor of PTDM (Table 2). Thus, 18% of African American recipients and 12% of Caucasians ($P = 0.01$ by chi square) developed

**Fig. 3.** Incidence of PTDM in patients classified according to their body weight at the time of transplantation (x axis) and according to their race: Caucasians (□) and African Americans (■).

DM after transplantation. The number of non-Caucasian, non-African American recipients is very small in our patient population (1.6%); thus, these patients could not be analyzed separately. The only statistically significant difference noted between African American and Caucasian recipients was in the recipients' weights, which were higher in the former than in the latter group (77.5 ± 20 vs. 74 ± 18 kg, $P = 0.01$). This difference is relevant because the weight of the recipient at the time of transplantation also correlated significantly with the development of PTDM (Table 2). This is displayed graphically in Figure 3, where it can be observed that the risk of PTDM increases significantly with increasing weight at the time of transplantation in both Caucasians and African Americans. However, for each weight group, the incidence of PTDM was higher in African Americans than in Caucasians.

Table 2 also shows that the incidence of PTDM was significantly higher in males than in females (15.2 vs. 10.4%, $P = 0.002$ by chi square). However, by multivariate analysis, the recipient's gender was not an independent risk factor for diabetes. Similarly, PTDM developed more commonly after CAD kidney transplantation (14.5%) than in recipients of LRD (10.4%, $P = 0.01$), but the multivariate analysis indicates that the origin of the donor graft is not an independent predictor of PTDM. Other donor variables, including age, race, and gender did not correlate with the incidence of PTDM. Of interest, the incidence of PTDM did not correlate significantly with the amount of weight gain that the patient had during the first year post-transplant.

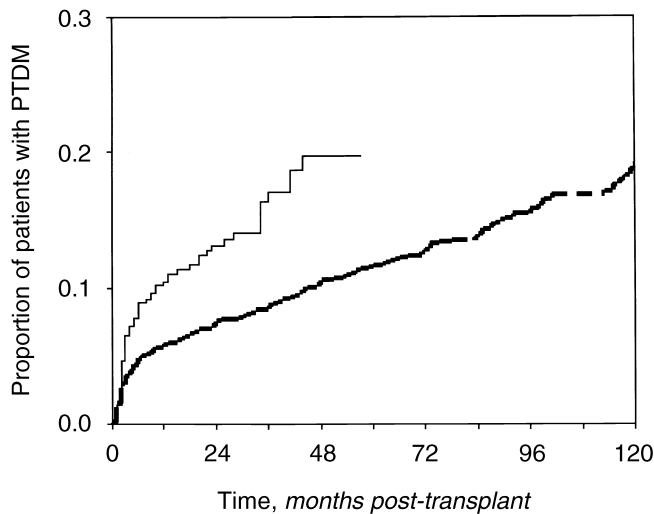


Fig. 4. Incidence of PTDM in patients transplanted prior to 1995 (heavy dashed line) or after 1995 (thin solid line; Kaplan–Meier plots).

Table 3. Comparison of the characteristics of patients transplanted prior to or after 1995 in our institution

Patient characteristic	Before 1995	After 1995	<i>P</i>
Demographics			
Age	40 ± 14	43 ± 14	<0.0001 ^b
Gender % males	59%	60%	NS ^a
Race % African American	11%	12%	NS ^a
Weight at transplant kg	73 ± 18	78 ± 19	<0.0001 ^b
Donor type % cadaveric	71%	69%	NS ^a
Immunosuppression			
Prednisone mg/kg/first year	101 ± 48	91 ± 20	<0.0001 ^b
CsA mg/kg/first year	2057 ± 916	2066 ± 1188	NS ^b
CsA level pg/mL ^d	99.8 ± 88	242 ± 105	<0.0001 ^c

^a Chi-square; ^b Student *t* test; ^c Mann-Whitney nonparametric test; ^d Average level during the first year

PTDM versus transplantation year

The incidence of PTDM was 1.9 times higher in patients transplanted since 1995 compared with those transplanted prior to that year (Table 2). Furthermore, the multivariate analysis shows that this correlation is statistically independent from all other variables tested. Kaplan–Meier curves of PTDM in recipients transplanted prior to and after 1995 are displayed in Figure 4. As can be seen, since July of 1995, the risk of PTDM has increased both during the first six-months post-transplant and beyond, with a significantly faster rate of increase in the number of PTDM cases. Thus, at one and three years, the incidences of PTDM were 6 and 8.7% in patients transplanted before 1995 and 10.6 and 17.1% in those transplanted since 1995.

It is likely that several factors contributed to the increased occurrence of PTDM since 1995. For example, Table 3 displays a comparison between the patient characteristics prior to and after 1995. As can be seen, after

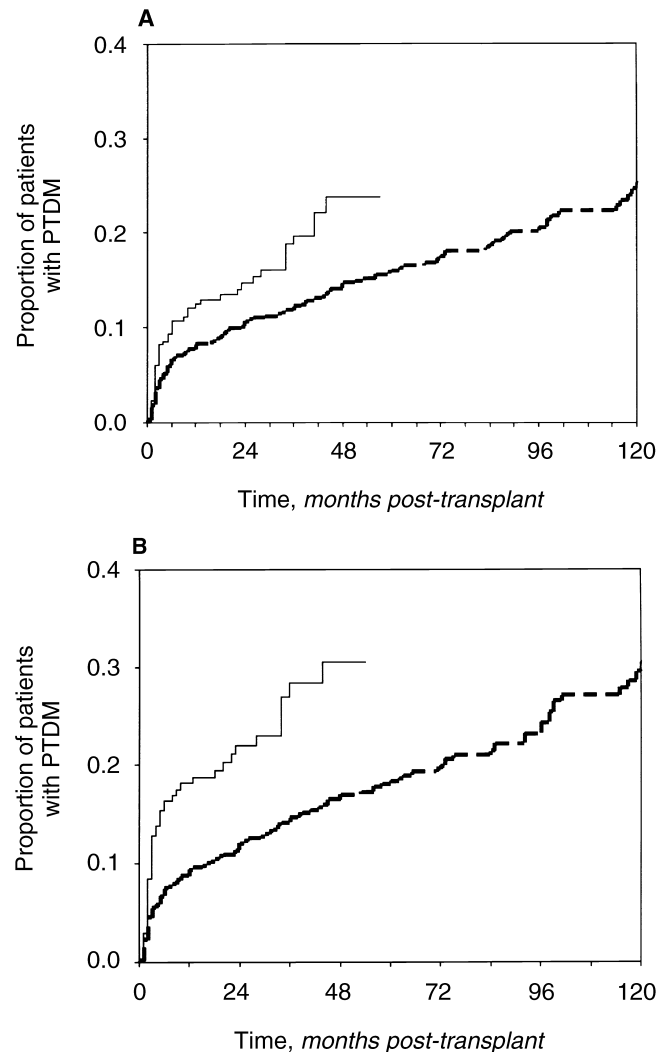


Fig. 5. Incidence of PTDM in subgroups of patients transplanted prior to 1995 (heavy dashed line) or after 1995 (thin solid line; Kaplan–Meier plots). (A) Only patients >70 kg at the time of transplantation. (B) Only recipients older than 45 years old at the time of transplant.

July of 1995, the recipient population became significantly older and heavier. However, Figure 5 re-emphasizes that the correlation between the date of transplantation and PTDM is statistically independent from the age and/or weight of the recipient. Thus, it can be seen that the incidence of PTDM is significantly higher in obese recipients (Fig. 5, top) and in recipients older than 45 years old (Fig. 5, bottom) transplanted after 1995 than before that year. It should also be noted in Table 3 that significant changes in immunosuppression have also occurred since 1995. Thus, the cumulative dose of corticosteroid received by patients transplanted after July of 1995 was significantly lower than prior to that date. This reduction is not the result of a protocol change but the result of the significant decrease in the number of acute rejection episodes during the first year post-

transplant (before 1995, 1 ± 1.4 episodes per patient vs. after 1995, 0.5 ± 0.5 , $P < 0.0001$ by Wilcoxon). The cumulative dose of CsA has not changed significantly since 1995 (Table 3). However, the average CsA level during the first year post-transplant was significantly higher in patients transplanted after 1995 than in those transplanted before that date, most likely reflecting the use of better absorbed formulations of CsA.

DISCUSSION

In the present study, we evaluated the incidence of PTDM in a large group of renal allograft recipients, transplanted in a single institution, and treated with uniform CsA-based immunosuppressive protocols. The incidence of PTDM reported here is similar to that noted in other studies. However, there is a significant variability in the reported incidence of PTDM, most likely because of at least three reasons. First, the criteria used to diagnose PTDM are quite variable among studies [12]. Second, variability in the immunosuppressive protocols used in different transplant centers will have an impact in the incidence of PTDM. For example, the incidence of PTDM is significantly higher in transplant recipients treated with tacrolimus than in those treated with CsA [13]. Finally, the reported incidence of PTDM will vary according to the length of patient follow-up because, as shown here, the percentage of patients who develop PTDM increases continuously post-transplant. Regarding this latter point, these results showed that there are two distinct periods of PTDM development. The first, a period of high risk, comprises the first six-months post-transplant. The second comprises the rest of the post-transplant time when there is a continuous increase in the number of patients with PTDM. In this study, we diagnosed PTDM as the need for hypoglycemic medications. Thus, the incidence of PTDM reported here, although high, is likely to be an underestimate of the true magnitude of the problem. This is particularly relevant when we consider that the incidence of PTDM has increased rather sharply since 1995.

The results of this analysis showed that the risk of PTDM is higher in African American recipients than in Caucasian recipients. This finding is consistent with previous observations in transplant recipients [12] and also with the observation that, in the general population, the incidence of type II DM is significantly higher in African Americans than in Caucasians [14, 15]. Furthermore, among nondiabetic subjects, the incidence of hyperinsulinemia and insulin resistance is also higher in African Americans than in Caucasians [15]. Thus, it is likely that more African Americans than Caucasians have insulin resistance prior to transplantation, and in these patients, treatment with immunosuppressive drugs that are diabetogenic would result in PTDM. Previous

studies showed that abnormalities in insulin/glucose metabolism are racially diverse [16]. Thus, it is likely that the mechanisms of PTDM in individuals of different racial groups may also be different.

We showed here that weight is a risk factor for PTDM and that African American recipients are significantly heavier than Caucasians. However, we showed that for patients with similar body weights, the risk of PTDM is still higher in African Americans. It should be emphasized that in renal transplant recipients, the risk of PTDM increases continuously for every increment of body weights above 60 kg, clearly below what may be considered to be an overweight range for most patients. Weight gain is a very common problem post-transplantation. However, in this study, we did not find a significant correlation between weight gain during the first year post-transplant and PTDM but rather between pretransplant weight and PTDM.

For all racial and weight groups and for both patients transplanted in the remote past or more recently, the age of the recipient at the time of transplantation is statistically the strongest predictor of the risk for PTDM. The increased risk of PTDM in older recipients has two distinct components. First, compared with younger recipients, patients older than 45 years have a marked increase in the incidence of PTDM during the first six months post-transplant when the patient is receiving the highest doses of corticosteroids. Second, beyond six months post-transplant, the rate of increase in the number of cases of PTDM is faster in older than in younger individuals. It seems reasonable to postulate that PTDM may comprise at least two subpopulations of individuals. The first, including patients who develop diabetes early post-transplant, most likely represents patients who had insulin resistance prior to the transplant that was made worse by high doses of steroids, requiring the initiation of hypoglycemic therapy. The second group of patients who develop PTDM beyond six months post-transplant and may represent newly acquired diabetic individuals, either with hyperinsulinemia and insulin resistance or with hypoinsulinemia [12].

For the first time, we showed here that the incidence of PTDM has increased rather sharply since 1995 to the present time. In fact, the number of PTDM cases has nearly doubled since 1995, and the linear shape of the Kaplan–Meier plots suggests that more than 40% of recipients transplanted since 1995 may acquire DM within five-years post-transplant. These results suggest that the increase in PTDM is multifactorial, including both changes in patients' risk profiles and changes in immunosuppressive medications. Thus, since 1995, renal transplant recipients in our institution have become significantly heavier and significantly older. However, the increased incidence of PTDM since 1995 is statistically independent from these two factors. We postulate that

the introduction of newer preparations of CsA in mid-1995 has resulted in higher exposure to this drug that is diabetogenic most likely due to direct inhibition of insulin synthesis and/or secretion mediated by a direct toxic effect on insulin producing cells of the pancreas [12, 17, 18]. Of interest, the increase in PTDM has occurred despite the fact that the cumulative doses of corticosteroids have been reduced. Since 1995, other changes in immunosuppressive protocols were introduced in our program and in most transplant programs, including the substitution of Imuran for Cellcept and, since mid-1998, the use of anti-IL-2R antibodies. However, there is no evidence that these drugs are diabetogenic [12].

Improvements in graft survival over the last two decades [3] have made it increasingly clear that patient death is a frequent cause of renal transplantation failure [4, 5]. Because most of the excess mortality of renal allograft recipients is due to cardiovascular causes [6], it is particularly worrisome to note that the incidence of PTDM is increasing in this population of patients. PTDM increases patient morbidity and likely mortality following transplantation [reviewed in 12]. In addition, the increase in PTDM may also indicate that there has been an increase in the number of patients with insulin resistance, another worrisome event since this metabolic anomaly is also associated with increased cardiovascular risk [10, 11]. The results of these studies will help in identifying patients at high risk for PTDM, thus encouraging close monitoring of glucose levels and prompt therapy of hyperglycemia. Additional studies to delineate the etio-pathogenesis of PTDM and specific treatment options, such as the use of thiazolidinediones, are warranted.

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Reprint requests to Fernando G. Cosio, M.D., Division of Nephrology, The Ohio State University, N210 Means Hall, 1654 Upham Drive, Columbus, Ohio 43210-1250, USA.
E-mail: cosio.1@osu.edu

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