

Original Article

Post Transplant Diabetes Mellitus in Ahmed Gasim Kidney Transplant Center, Sudan

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Abstract

Introduction: New onset post transplant diabetes mellitus (PTDM) is a common complication of kidney transplantation with a negative impact on patient and graft survival. Non-white ethnicity is a well known risk factor for PTDM.

Methods: This is a retrospective study of 221 Sudanese patients who received live donor kidney transplantation in Ahmed Gasim kidney transplant center between December 2001 and December 2007, focusing on the incidence, clinical course and prognosis of PTDM during the first post transplant year, and relating this to calcineurin inhibitor use.

Results: The 12 months cumulative incidence of PTDM in our transplant population was 17.6% and all cases required treatment with insulin. 53.8% of PTDM cases were transient with a median duration of 76 days; by 12 months post transplant only 6.2% of patients were receiving insulin. The 12 months cumulative incidence of PTDM was higher in the tacrolimus compared to cyclosporine groups (25.4% versus 6.6%; OR 4.8, 95% CI: 1.9-12.1; P=0.00). During the follow up period 57.6% of PTDM patients in the tacrolimus group were able to discontinue insulin compared to 33.3% of PTDM patients in the cyclosporine groups (OR 2.7, 95% CI: 0.4-17; P=0.3). By 12 months post transplant, the proportion of patients receiving insulin was not significantly different between the two groups (8.0% versus 4.0%; OR 2.1, 95% CI 0.5-8.4; P = 0.2).

Conclusion: The incidence of PTDM in our transplant population is not different from that reported in published randomized controlled trials and similarly, in the majority of cases PTDM was transient.

Key words: Post transplant diabetes mellitus, kidney transplantation, tacrolimus, cyclosporine, calcineurin inhibitor

Introduction

The development of diabetes mellitus after kidney transplantation was first described in 1964 by Starzl, who called it 'steroid diabetes'; Now, post transplant diabetes mellitus (PTDM) is recognized as being a common complication of kidney transplantation. [1,2] The best method for determining the cumulative incidence of PTDM associated with the use of different immunosuppressive agents is from randomized controlled trials, but the results from these trials have been quite variable; 74% of this variability is explained by the type of immunosuppressive regimen. [1] The reported 12 months cumulative incidence of PTDM is 2-13.3% in patients receiving cyclosporine, azathioprine and prednisolone; 11.6 - 25.4% in patients receiving tacrolimus, azathioprine and prednisolone; and 4.7-12.2% in patients receiving tacrolimus, mycophenolate mofetil and prednisolone. [1]

A number of large studies compared the cumulative incidence of PTDM in tacrolimus and cyclosporine treated patients, and showed that tacrolimus was associated with a higher relative risk of PTDM when compared to cyclosporine. [3,4] Large studies have also shown that PTDM is associated with a higher risk of patient mortality and graft loss, even when graft loss was censored for patient death. [1,3] Nevertheless, tacrolimus is associated with improved graft and patient survival, and with a significantly reduced risk of acute rejection and steroid resistant acute rejection. [3-5]

Besides calcineurin inhibitors, a number of risk factors for PTDM have been identified, including: non-white ethnicity, [1,3,6-8] pulse steroid treatment for acute rejection, [1] chronic hepatitis C virus infection (HCV) [3], and female gender [1,3].

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Table 1: Characteristics of patients in the tacrolimus and cyclosporine groups

Characteristic	tacrolimus (N = 130)	cyclosporine (N = 91)	P value
Age at transplant (mean \pm SD)	34 \pm 13 years	36 \pm 11 years	0.2
Pediatric patients	14.7 %	4.6 %	0.01
Males	73.8 %	80.2 %	0.2
Chronic HCV infection	4.2 %	10.4 %	0.08

Some argue that it would be advisable to avoid the use of tacrolimus in patients who are already at high risk of PTDM because of non-modifiable risk factors, such as non-white ethnicity. However, those are the patients who are most likely to benefit from tacrolimus, because this is one of the factors known to impose a higher risk of graft loss.

Here we present a study of the incidence, clinical correlates and outcome of PTDM in a group of Sudanese patients, relating this to calcineurin inhibitor use. We hope to provide an insight into the best management of this common complication.

Patients and Methods

This is a retrospective study of a group of Sudanese patients who received living donor kidney transplantation at Ahmed Gasim kidney transplant center, Khartoum, Sudan, in the period from December 2000 to December 2007. Only patients who were diabetic before the transplant and patients who had primary graft non function were excluded from the analysis.

All patients received intravenous methyl prednisolone 500 mg during the transplant surgery before removal of the vascular clamp, followed by a three drug regimen composed of cyclosporine (initial dose: 6-8 mg/kg/day, target trough level: 200–300 ng/ml reduced gradually to 100–150 ng/ml after 6 months) or tacrolimus (initial dose: 0.2–0.3 mg/kg/d, target trough level: 15–20 ng/ml reduced gradually to 5-7 ng/ml after 6 months) in addition to azathioprine (1.5–2 mg/kg/d) and prednisolone (20-30 mg/d, reduced gradually to 5–7.5 mg/d after 3 months). Prior to February 2004, all patients were maintained on cyclosporine; as from February 2004, tacrolimus became the calcineurin inhibitor of choice. All patients received oral trimethoprim–sulphamethoxazole for the first 6 months after transplantation. Clinically diagnosed and/or biopsy proven acute rejection was treated with methylprednisolone 500 mg daily for 3 days.

Data were collected by medical records review from the time of transplant until the end of the first post transplant year, the end of December 2007, death, or graft failure. Patients were divided into two groups according to the

calcineurin inhibitor they used and examined for the presence or absence of PTDM and its clinical correlates.

PTDM was defined as two random blood glucose values \geq 200 mg/dl and/or fasting blood glucose values \geq 126 mg/dl taken on two separate occasions, in accordance with the definition of diabetes mellitus described by the WHO [9], and the international consensus guidelines on new-onset diabetes after transplantation [10]. Levels were confirmed over two weeks period. All such patients were treated with insulin. Resolution of PTDM was defined by fasting blood glucose values \leq 115 mg/dl taken on two separate occasions without insulin or oral hypoglycaemic agents.

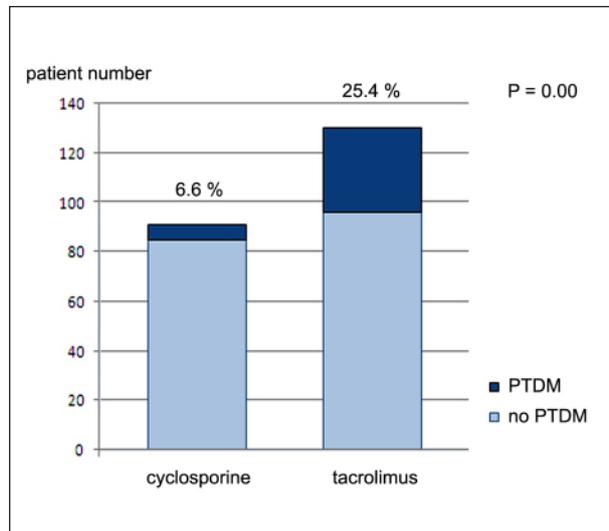
The 12 months cumulative incidence and clinical correlates of PTDM were studied and compared for the tacrolimus versus cyclosporine groups. PTDM was studied for possible association with patients age, gender, HCV infection, and the use of pulse steroids therapy for clinically diagnosed and/or biopsy proven acute rejection.

SPSS 15 for Windows was used to perform statistical analysis. Cross tabulation and the Chi square analysis was used to study possible risk factors and to test for their statistical significance. Results were considered statistically significant when $P < 0.05$.

Results

The study included 221 kidney transplant recipients, the great majority (95.5%) received the kidneys from live related donors, and 10 patients (4.5%) received the kidneys from live un-related donors. The mean age of patients was 35 \pm 12 years (range: 8–65 years), including 23 children (10.4%) aged 18 years or less and the majority were males (76.5%). Thirteen patients (5.9%) had chronic HCV infection. The median duration of follow up was 29 months and 73.3% of patients had a minimum follow up of 12 months.

Ninety-one patients were maintained on cyclosporine while 130 patients were maintained on tacrolimus, three of whom were subsequently switched to cyclosporine during the first post transplant year because of suspected nephrotoxicity, gastrointestinal intolerance or bone

Figure 1: Cumulative incidence of PTDM in the tacrolimus and cyclosporine groups

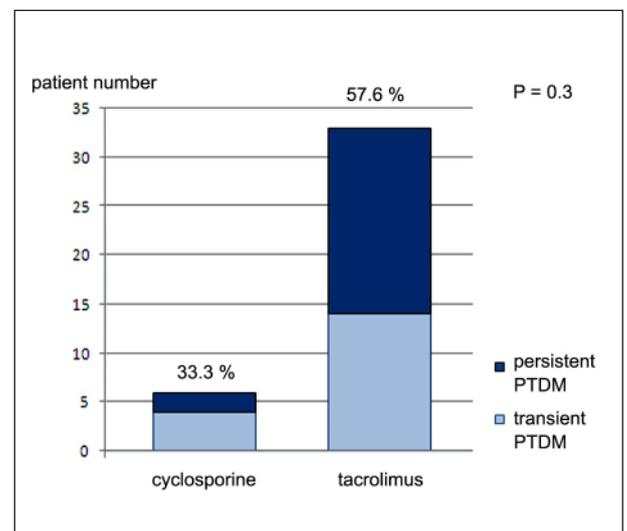
marrow suppression. Also, five patients from the cyclosporine group were switched from azathioprine to mycophenolate mofetil. The tacrolimus and cyclosporine groups were largely similar, but the tacrolimus group contained more paediatric patients (14.7% versus 4.6%, $P=0.01$) (table 1).

PTDM was diagnosed in 39 patients, with an overall 12 month cumulative incidence of 17.6%. The median time for diagnosis was 45 days post transplant, with 67.6% of cases being diagnosed within the first three months, and 94.6% of cases being diagnosed within the first six months. No cases of PTDM were diagnosed more than 7 months post transplant.

The overall prevalence of PTDM was 5.5% (12/219) at one month post transplant, 11.7% (24/206) at three months post transplant, 11.6% (22/190) at six months post transplant, and 6.2% (10/162) at 12 months post transplant.

Overall, PTDM resolved in 21 of 39 patients during the follow up period (53.8%). However, in 27 patients with PTDM who were followed up for 12 months or more, the resolution rate was 66.7%. Transient PTDM had a median duration of 76 days (range: 16-270 days), it persisted for less than 3 months in 66.7% of cases and for less than 6 months in 90.5% of cases. Transient PTDM tended to occur later than persistent PTDM, with a median time of onset of 90 days versus 33 days post transplant.

All PTDM patients were treated by regular insulin, and 16% had at least one episode of diabetic ketoacidosis. PTDM patients needed re-hospitalization during the first post transplant year more often than did patients

Figure 2: Resolution rate of PTDM in the tacrolimus and cyclosporine groups

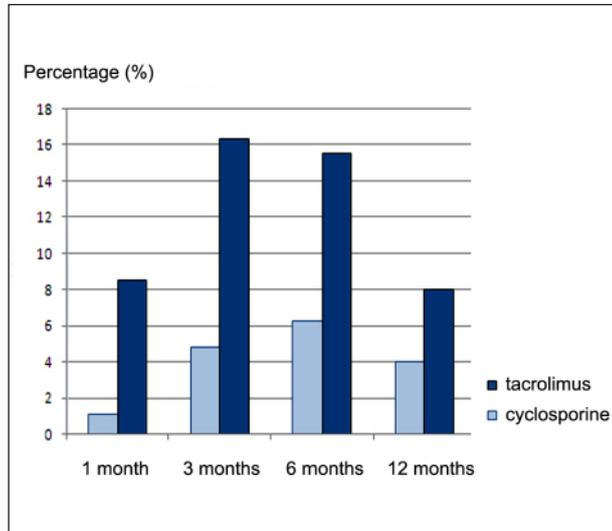
without PTDM (96.4% versus 43.8%, $P=0.00$), mainly for diabetes control or the treatment of infections.

The 12 months cumulative incidence of PTDM was higher for the tacrolimus compared to the cyclosporine groups (25.4% versus 6.6%; OR 4.8, 95% CI: 1.9-12.1; $P=0.00$). PTDM tended to occur earlier in the tacrolimus group, with a median time of onset of 39 days post transplant compared to 75 days in the cyclosporine group (figure 1).

During the follow up period, the diabetic status was reversed in 57.6% of PTDM patients in the tacrolimus group compared to 33.3% of PTDM patients in the cyclosporine group (OR 2.7, 95% CI: 0.4-17; $P=0.3$) (figure 2). Among patients who had been follow up for 12 months or more, the diabetic status was reversed in 72.7 (16/22) of PTDM patients in the tacrolimus group compared to 40% (2/5) of PTDM patients in the cyclosporine group (OR 4, 95% CI: 0.5-30.2; $P=0.2$).

The prevalence of PTDM was significantly higher in the tacrolimus compared to the cyclosporine group at one month post transplant (8.5% versus 1.1%; OR 8.1, 95% CI: 1-64.2; $P=0.02$), at three months post transplant (16.3% versus 4.8%; OR 3.8, 95% CI: 1.3-11.7; $P=0.01$), and at six months post transplant (15.5% versus 6.3%; OR 2.7, 95% CI: 1-7.8; $P=0.04$). At 12 months post transplant, the difference in the prevalence of PTDM between the two groups was less marked and did not reach statistical significance (8.0% versus 4.0%; OR 2.1, 95% CI 0.5-8.4; $P=0.2$) (figure 3).

The PTDM and non-PTDM groups were compared for a number of possible risk factors. The only identified

Figure 3: prevalence of PTDM at different time points post transplant

risk factors for PTDM were the use of tacrolimus versus cyclosporine (25.4% versus 6.6%; OR 4.8, 95% CI: 1.9-12.1; $P=0.00$) and female gender (26.9% versus 14.8%; OR 2.1, 95% CI: 1-4.5; $P=0.04$). Patients with chronic HCV infection tended to have a higher incidence of PTDM (38.5% versus 16.8%; OR 3.1, 95% CI: 0.9-10.1; $P=0.07$) as did patients who received at least one course of pulse steroid treatment for acute rejection during the first post transplant year (25.9% versus 15.2%; OR 2, 95% CI: 0.9-4; $P=0.06$); however, this association did not reach statistical significance. Pediatric age group was not associated with a higher incidence of PTDM (17.4% versus 18.1%; OR 1, 95% CI: 0.3-3; $P=0.6$). The incidence of PTDM among patients who had no episodes of acute rejection was 15.2% (25/164), the incidence of PTDM among patients who had one, two or three episodes of acute rejection within the first year was 21.3% (10/47), 42.9% (3/7) and 100% (1/1) respectively ($P = 0.03$).

Discussion

The cumulative incidence of PTDM at 12 months post-transplant in our transplant population was 17.6%; this is comparable to the incidence reported in the literature. A considerable proportion of PTDM cases resolved within the study period (53.8%), and among patients who had been followed up for at least 12 months the resolution rate was 66.7%; consequently, the prevalence of PTDM at 12 months post transplant was only 6.2%. PTDM was associated with significant morbidity, the incidence of DKA was rather high (16%), and all patients were treated with regular insulin. PTDM patients were much more

likely to need hospital admission than patients who did not develop PTDM, mainly for diabetes control and the treatment of infections.

The cumulative incidence of PTDM in the cyclosporine group (6.6%) is similar to the estimates reported from randomized controlled trials in patients receiving cyclosporine, azathioprine and prednisolone (2-13.3%). [1] Similarly, the cumulative incidence of PTDM in the tacrolimus group (25.4%) was within the reported range in randomized controlled trials in patients receiving tacrolimus, azathioprine and prednisolone (11.6-25.4%). [1]

The cumulative incidence of PTDM in the cyclosporine group (6.6%) is much lower than the incidence reported in a group of cyclosporine treated patients of Arab origin in a Kuwaiti center (29.6%), which was partly attributed to the fact that Kuwait has a high background incidence of obesity and Type II diabetes mellitus [11]; the incidence was also lower than the incidence reported from a group of cyclosporine treated Saudi patients (41.4%). [12]

The cumulative incidence of PTDM in the tacrolimus group (25.4%) is also lower than the incidence reported by Hricik et al in a group of tacrolimus treated African American kidney transplant recipients (36%). [13]

In this study, the use of tacrolimus compared with cyclosporine was associated with a significantly higher risk of PTDM (25.4% versus 6.6%; OR 4.8, 95% CI: 1.9-12.1; $P=0.000$). The observed difference is consistent with the previous observation that despite the higher risk of PTDM attributed to non-white ethnicity, tacrolimus was associated with a lower relative risk of PTDM in non-white patients (29% versus 7.8%; RR 3.7) than white patients (12% versus 1.2%; RR 10.6) when compared with cyclosporine. [14]

In this study, 57.6% of tacrolimus treated PTDM patients were able to discontinue insulin therapy during the study period, and among those who had been followed up for 12 months 72.7% were able to discontinue insulin therapy within the first post transplant year. In the US multicentre study, only 23.3% of tacrolimus treated PTDM patients discontinued insulin within the first year, and the rate of reversal of insulin dependence was only 41.2% by 5 years. [15] In the European multicentre study, 8.3% of tacrolimus treated patients developed insulin dependent PTDM, and by 12 months, the proportion of tacrolimus treated patients receiving insulin reduced to 5.5%. [16]

In this study, 33.3% of cyclosporine treated PTDM patients were able to discontinue insulin therapy during the study period, and among those who had been followed up for 12 months 40% were able to discontinue insulin therapy within the first post transplant year. In the US multicentre study, only 16.7% of cyclosporine treated PTDM patients

discontinued insulin within the first year. [15] Also, in the European multicentre study, 2.2% of cyclosporine treated patients developed insulin dependent PTDM, and the same proportion (2.2%) continued to receive insulin at 12 months. [16]

The use of tacrolimus and female gender were the only statistically significant risk factor for PTDM in our patient group, although chronic HCV infection and the need for at least one course of pulse steroid treatment for acute rejection during the first post transplant year had a clear tendency to be associated with PTDM. The incidence of PTDM increased significantly with the number of pulse steroid courses used during the first post transplant year.

All our cases of transient PTDM experienced resolution of their diabetes within 12 months of transplant, this concurs with Kiberd et al, who found that resolution occurred within six months for 94% of his patients. [17] If PTDM persists up to 12 months post transplant, it is unlikely to resolve; and switching to cyclosporine may be a valid therapeutic option; the reported success rate of this approach is (44-65%). [18-20]

The choice of calcineurin inhibitor on the bases of diabetogenic risk should not be made at the expense of efficacy; measures such as steroid minimization or withdrawal and lower tacrolimus exposure may help maintain better long term survival.

Conclusion

The incidence of PTDM in our transplant population is no different from that reported in published randomized controlled trials, and a considerable proportion of cases are transient. The resolution rate among our patients was remarkable. The transient nature of most PTDM cases in our population mandates an individualized approach for management, so as not to deprive our patients from the well known benefits of tacrolimus on graft and patient survival.

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