Abstract
Post-transplant diabetes mellitus (PTDM) is a key risk factor for cardiovascular disease, which itself is a leading cause of death with a functioning graft. In a published review of the literature on PTDM and immunosuppression, most cases of PTDM were diagnosed within the first 3 months post-transplantation. In renal transplantation, the type of immunosuppressive regimen accounted for 74% of the variability recorded in the 12 month cumulative incidence of PTDM between studies ($P = 0.0004$), with inclusion of corticosteroids and/or high-dose ciclosporin or tacrolimus being the main risk factors for development of PTDM. Other key risk factors were recipient age and non-white ethnicity. The diabetic potential of any immunosuppressive protocol depends on the combination of agents used and the corresponding doses. Therefore, we conducted an analysis to investigate the impact of different tacrolimus-based regimens employed over the past decade together with the time of study initiation on the incidence of PTDM. There was a progressive decline in the incidence of PTDM with year of study initiation, from 20% in the early 1990s to 0–5% most recently. The low incidences of PTDM were achieved with those protocols employing lower blood levels of tacrolimus and/or corticosteroid elimination. These results emphasize the importance of reducing the immunosuppressive medication load and the role of corticosteroids in the development of PTDM. Evolving tacrolimus-based immunosuppressive protocols for renal transplantation over the last 10 years, particularly in terms of tacrolimus dosing and corticosteroid elimination, has led to a reduction in PTDM-related morbidity without compromising efficacy.

Keywords: cardiovascular risk; corticosteroids; immunosuppression; post-transplant diabetes mellitus; tacrolimus

Introduction
Despite the remarkable improvements seen over the past decade in 1 year renal allograft survival, little change has been reported in terms of long-term graft survival [1]. It is now well known that the two leading causes of late renal allograft loss are chronic allograft nephropathy and death with a functioning graft (DWFG) [2,3]. In an analysis of United Network for Organ Sharing (UNOS) registry data for 86,502 kidney transplant recipients transplanted between 1988 and 1997, > 42% of all renal grafts lost were a result of DWFG [4]. Moreover, 36% of these deaths were caused by cardiovascular disease, making this the leading cause of DWFG. In support of this finding is a report by the US Renal Data System, which states that ischaemic heart disease is the single largest cause of death following a successful transplant [5]. Given this association, it may be postulated that factors that increase post-transplant cardiovascular risk, including hypertension, hyperlipidaemia and diabetes mellitus, also serve to increase the risk for DWFG [6]. This is highlighted in the aforementioned report of UNOS registry data, which concludes: ‘Attention to atherosclerotic risk factors may be the most important challenge to further improve the longevity of patients with successful renal transplants’ [4].

This paper considers one of these atherosclerotic risk factors, namely post-transplant diabetes mellitus (PTDM), with discussion focusing on risk factors for PTDM and the decline in incidence of PTDM over the last 10 years with tacrolimus-based immunosuppressive regimens.

Post-transplant diabetes mellitus: incidence, risk factors and prognosis
PTDM is a frequent complication following renal transplantation and serves as a key risk factor for post-transplant cardiovascular disease. Although the incidence, risk factors and clinical relevance of PTDM
vary among reports from clinical studies [7], preventing PTDM is likely to have a positive impact on survival rates.

In an effort to examine the 12 month cumulative incidence of PTDM, the risk factors for its development and prognostic implications, Montori et al. carried out a systematic review of the literature on PTDM and immunosuppression up to September 2000 [8]. Inclusion criteria for this analysis were randomized, controlled trials, cohort studies or case-controlled studies that provided data on PTDM after any solid organ transplantation except pancreas and islet cell transplantation. In addition, only those studies that had >1-year follow-up of adult transplant recipients with new-onset PTDM, with <10% loss to follow-up, were eligible.

The search for relevant publications yielded 27 full reports, involving 3611 transplant recipients in 19 studies. Results of the analysis demonstrated that most cases of PTDM were diagnosed within the first 3 months following transplantation. In the 12 studies of kidney transplantation, the estimated incidence of PTDM ranged from 2 to 50%. The type of immunosuppressive regimen (corticosteroids, ciclosporin, high- or low-dose tacrolimus) was found to account for 74% of the variability in the 12 month cumulative incidence of PTDM between the studies ($P = 0.0004$).

The main risk factors for the development of PTDM were transplant recipient age, non-white ethnicity and immunosuppression. As illustrated in Figure 1, during the early years of transplantation, conventional immunosuppressive regimens included high-dose steroids, which resulted in high rates of PTDM. In more recent reports, there was an association between the use of corticosteroids for the treatment of acute rejection and PTDM, with up to 76% of PTDM cases diagnosed during or in the month after antirejection treatment. High-dose tacrolimus ($>0.2 \text{ mg/kg/day}$) was also associated with increased risk of PTDM; during the initial phase III studies of tacrolimus and ciclosporin in kidney transplantation, the incidence of PTDM was significantly greater in

patients treated with high-dose tacrolimus vs ciclosporin-based triple therapy [relative risk (RR) 5.0, 95% confidence interval (CI) 2.2–11.5; Figure 1]. However, in more recent trials, patients treated with low-dose tacrolimus (0.15–0.2 mg/kg/day) were not at increased risk of developing PTDM compared with patients receiving ciclosporin-based triple therapy. An additional risk factor for PTDM was found to be acute rejection. Specifically, patients who suffered a rejection episode within the first year post-transplant were at high risk of developing PTDM. In the 12 studies, the estimated incidence of PTDM ranged from 2 to 50%. The type of immunosuppressive regimen (corticosteroids, ciclosporin, high- or low-dose tacrolimus) was found to account for 74% of the variability in the 12 month cumulative incidence of PTDM between the studies ($P = 0.0004$).

In terms of prognosis, the results of the analysis indicated that PTDM was associated with a small decrease in mortality. However, the increase in patient survival over time suggests that the prognosis has improved. Most encouraging was the proportion of patients with PTDM able to discontinue glucose-lowering treatments. This was large in both tacrolimus (30–90%) and ciclosporin-treated patients (60–100%).

**Analysis of post-transplant diabetes mellitus with tacrolimus-based immunosuppressive regimens**

Over the last 10 years, extensive clinical experience with the use of tacrolimus as a cornerstone immunosuppressant in renal transplantation has been acquired. During this period, tacrolimus has been used in combination with various adjunctive immunosuppressants, such as corticosteroids, azathioprine, mycophenolate mofetil (MMF), sirolimus and the anti-interleukin-2-receptor monoclonal antibodies daclizumab and basiliximab. Since the glucose metabolism disturbance potential of any immunosuppressive regimen will depend on each single agent used and the corresponding dose employed, we conducted an analysis to investigate the impact of different tacrolimus-based regimens employed over the past decade on the incidence of PTDM, as well as the time of study initiation.

Only published reports of prospective, randomized, controlled trials providing 6–12 months of follow-up data were included in the analysis. Studies had to have included >50 adult primary renal transplant recipients in each tacrolimus treatment arm. A total of 16 renal studies (12 from Europe, four from the USA) with trial initiation dates from 1993 to 2000 provided data on 5355 kidney transplant recipients and 32 tacrolimus-based treatment groups [9–25]. Use of adjunctive agents, such as MMF, daclizumab, basiliximab and sirolimus, varied among the studies.

Definitions of glucose metabolism disturbances and diabetes and the appropriate terms to apply to transplantation studies have been the subject of continuous review over the past decade. The current American Diabetes Association criteria for diagnosis of diabetes mellitus are: symptoms of diabetes plus casual plasma glucose concentration $\geq 200 \text{ mg/dl (11.1 mmol/l)}$; or fasting plasma glucose $\geq 126 \text{ mg/dl}$. 

![Figure 1](image_url)
Post-transplant diabetes mellitus: the last 10 years with tacrolimus

The definition used in our analysis was 

(7.0 mmol/l); or a 2 h post-load glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test [26]. The definition used in our analysis was >30 days’ insulin requirement in patients not diabetic prior to transplant. Although this definition tends to underestimate the overall effects of immunosuppression on glucose metabolism, it has been applied consistently across all tacrolimus studies and hence avoids the pitfalls associated with comparing different definitions across studies. Furthermore, this term reflects current practice in transplantation medicine and is used in most randomized, controlled trials of immunosuppressive regimens.

Results of the analysis indicated a progressive decrease in the reported incidence of PTDM following renal transplantation with year of study initiation, from as high as 20% in the early 1990s to 0–5% most recently (Figure 2) [9–22,24,25]. Notably, these low incidences of PTDM were achieved in studies that employed low blood levels of tacrolimus and eliminated corticosteroids from tacrolimus-based regimens.

Through continuous development of tacrolimus dosing—as a result of increasing experience gained in the use of the drug and changing immunosuppressive regimens—it has been possible to achieve low trough levels of tacrolimus in many transplant studies. Consequently, the designs of the most recent tacrolimus trials are in marked contrast to the earlier studies. In 1997, Pirsch et al. reported a high incidence of PTDM (19.9%) at 1 year post-transplant with a regimen comprising tacrolimus at relatively high trough concentrations (10–25 ng/ml in the first 3 months) plus corticosteroids and azathioprine [9]. However, in 2000, Johnson et al. demonstrated that a lower 12 month incidence of PTDM (6.5%) could be achieved by using lower trough concentrations of tacrolimus (8–16 ng/ml in the first 3 months), combined with MMF and a rapid tapering of corticosteroids [10].

Recently, Rostaing et al. showed that by employing induction therapy with daclizumab plus concomitant MMF therapy, it is possible to taper tacrolimus blood concentrations rapidly (10–20 ng/ml up to week 3, 10–15 ng/ml in weeks 3–6 and 5–10 ng/ml from week 6 onward) and completely avoid the use of maintenance corticosteroids [13]. The results of this European multicentre study demonstrated the advantages of eliminating corticosteroids from tacrolimus-based regimens. At 6 months post-transplant, treatment with daclizumab, tacrolimus plus MMF resulted in a significant reduction in the incidence of PTDM compared with the standard arm, which employed tacrolimus, MMF and concomitant corticosteroids (P = 0.001; Table 1). Of particular importance was the finding that omission of maintenance corticosteroids did not place patients at an increased risk of acute rejection, the incidence of which was identical in each treatment arm. These results support the findings of Montori et al., showing that corticosteroid treatment increases the risk of PTDM.

Additional corroboration comes from the results of a subanalysis of all 12 European kidney studies, whereby the tacrolimus-based, corticosteroid-free treatment arms were compared with the reference tacrolimus-based, corticosteroid-containing treatment groups for the mean incidence of PTDM and acute rejection [13–25]. The findings were consistent with those reported by Rostaing et al. In the four tacrolimus-based treatment groups in which corticosteroids were absent [13,14,24], there was a reduction in the mean incidence of PTDM (2.2%) compared with the incidence reported in the 20 tacrolimus-based treatment groups in which corticosteroids had been administered (4.8%) [13,15–22,24,25]. Furthermore, there was no compromise in efficacy, with comparable incidences of acute rejection (26 vs 21%, respectively) [13–21,23–25]. One of the studies included in this particular subanalysis was a comparison of tacrolimus and ciclosporin monotherapy [14]. Importantly, no cases of PTDM were reported for either treatment group at 6 months post-transplant.

Together, the results of this analysis of PTDM and tacrolimus-based therapy underline not only the importance of reducing the immunosuppressive medication load, but also the key role that corticosteroids play in the development of this disorder in the renal

![Fig. 2. Cumulative incidence of post-transplant diabetes mellitus (PTDM) after renal transplantation in 32 tacrolimus-based treatment groups. Eight of the 32 tacrolimus-based study groups are from four US studies [9–12] and 24 are from 12 European studies [13–22,24,25]. Linear regression was used to find the best fitting line relating the cumulative incidence of PTDM (measured at 6 or 12 months) to the year of study initiation.](image)

Table 1. Incidence of acute rejection and post-transplant diabetes mellitus with tacrolimus-based regimens [13]

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Tacrolimus + MMF + corticosteroids</th>
<th>Tacrolimus + MMF + daclizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy-proven acute rejection (%)</td>
<td>16.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Corticosteroid-resistant acute rejection (%)</td>
<td>4.3</td>
<td>5.0</td>
</tr>
<tr>
<td>PTDM (%)</td>
<td>5.4</td>
<td>0.4*</td>
</tr>
</tbody>
</table>

MMF = mycophenolate mofetil; PTDM = post-transplant diabetes mellitus.

*P = 0.001 for the difference between the two treatment groups, Fisher’s exact test.
transplant patient. It may be postulated that in patients at high risk of PTDM, administering an immunosuppressive regimen that omits corticosteroids would be of considerable benefit.

Conclusions

Transplant recipient age, non-white ethnicity and the immunosuppressive regimen play a significant role in the development of PTDM in transplant patients. The majority of PTDM cases are diagnosed early post-transplant. Importantly, the majority of patients are able to discontinue glucose-lowering treatments.

The past decade has witnessed a considerable decline in the proportion of patients receiving immunosuppressive therapy based on tacrolimus who develop PTDM. This may, in part, be due to increasing experience with use of tacrolimus and changing combination therapies that have enabled employment of lower initial doses, more rapid tapering and lower maintenance levels of this cornerstone immunosuppressant. Moreover, corticosteroids play a significant role in the development of PTDM, and the corticosteroid-sparing properties of tacrolimus together with the introduction of new adjunctive agents have facilitated corticosteroid withdrawal and avoidance. For tacrolimus-based immunosuppression, the sum of all these changes has led to a reduction in PTDM-related morbidity without compromising its excellent efficacy profile.

Conflict of interest statement. None declared.

References

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