Post-transplant diabetes mellitus in lung transplant recipients: incidence and risk factors

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Abstract

Objective: Post-transplant diabetes mellitus (PTDM) is a common and potentially serious complication after solid organ transplantation. There are only a few data, however, about the incidence of DM in patients undergoing lung transplantation.

Patients and methods: The medical records of 119 consecutive patients who underwent lung transplantation from 1998 to September 2004 were reviewed. Patients were divided in three groups according to their diabetes status, including pre-transplant DM, the PTDM group and those without DM. Patient records and all laboratory data were reviewed and the clinical course of diabetes was monitored. All recipients were treated with tacrolimus based regimen.

Results: Mean follow-up for all patients was 25 ± 10. Twenty-three patients had DM in the pre-lung transplantation (LTX) DM group. PTDM developed in 34 of the remaining 96 patients (35.4%) with an incidence of 20%, 23% after 6 months and 12 months post-transplant. No significant difference was noted between 12 and 24 months post-LTX. The patients who developed DM were older (57 ± 15 vs 53 ± 13 years, p = 0.009), had increased BMI (26 ± 5 vs 24 ± 4, p = 0.0001), shorter time from diagnosis to LTX (21 ± 13 vs 28 ± 18 months, p = 0.007) more cytomegalovirus infection and more acute rejection and hyperglycemia in the first month after LTX. Four patients died in the PTDM group compared to nine patients in the no-DM group (12% vs 14%; p = 0.72).

Conclusions: Post-transplant diabetes is a common complication in lung transplant patients receiving tacrolimus-based immunosuppression. The risk for developing PTDM is greatest among older recipients, those obese, and among recipients with more rejection episodes.

Keywords: Lung transplantation; Diabetes; Rejection; Tacrolimus

1. Introduction

Post-transplant diabetes mellitus (PTDM) is a common and potentially serious complication after solid organ transplantation. The prevalence of PTDM among nondiabetics has been reported to occur in 2.5—24% of renal allograft recipients [1—3], and is associated with decreased graft [3—5] and patient survival [6—8] as well as an increased risk for infection and cardiovascular disease [5,9].

Patients undergoing lung transplantation receive medications that can lead to impaired glucose tolerance and DM [8]. Various combinations of immunosuppressive agents have been reported to be risk factors for PTDM including calcineurin inhibitors and glucocorticoids [10—12]. In addition, the operation causes a major stress response. Registry data and two large multicenter trials concluded that the incidence of PTDM among kidney recipients was significantly higher in patients receiving tacrolimus [10,13,14].

Only a few studies have evaluated the prevalence and the incidence of DM in patients undergoing lung transplantation. Our study goal was to define the prevalence and the incidence of DM in patients undergoing lung transplantation. We also hypothesized that the prevalence of DM increases after lung transplantation.

2. Patients and methods

2.1. Patients

We reviewed the medical records of 119 consecutive patients who underwent lung and heart lung transplantation from 1998 to September 2004.

Standardized surgical techniques were used for the operations and these are described elsewhere [15,16].
Patients who died within the first 30 days after their transplant operation were excluded. Most of these patients remained hospitalized after their transplant operation and were under high stress and on corticosteroids, so no definite diagnosis of diabetes could be made.

We included patients with cystic fibrosis who developed diabetes and patients with pre-existing diabetes mellitus.

The local ethics committee approved the study protocol.

### 2.2. Immunosuppression and prophylaxis

All lung transplant recipients at our center receive initial immunosuppression according to the following protocol: (1) intravenous (IV) methylprednisolone 500 mg intraoperatively, prior to graft reperfusion; followed by six doses of IV methylprednisolone 125 mg q 8 h postoperatively, followed by standard prednisone oral taper; (2) mycophenolate mofetil 1 g twice daily; and (3) tacrolimus titrated to whole blood trough levels of 15—20 ng/ml for 2 weeks.

The patients are subsequently maintained on a triple regimen: (1) oral prednisone, 0.25 mg/kg/day over the first 6—9 months, then 15 mg every other day to 1 year; (2) tacrolimus titrated to whole blood levels of 8—12 ng/ml; and (3) mycophenolate mofetil 0.5 g bid.

Rejection episodes are treated with IV methylprednisolone 1 g/day for 3 days, followed by tapering down.

Every patient also receives trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis carinii* infection, one tablet (960 mg) three times weekly. If the recipients or donors have positive serology for cytomegalovirus (CMV), IV ganciclovir is added to the protocol at 5 mg/kg bid for 5 days, followed by valganciclovir for 3 months, and prophylaxis against *Aspergillus* infection with itraconazole 200 mg bid for 6 months.

### 2.3. Definitions

Patients were divided to three groups according to the diabetes status. Group one included pretransplant DM, group two included the PTDM and group 3 were all lung recipients without DM.

Hyperglycemia in the immediate post-transplant period is a common occurrence in thoracic transplantation. For this reason, post-transplant diabetes mellitus was defined as hyperglycemia after 1-month post-transplant requiring oral hypoglycemic agents or insulin therapy. Onset of diabetes was defined as the date on which an oral hypoglycemic agent or insulin was instituted.

### 2.4. Clinical course and diabetes outcome

All patients are routinely followed at the clinic with complete blood counts, blood chemistry, measurements of drug levels, chest radiographs, pulmonary function testing, and surveillance bronchoscopies.

We also followed the basal metabolic rate (BMI) of the recipients. The BMI is calculated by dividing the weight (kg) by the square of height (m). A BMI > 25 has been proposed to signify overweight, and > 30 obese.

Patient records and laboratory data were reviewed, and the following information was analyzed: type of transplant, BMI, age at transplant, use of maintenance corticosteroids, time to development of diabetes, length of follow-up, and diabetes outcome.

The clinical course of diabetes was monitored, with particular attention given to changes in immunosuppressive regimen and diabetes therapy. Mean tacrolimus dosage (mg/kg/day), whole blood tacrolimus level (ng/ml), and steroid dosage (mg/kg/day) were recorded before lung transplantation (LTX), at 1, 3, 6, 12, 24 and 36 months post-LTX. For patients who became diabetic during pulsed corticosteroid therapy, their maintenance prednisone dose before the pulse was used as the steroid dose at diabetes onset.

#### 2.4.1. Statistical analysis

Results are shown as mean ± standard deviation. Pearson correlation coefficient (r) and the significance for it (p) were calculated between the variables.

To analyze differences in the distribution of categorical data, chi-square test or Fisher’s exact test was used, as appropriate.

To predict PTDM, a stepwise logistic regression was fitted to the data. Odds ratios and 95% confidence intervals were calculated from the model.

A p value of 0.05 or less was considered statistically significant.

### 3. Results

#### 3.1. Clinical characteristics of the study population

The study included 119 consecutive adult patients who underwent lung transplantation at Rabin Medical Center, Israel. Mean follow-up was 26 ± 10 (range 3—36 months) in the PTDM and 25.7 ± 12 (range 4—36 months) in the no-DM group, without significant differences between groups.

The demographic and clinical characteristics of the three groups are presented in Table 1. The main indications for LTX were emphysema and IPF without significant different between the groups. CF was the indication for LTX in three patients in the PTDM and in five patients in the no-DM groups (p = NS). Other indications included sarcoidosis in one patient in the PTDM and two patients in the no DM, Scleroderma in one patient in PTDM and two patients in the no-DM group. Lymphangioleiomyomatosis in one patient in the no-DM group and three patients with primary pulmonary hypertension in the no-DM group.

Significant differences in the clinical parameters were noted between the PTDM and the group without DM (no-DM group). The patients who developed DM were older (57 ± 15 vs 53 ± 13 years, p = 0.009), had increased BMI (25 ± 5 vs 24 ± 4, p = 0.0001) and shorter time from diagnosis to LTX (21 ± 13 vs 28 ± 18 months, p = 0.007). In addition, acute CMV infection was significantly more common among patients with PTDM than among no-DM group (12% vs 8%, p = 0.004). Similarly, acute rejection and hyperglycemia in the first month after LTX were more common among the PTDM group than the no-DM group (p = 0.009 and p = 0.001, respectively).

The creatinine levels in the baseline and after follow-up were similar in both groups (Table 1).
3.2. Incidence of diabetes mellitus after lung transplantation

Twenty-three patients developed diabetes mellitus pre-lung transplantation (pre-LTX DM group).

PTDM was developed in 34 of the remaining 96 patients (35.4%) during 36 months post-LTX (Fig. 1). The incidence of PTDM was 20%, 23% after 6 months and 12 months post-LTX. No significant difference was noted between 12 and 24 months post-LTX.

Fig. 2 summarizes the number of patients with PTDM that were treated with insulin. As shown, during 6—36 months after LTX, 68—87% of the patients with PTDM treated with insulin.

3.3. Mortality

Kaplan—Meier survival estimates for the patients with and without post-transplantation diabetes mellitus are presented in Fig. 3. Four patients died in the PTDM group (12%) compared to 9 patients in the no-DM group (14%) without significant differences between the groups ($p = 0.72$).

4. Discussion

The results of this study confirm that post-transplant diabetes is a relatively common complication in lung transplant recipients.

Previous studies reported that the incidence of diabetes in pediatric heart-lung/lung recipients is twice that in heart recipients. This most likely reflects higher tacrolimus and steroid doses in the former group, as was previously shown [17,18].

Glucocorticoids are one of the major risk factors for PTDM, with some earlier studies reporting an incidence as high as 40—60% [10,19,20]. These agents lead to elevated blood glucose by enhanced hepatic gluconeogenesis, and as a result of inducing insulin resistance both directly and as a consequence of weight gain through increased appetite. In our study, steroid pulse therapy to treat rejection and hyperglycemia in the first month after LTX were more common among PTDM group than the no-DM group ($p = 0.009$ and $p = 0.001$, respectively). Accumulated glucocorticoid dose has also been reported to increase the incidence of PTDM. In a previous study, the risk of developing PTDM was 5%
of PTDM increases continuously for body weight above 60 kg recipients treated with cyclosporine and found that the risk of developing PTDM over several immunosuppressive eras. Boudreaux et al. [21] found that the incidence of PTDM is greater in patients heavier than 70 kg (21.1% vs 5.1%). More recently, Cosio et al. [2] followed 2078 renal transplant recipients treated with cyclosporine and found that the risk of PTDM increases continuously for body weight above 60 kg (hazard ratio; 1.4). However, BMI (kg/m²) rather than absolute body weight is considered a better marker of obesity. In fact, BMI at transplant was a significant risk factor for developing PTDM in our study.

Motoo et al. [22] evaluated the incidence and risk factors for PTDM in 528 kidney recipients using different immunosuppressive agents. Overall, the number of patients needing insulin was 7.4% without a significant statistical difference between the groups. Similar to our results, the characteristics of patients with PTDM included older age, greater BMI at transplant, more acute rejection episodes and the use of tacrolimus. They also observed that new insulin use occurred sooner and with less total glucocorticoid dose secondary to tacrolimus [22].

According to our results and previous data, development of DM did not appear to be associated with worse outcomes after transplantation [18,22]. There are many explanations for that. End organ damage occurs after a significant number of years of DM. Despite a relatively long follow-up for this transplant cohort, there was probably not enough time to detect differences. Another factor in the lack of differences might have been the multiple competing conditions that can lead to early death in patients after lung transplantation.

The effect of DM after lung transplantation has not been studied extensively. The relatively poor survival of lung transplant recipients makes it difficult to assess the long-term effects of DM. In addition, for some complications like renal dysfunction it is difficult to assess the effect of DM in the setting of calcineurin inhibitor use. Also, the need for insulin use (subcutaneous injections) and its effect on quality of life have not been studied, but patients should be alerted to the potential need of such therapy post-transplant.

PTLD has also been reported in patients receiving cyclosporine-based immunosuppression. Various studies report the incidence of PTDM secondary to cyclosporine to be less than or equal to tacrolimus therapy [23,24]. Our study included however, only patients treated with tacrolimus (FK 506) based regimen.

Recently, the ISHLT (International Society for Heart and Lung Transplantation) published the registry’s current incidents of the PTDM [25]. They reported that the relative risk for mortality due to PTDM is 1.37 (CI 1.11–1.69). The incidence of PTDM in the first year and 5 years post-transplantation are 29.6% and 33.5%, respectively. These data are slightly lower than the findings in our cohort. Partial explanation could be the higher tacrolimus and steroid doses in our series.

What is the potential mechanism of PTDM? Direct islet cell toxicity has been attributed to tacrolimus through inhibition of insulin gene expression. It does so by binding FKBP-12 and thereby inhibiting calcineurin phosphatase, whose function contributes in part to insulin production in beta cells. By inhibiting calcineurin phosphatase, tacrolimus also prevents the phosphorylation of CREB (cyclic AMP response element binding protein), a ubiquitous inducible trans-activator of multiple genes including those involved in insulin signaling and beta cell survival. These inhibitory effects on calcineurin phosphatase, and on CREB activity, have not been demonstrated with sirolimus. The diabetogenic potential for anti-rejection drugs appears to be dual, directed both at insulin secretion and insulin resistance. Some recent investigations suggest that while many agents (including tacrolimus, mycophenolate mofetil and sirolimus) suppress insulin secretion from cultured islets in vitro, the degree of tacrolimus inhibition may be greater. Of note, the role of tacrolimus inducing PTDM may be directly related to the concentration of the drug. Moreover, a prospective study of the influence of sirolimus on glucose metabolism demonstrated that indices of insulin resistance were elevated in patients receiving tacrolimus. This effect appeared limited to patients who had tacrolimus trough levels above 15 ng/ml. Earlier trials often used high tacrolimus trough levels up to 25 ng/ml especially the first few months after transplant. However, studies in which tacrolimus concentrations were kept under 15 ng/ml showed no significant difference in PTDM between tacrolimus and cyclosporine [11–13]. Our results, using target trough levels of 10–12 ng/ml for tacrolimus were in the lower end of the risk range.

Our study has some important limitations. First, there is a lack of fasting blood glucose information before and after patients lung transplantation. This might have missed some more subtle forms of diabetes. However, most patients with DM would have been identified at a later time point. Second, no clear mechanism of DM was identified. Finally, the lack of an effect of many variables on the development of post-transplant DM and post-transplant outcomes might have been overlooked. Future studies that include recent variables collected prospectively, with larger number of patients can answer these questions.

In summary, PTDM is a common complication in lung transplant patients receiving tacrolimus-based immunosuppression. The risk for developing PTDM is greatest among older recipients, those obese at the time of transplant, those...
with CMV infection and those with more acute rejection episodes. These data suggest that reduction in PTDM risk is best targeted by weight reduction and dietary control in the obese population prior to transplant.

References


