High Incidence of Tacrolimus-Associated Posttransplantation Diabetes in the Korean Renal Allograft Recipients According to American Diabetes Association Criteria

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OBJECTIVE — The incidence of posttransplantation diabetes mellitus (PTDM) has been reported to vary according to different study populations or different definitions. In this study, using American Diabetes Association criteria, the incidence and clinical characteristics of PTDM in Korean renal allograft recipients undergoing tacrolimus-based immunosuppression were examined.

RESEARCH DESIGN AND METHODS — A total of 21 patients taking tacrolimus as primary immunosuppressant were recruited and tested with a serial 75-g oral glucose tolerance test at 0, 1, 3, and 6 months after renal transplantation.

RESULTS — The cumulative incidence of PTDM was 52.4% at 1 month and 57.1% at 3 and 6 months after renal transplantation.

CONCLUSIONS — Routine screening for PTDM is necessary in patients over 40 years of age who are undergoing a relatively higher dose tacrolimus therapy during the early course of postrenal transplantation.

Diabetes Care 26:1123–1128, 2003

Tacrolimus is an effective alternative to cyclosporine as a primary immunosuppressant after kidney transplantation (1–4). The diabetogenic potential of tacrolimus is much higher than that of cyclosporine in the early posttransplantation period (5–7). Despite its excellent prophylactic effect on renal allograft rejection, posttransplantation diabetes mellitus (PTDM) has become a major drawback in its clinical application (8–12). A temporal trend of the incidence of PTDM has been demonstrated to show a bimodal pattern corresponding to the early kidney transplantation era using high-dose steroids in the 1960s and to the introduction of tacrolimus in the 1990s (5).

Tacrolimus inhibits the transcription of the insulin gene by inhibition of calcineurin after binding to FK506-binding protein 12 (FKBP12) (13,14). In contrast, sirolimus, which also binds to FKBP12, interacts with mammalian target of rapamycin, so-called mTOR, instead of calcineurin and frequently causes hyperlipidemia by inhibition of insulin action (15). Tacrolimus-induced PTDM has been proven to be reversible after withdrawing tacrolimus (13,14,16), and we have recently reported a case showing complete insulin independence after severe diabetic ketoacidosis associated with tacrolimus treatment (17).

It has been reported that PTDM is associated with diabetic microvascular complications, an increased frequency of sepsis as a cause of death, and a risk of developing graft failure (18). Considering the well-known serious clinical outcomes of hyperglycemia and the established benefits of intensive glycemic control (19,20), the chronic metabolic derangement in PTDM, even though the severity of which is mild, could lead to many diabetes complications and should be corrected appropriately. Therefore, in this study, to define PTDM we used the American Diabetes Association (ADA) criteria for the diagnosis of diabetes (21), which is more stringent than ever.

Ethnic difference contributes to the variable susceptibility to developing PTDM (5,12,22,23). Interestingly, most type 2 diabetic patients in Korea are characterized by defects in insulin secretion.
Table 1—Comparison of baseline clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-PTDM</th>
<th>PTDM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age (female:male)</td>
<td>27±2</td>
<td>41±4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sex (male:female)</td>
<td>2.7</td>
<td>9.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.1±1.0</td>
<td>23.1±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Family history of diabetes*</td>
<td>1/9 (11.1%)</td>
<td>3/12 (25.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>144±3</td>
<td>140±6</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86±3</td>
<td>80±3</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>4.9±0.3</td>
<td>5.6±0.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.0±0.2</td>
<td>4.8±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma C-peptide (nmol/l)</td>
<td>2.4±0.6</td>
<td>2.3±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol/l)</td>
<td>55.8±35.2</td>
<td>80.4±18.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.5±1.7</td>
<td>3.5±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA-BC</td>
<td>95.5±36.3</td>
<td>121.5±27.7</td>
<td>NS</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>2.3±1.4</td>
<td>5.8±4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.1±0.3</td>
<td>4.1±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1±0.1</td>
<td>1.6±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.5±0.2</td>
<td>2.3±0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SEM unless otherwise indicated. *Family history of clinical diabetes in a first-degree relative. NS, not significant.

PTDM associated with tacrolimus

rather than insulin resistance (24,25). Thus, tacrolimus-based immunosuppression, which causes β-cell toxicity and subsequent insulin secretory defects, may exert more detrimental effects in the Korean population.

In this background, we examined the incidence and clinical characteristics of PTDM defined by ADA criteria in the Korean patients receiving tacrolimus-based immunosuppression after kidney transplantation.

**RESEARCH DESIGN AND METHODS**

**Subjects**

The following criteria were used to determine which patients were eligible to participate in the study: age 18 years or older, recipients of a kidney allograft, no known history of clinical diabetes, no current use of steroids or other immunosuppressive agents, and no previous history of organ transplantation. The study protocol was approved by the Institutional Review Board of Clinical Research Institute at Seoul National University Hospital, and informed consent was obtained from each patient. A total of 21 patients (11 men and 10 women) from Seoul National University Hospital were enrolled in this study. The mean age of the patients was 35 years (range 18–58). Altogether, 18 patients received a renal allograft from a living-related donor, and 3 patients received an allograft from their spouse. Patients undergoing cadaver-donor kidney transplantation were not included. The study protocol was approved by the Institutional Review Board of Clinical Research Institute at Seoul National University Hospital. Informed consent was obtained from each patient.

**Immunosuppression**

The immunosuppressive regimen consisted of tacrolimus and glucocorticoid in all patients. The initial tacrolimus dose was 0.075 mg/kg body wt given twice daily starting on day −1. The target plasma tacrolimus trough levels for all patients were 10–15 ng/ml from day 1 until day 90. Thereafter, they were adjusted gradually to 5–10 ng/ml. The steroid dose consisted of 300 mg methylprednisolone on day 0. Thereafter, 60 mg prednisolone per day was administered, which was gradually tapered to a maintenance dose of 10–15 mg/day.

**Measurements**

The 75-g oral glucose tolerance test (OGTT) was used to assess the glucose tolerance and to measure the insulin response to a glucose load on four occasions (day −1 and months 1, 3, and 6). OGTT was not performed in the patients who developed PTDM requiring insulin or oral antidiabetic therapy (n = 4). All tests were performed in the morning after an overnight fast, and the blood pressure, height, and weight were measured before OGTT of each visit. The HbA1c, HLA type, anti-hepatitis C virus (HCV) antibody, total cholesterol, triglyceride, and HDL cholesterol levels were measured by routine assays in the Department of Clinical Pathology at Seoul National University Hospital. The LDL cholesterol level was calculated by Friedewald’s equation. The fasting plasma insulin and C-peptide levels were determined by radioimmunoassay (BioSource Europe S.A., Nivelles, Belgium) in a single large batch.

Using the plasma glucose and insulin data obtained from the OGTT, the homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-BC) were calculated (26). The insulinogenic index, which has been demonstrated to show an excellent correlation with acute insulin response (27), was used to estimate the early insulin secretion using OGTT data.

**Definition**

In this study, the ADA criteria were used to diagnose PTDM. Briefly, the symptoms of typical diabetes plus casual plasma glucose concentration ≥11.1 mmol/l, fasting plasma glucose (FPG) ≥7.0 mmol/l with no calorie intake for at least 8 h, or 2-h plasma glucose during an OGTT (2-h PG) ≥11.1 mmol/l was defined as PTDM. In addition, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were defined as FPG ≥6.1<7.0 mmol/l and 2-h PG ≥7.8<11.1 mmol/l, respectively.

**Statistical analysis**

All continuous variables were expressed as mean ± SEM. We performed Fisher’s exact test, Mann-Whitney test, and multiple logistic regression test using SPSS software (SPSS, Chicago, IL). For the serial change in each variable, we performed repeated measures ANOVA with GraphPad InStat (GraphPad software,
San Diego, CA). A $P$ value $<0.05$ was considered statistically significant.

**RESULTS**

Incidence and clinical characteristics of PTDM

The cumulative incidence of PTDM according to ADA criteria was 52.4% (11 of 21) at month 1 and 57.1% (12 of 21) at months 3 and 6. Four patients in the PTDM group required pharmacological treatment for glycemic control, and they all needed insulin therapy for $>1$ month during the study period. The baseline characteristics are summarized in Table 1, and the plasma glucose and insulin levels during OGTT are shown in Fig. 1. At baseline, the PTDM group was older, had a higher FPG level, a higher plasma insulin level, and a higher HOMA-IR than the non-PTDM group (Table 1 and Fig. 1).

Multiple logistic regression analysis revealed that only the age at transplantation has the predictive value for the future PTDM ($P = 0.039$). Of note, all patients $>40$ years of age developed PTDM ($n = 7$), and the relative risk of age $>40$ years in the development of PTDM was 2.8 (95% CI 1.39–5.66).

Before transplantation, there were 10 patients with normal glucose tolerance, 2 with IFG, 7 with IGT, and 2 with both IFG and IGT. The category of glucose tolerance at the baseline was not predictive for future PTDM. The frequency of HLA A11 and HLA B62 was higher in the PTDM group than in the non-PTDM group (28.5 vs. 0% and 23.8 vs. 0%, respectively), which was statistically significant ($P < 0.05$). There were no baseline differences in blood pressure, serum lipid profile, plasma C-peptide level, HbA1c, HOMA-BC, insulinogenic index, or area under the curve (AUC) for plasma insulin during the OGTT (Table 1, Figs. 2 and 3). In addition, there was no difference in the frequency of $\beta$-blocker medication (33.3 vs. 44.4%), episode of acute rejection (8.3 vs. 11.1%), and seropositivity for HCV infection (0 vs. 11.1%) between the PTDM and non-PTDM groups, respectively.

Serial changes in insulin resistance and insulin secretion

At baseline, both groups had a very high HOMA-IR, which showed a rapid decline after renal transplantation. The baseline HOMA-IR of the PTDM group was significantly higher than that of the non-PTDM group, but it was similar between two groups at 1, 3, and 6 months after transplantation (Fig. 4). There was no remarkable change in the BMI of each group during the follow-up period (Fig. 4).

Both the HOMA-BC and AUC for the plasma insulin level during the OGTT in the PTDM group showed a marked reduction compared with baseline values at 1 and 3 months after transplantation. Thereafter, this notably decreased HOMA-BC and AUC for the plasma insulin level in the PTDM group and showed a tendency to be restored to that of the non-PTDM group after 6 months (Fig. 2). However, the insulinogenic index of the PTDM group was still lower at 6 months compared with that of the non-PTDM group (Fig. 3). There were no significant differences in the indexes of insulin secretion in the non-PTDM group throughout the study period.

Figure 1—Changes in plasma glucose and insulin level during OGTT before and after kidney transplantation. A–D: Plasma glucose level during OGTT. E–H: Plasma insulin level during OGTT. ○, non-PTDM; ●, PTDM. *$P < 0.05$ compared with each control. Data are expressed as mean ± SEM.
Immunosuppressive treatment
The plasma tacrolimus trough level did not show any difference between the two groups throughout the study period. The cumulative dose of prednisolone during the previous 30 days was also similar between both groups (Table 2).

CONCLUSIONS — In this study, the cumulative incidence of PTDM according to ADA criteria was 57.1% at 6 months of postrenal transplantation, which was considerably high compared with the incidence of PTDM from previous studies (5). Considering that the prevalence of diabetes in the age group of 30–64 years in Korea is 7.2% (28), and the 1-year prevalence of PTDM associated with cyclosporin A–based immunosuppression is 23.7% (29), the incidence of PTDM in this study is very high. Several factors might explain this unexpectedly high incidence of PTDM. First, we can consider the ethnic difference. In general, non-Caucasian patients experienced a twofold increase in the risk of PTDM compared with Caucasian (5). Hricik et al. (23) recently reported that African-Americans were more susceptible to PTDM than Caucasians, despite similar doses of corticosteroids and lower trough levels of tacrolimus. Because the main mechanism of tacrolimus-associated PTDM is the decrease in insulin secretory capacity (13,14,16), and most type 2 diabetic patients in Korea are characterized by insulin secretory defect (24,25), the Korean population may be more susceptible to the tacrolimus-associated PTDM. Second, the ADA criteria revised in 1997 are even stricter than other definitions previously used and have the power to detect mild asymptomatic diabetes. In reanalyzing our data using other definitions of PTDM used in previous studies, such as FPG ≥7.8 mmol/l alone or requirement of insulin therapy for more than 1 month, the incidence of PTDM was 28.6 and 19.0%, respectively. Thus, in this study, mild asymptomatic cases could be effectively detected by ADA criteria. Considering the serious clinical outcomes of chronic hyperglycemia in the patients with renal transplantation (18), the PTDM, even though the severity of which is mild, should be detected and corrected appropriately.

At baseline, the patients who developed PTDM were older, had higher blood glucose and insulin values, a significantly higher frequency of insulin resistance, and a tendency for higher triglyceride values, which are well-known risk factors for the development of diabetes (30). Multivariate analysis revealed that only the age at transplantation has the predictive value for the future PTDM. Therefore, the age itself might contribute to other features of insulin resistance. Of note, all patients >40 years developed PTDM, and the relative risk of age >40 in the development of PTDM was 2.8.

It has been hypothesized that the diabetogenic effect of tacrolimus may be enhanced by HCV infection (31), but we could not test this hypothesis because only one patient turned out to be positive for HCV infection. In addition, we could not observe any difference in prednisolone dose, use of β-blocker, episode...
of graft rejection, BMI change, duration of dialysis, and renal function between the two groups (some data are not shown).

We could observe a dramatic change in insulin secretory capacity in the PTDM group. Because the inhibitory effect of tacrolimus on insulin production is both time- and dose-dependent (13), and the tacrolimus trough level was titrated at 10–15 ng/ml during the first 3 months, the maximally suppressed insulin production might have resulted at ~3 months in this study. Thereafter, the suppressed insulin secretory capacity appeared to be partially restored. However, there was no difference in the plasma trough level of tacrolimus between the two groups. It was reported that the pharmacokinetic profiles of tacrolimus showed considerable interindividual differences, and the trough plasma level might not be a good pharmacokinetic parameter (32). In this regard, it appears that the plasma trough level of tacrolimus to partially restore. However, we could not confirm this result firmly, as this study was not designed to examine differences in sex. In addition, the frequency of HLA A11 and HLA B62 was higher in the PTDM than in the non-PTDM group. A few studies have reported that certain HLA types are associated with the development of PTDM (38,39), but there is no specific HLA antigen that can be used to predict future PTDM effectively.

This study had limitations in that the number of patients was relatively small and because of the lack of a control group. Comparing with the historical control in Korean patients under cyclosporin A (29), the incidence of PTDM with tacrolimus in the current study is still higher (57.1 vs. 23.7%).

Using ADA criteria, we showed a high incidence of PTDM in the Korean renal allograft recipients treated with a tacrolimus-based regimen. The baseline characteristics of the PTDM group were old age, high BMI, high fasting glucose level, high plasma insulin level, and high HOMA-IR. Among them, old age, especially >40 years, was the only independent risk factor. The insulin secretory capacity was maximally suppressed 3 months after transplantation, when a relatively higher dose of tacrolimus was administered. Routine screening for PTDM is necessary in patients >40 years of age who are undergoing a relatively higher-dose tacrolimus therapy during the early course of postrenal transplantation.

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**Table 2—Comparison of the plasma tacrolimus trough level and the cumulative dose of prednisolone during the previous 30 days before each visit**

<table>
<thead>
<tr>
<th>Plasma tacrolimus trough level (ng/ml)</th>
<th>Non-PTDM</th>
<th>PTDM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>13.6 ± 0.9</td>
<td>13.5 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>3 months</td>
<td>14.0 ± 1.2</td>
<td>12.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>6 months</td>
<td>9.9 ± 0.9</td>
<td>10.6 ± 1.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative prednisolone dose (g/previous 30 days)</th>
<th>Non-PTDM</th>
<th>PTDM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>1.69 ± 0.18</td>
<td>1.57 ± 0.12</td>
<td>NS</td>
</tr>
<tr>
<td>3 months</td>
<td>0.35 ± 0.04</td>
<td>0.41 ± 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>6 months</td>
<td>0.24 ± 0.03</td>
<td>0.27 ± 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SEM.

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**References**

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