Risk Factors Associated With the Onset and Progression of Posttransplantation Diabetes in Renal Allograft Recipients

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OBJECTIVE — The aim of this study was to assess the incidence of posttransplantation diabetes mellitus (PTDM) in renal allograft recipients and to investigate factors contributing to the onset and progression of PTDM and its underlying pathogenic mechanism(s).

RESEARCH DESIGN AND METHODS — A total of 77 patients with normal glucose tolerance (NGT) were enrolled in this study. An oral glucose tolerance test was performed 1 week before transplantation and repeated at 1 and 7 years after transplantation.

RESULTS — The overall incidence of PTDM was 39% at 1 year and 35.1% at 7 years posttransplantation. The incidence for each category of PTDM was as follows: persistent PTDM (P-PTDM) (patients who developed diabetes mellitus within 1 year of transplantation and remained diabetic during 7 years), 23.4%; transient PTDM (T-PTDM) (patients who developed diabetes mellitus during the 1st year after transplantation but eventually recovered to have NGT), 15.6%; late PTDM (L-PTDM) (patients who developed diabetes mellitus later than 1 year after transplantation), 11.7%; and non-PTDM during 7 years (N-PTDM$_7$) (patients who did not develop diabetes mellitus during 7 years), 49.3%. Older age (≥40 years) at transplantation was a higher risk factor for P-PTDM, whereas a high BMI (≥25 kg/m^2) and impaired fasting glucose (IFG) at 1 year posttransplantation were higher risk factors for L-PTDM. Impaired insulin secretion rather than insulin resistance was significantly associated with the development of P- and L-PTDM.

CONCLUSIONS — Impaired insulin secretion may be the main mechanism for the development of PTDM. Older age at transplantation seems to be associated with P-PTDM, whereas a high BMI and IFG at 1 year after transplantation were associated with L-PTDM.

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Abbreviations: AUC, area under the curve; CsA, cyclosporine A; E-PTDM, early posttransplantation diabetes; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; L-PTDM, late posttransplantation diabetes mellitus; MMF, mycophenolate mofetil; NGT, normal glucose tolerance; N-PTDM$_1$, no posttransplantation diabetes mellitus until 1 year after transplantation; N-PTDM$_7$, no posttransplantation diabetes mellitus during 7 years; OGTT, oral glucose tolerance test; PTDM, posttransplantation diabetes mellitus; T-PTDM, transient posttransplantation diabetes mellitus; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Posttransplantation diabetes mellitus (PTDM) is a major complication after kidney transplantation and can lead to a wide range of complications including graft loss, increased mortality, increased number of rejections, and increased risk of cardiovascular disease (1–4). A recent meta-analysis of observational studies and randomized, controlled trials showed that the incidence of PTDM during the 1st year after transplantation varied from 2 to 50% (5). There have been several previous reports on PTDM in Korean patients, albeit for a short period of observation. We reported previously that the incidence of PTDM was 23.7% in 114 patients treated with cyclosporine A (CsA) at 9–12 months after transplantation (6), whereas Cho et al. (7) reported that it was 57.1% in 21 patients treated with tacrolimus at 6 months after transplantation in Korea.

PTDM and type 2 diabetes are similar in many ways. One example is that the onset of both can be insidious (8); individuals may experience glucose intolerance and remain asymptomatic for years before symptoms manifest clinically (9,10). Furthermore, PTDM is not always permanent and may resolve within weeks or months, sometimes without treatment (11). Although several recent reports on a consensus definition of PTDM have been published (5,8,12,13), there are still few studies about the long-term course of PTDM (14).

In this study, we classified patients on the basis of the time of onset and persistence of PTDM and investigated the risk factors associated with the onset and progression of PTDM, as well as its underlying pathogenic mechanism(s).

RESEARCH DESIGN AND METHODS

— Renal allograft recipients were eligible to participate in the study if they were aged ≥18 years, had no previous history of organ transplantation, and were not currently using steroids or other immunosuppressants. Patients were excluded if they had diabetes or impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) before transplan-

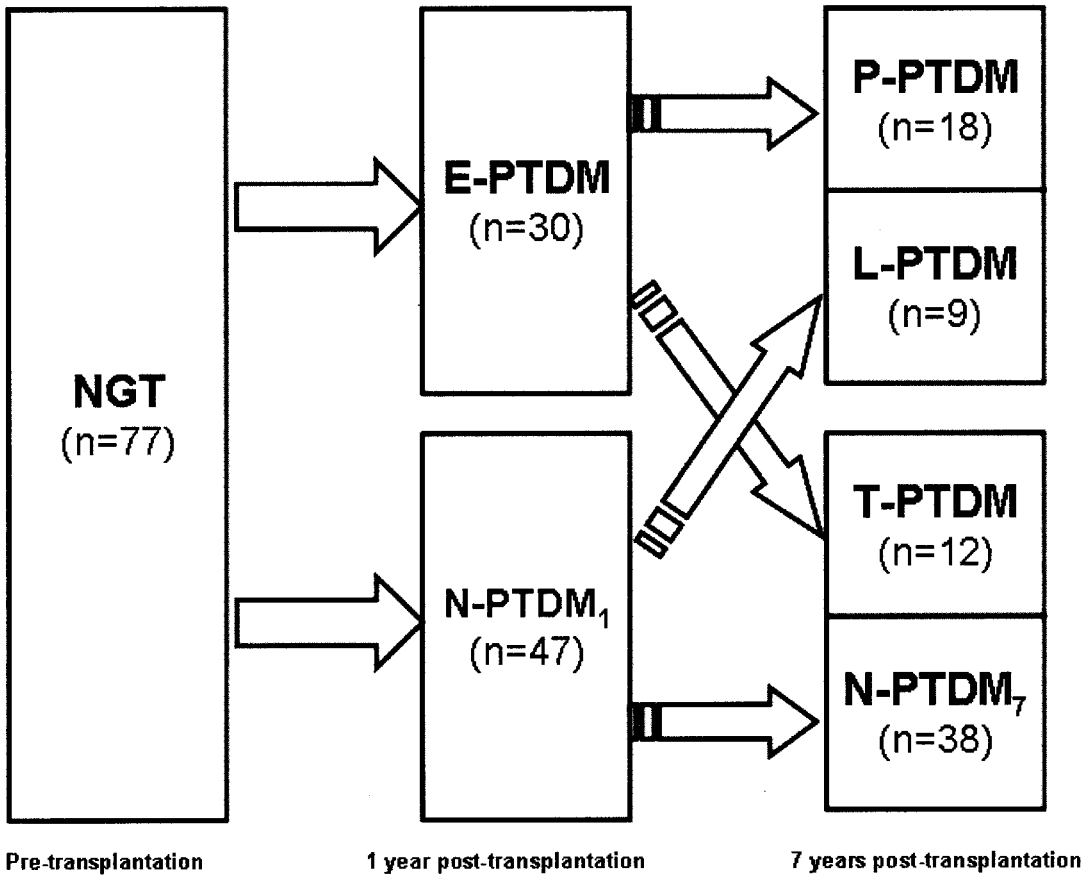

Figure 1—*Different courses of glucose metabolism in renal allograft recipients.*

tation, severe metabolic or infectious disease, or had received a cadaver donor kidney transplantation. Participation in this study was proposed to all eligible patients (n = 121) who underwent kidney transplantation from 1997 to 1998. Among these patients, 40 refused to undergo a follow-up oral glucose tolerance test (OGTT) at 7 years posttransplantation, and 4 were lost to follow-up: 1 died, 1 had graft failure due to acute rejection, and 2 were lost for unknown reasons. We enrolled a total 77 patients (50 men and 27 women) for this long-term study. Fifty-eight patients were treated with CsA as a primary immunosuppressant and 19 with tacrolimus. There were no significant differences in the various risk factors for PTDM between the 40 excluded patients and the 77 enrolled patients. The study protocol was approved by the ethics committee of the Yonsei University College of Medicine. All subjects were provided with adequate information regarding this study and gave informed consent.

Classification of recipients

In this study, American Diabetes Association criteria (15) were used for definition of PTDM (fasting plasma glucose [FPG] ≥7.0 mmol/l or 2-h postload glucose ≥11.1 mmol/l), IFG (FPG ≥5.6 and <7.0 mmol/l), IGT (2-h postload glucose ≥7.8 and <11.1 mmol/l), and normal glucose tolerance (NGT) (FPG <5.6 mmol/l and 2-h postload glucose <7.8 mmol/l). Patients were classified according to the onset and persistence of PTDM; groups were defined as follows: *1*) early PTDM (E-PTDM), patients who developed new-onset diabetes within 1 year posttransplantation; *2*) non-PTDM after 1 year (N-PTDM$_1$), patients who did not develop diabetes until at least 1 year after transplantation; *3*) persistent PTDM (P-PTDM), patients who developed diabetes within 1 year posttransplantation and persistently had diabetes for the duration of the 7-year follow-up; *4*) transient PTDM (T-PTDM), patients who developed diabetes during the 1st year after transplantation and eventually recovered to have NGT; *5*) late PTDM (L-PTDM), patients who developed diabetes 1 year after transplantation; and *6*) non-PTDM after 7 years (N-PTDM$_7$), patients who did not develop diabetes during the 7-year study period (Fig. 1).

Immunosuppression

The main immunosuppressive regimens consisted of calcineurin inhibitors (CsA or tacrolimus) and glucocorticoids. Calcineurin inhibitors were started 2 days before the transplantation. Initially the doses of CsA (10 mg/kg) and tacrolimus (0.3 mg/kg) were administered twice daily. The target trough levels of CsA and tacrolimus were as follows: *1*) months 0–3: 150–300 ng/ml for CsA and 10–20 ng/ml for tacrolimus; *2*) months 3–6: 150–200 ng/ml for CsA and 10–15 ng/ml for tacrolimus; and *3*) 6 months: 75–150 ng/ml for CsA and 8–10 ng/ml for tacrolimus. Administration of oral prednisolone at 1 mg/kg/day began 2 days before the transplantation. Methylprednisolone was administered intravenously for the first 4

Table 1—*Demographic and clinical characteristics of different courses of PTDM*

	P-PTDM	L-PTDM	T-PTDM	N-PTDM$_7$
n (% female)	18 (61.1)†	9 (28.6)	12 (33.3)	38 (26.3)
Age (years)	45.3 ± 10.1‡	34.7 ± 10.6	31.3 ± 9.7	34.2 ± 9.2
Family history of diabetes*	8 (44.4)	1 (11.1)	3 (25)	8 (21.1)
Duration of dialysis (months)	13.2 ± 16.1	7.6 ± 1	6.4 ± 8.6	17.7 ± 21.2
HCV infection	2 (11.1)	0 (0)	0 (0)	1 (2.6)
Donor type (LURDs)	8 (66.7)	2 (22.2)	6 (50)	8 (21.1)
Calcineurin inhibitor				
CsA	11 (61.1)	7 (77.8)	8 (66.7)	32 (84.2)
Tacrolimus	7 (38.9)	2 (22.2)	4 (33.3)	6 (15.8)
MMF	10 (55.6)	5 (55.6)	7 (58.3)	16 (42.1)
Acute rejection	4 (22.2)	1 (11.1)	8 (66.7)	0 (0)
BMI (kg/m^2)				
Before transplantation	22.8 ± 3.2	22.9 ± 3.7	19.5 ± 2.3	21.0 ± 2.3
1 year after transplantation	24.0 ± 3.3‡	24.0 ± 3.1†	20.0 ± 2.3	21.6 ± 2.7
FPG (mmol/l)				
Before transplantation	4.8 ± 0.4	4.4 ± 0.7	4.7 ± 0.4	4.7 ± 0.4
1 year after transplantation	6.5 ± 1.1‡	5.7 ± 0.6†	5.2 ± 0.6	5.3 ± 0.6
Total cholesterol (mmol/l)				
Before transplantation	4.4 ± 0.9	4.2 ± 1.0	4.2 ± 0.7	3.9 ± 0.9
1 year after transplantation	6.4 ± 1.0†	6.2 ± 0.8	5.7 ± 1.0	5.6 ± 1.1
Triglycerides (mmol/l)				
Before transplantation	2.2 ± 1.2	2.6 ± 1.1	1.9 ± 0.8	1.8 ± 1.1
1 year after transplantation	2.2 ± 0.7	2.8 ± 1.2	2.3 ± 2.7	2.1 ± 0.8

Data are expressed as *n* (%) or means ± SD. *Family history of diabetes in a first-degree relative. †$P < 0.05$, ‡$P < 0.001$ vs. N-PTDM$_7$. HCV, hepatitis C virus; LURD, living unrelated donor.

postoperative days in a tapered fashion: day 0, 1 g; day 1, 500 mg; day 2, 250 mg; and day 3, 60 mg. Administration of oral prednisolone began after the 4th post-transplantation day at 30 mg/day and was gradually tapered to 10 mg/day within 1 month. For acute rejection, a total of 2 g methylprednisolone was administered for 5 days. Forty-eight patients used a triple regimen including mycophenolate mofetil (MMF). For the triple regimen, the target plasma trough levels of CsA and tacrolimus were lower than those for the double regimen: 75–100 ng/ml for CsA and 5–10 ng/ml for tacrolimus.

Measurements

All samples were obtained in the morning after an overnight fast. Anthropometric measurements were taken during each visit. FPG, total cholesterol, and triglyceride levels were measured annually.

OGTT. All patients underwent a 75-g OGTT 1 week before kidney transplantation and again at years 1 and 7. For assays of plasma glucose and insulin, blood samples were taken at 0, 30, 60, 90, and 120 min after the ingestion of 75 g glucose.

Insulin secretion and sensitivity index. Insulin release was estimated by three equations documented to correlate well with insulin (Ins) secretion (Secr) as assessed by hyperglycemic clamp studies in patients with various degrees of glucose (Gluc) tolerance (16,17):

$$\text{SecrAUC} = \text{AUC}_{\text{Ins}}/\text{AUC}_{\text{Gluc}},$$

$$\text{Secr}_{1\text{PH}} = 1{,}283 + (1.829 \times \text{Ins}_{30\ \text{min}}) - (138.7 \times \text{Gluc}_{30\ \text{min}}) + (3.772 \times \text{Ins}_{0\ \text{min}})$$

and

$$\text{Secr}_{2\text{PH}} = 287 + (0.4164 \times \text{Ins}_{30\ \text{min}}) - (26.07 \times \text{Gluc}_{30\ \text{min}}) + (9.226 \times \text{Ins}_{30\ \text{min}})$$

where SecrAUC is secretion area under the curve (AUC), $\text{Secr}_{1\text{PH}}$ is first-phase insulin secretion, and $\text{Secr}_{2\text{PH}}$ is second-phase insulin secretion. The OGTT-derived insulin sensitivity index for transplantation (ISI_{TX}) was estimated by the following equation (17,18):

$$\text{ISI}_{\text{TX}} = 0.208 - 0.0032 \times \text{BMI (kg/m}^2) - 0.0000645 \times \text{Ins}_{120\ \text{min}}\ \text{(pmol/l)} - 0.00375 \times \text{Gluc}_{120\ \text{min}}\ \text{(mmol/l)}$$

Statistical analyses

All continuous variables were expressed as means ± SD. Student's *t* test or the Mann-Whitney *U* test was used to compare the continuous data between two groups. Pearson's χ^2 test or Fisher's exact test was used for categorical variables. The serial changes in insulin secretion and sensitivity were analyzed with the Kruskal-Wallis and repeated-measures ANOVA. Logistic regression analyses were used to identify risk factors for the development of the different courses of PTDM. All statistical tests of significance were two-tailed, and $P < 0.05$ was considered significant. All analyses were performed using SPSS for Windows (version 12; SPSS, Chicago, IL).

RESULTS

Incidences of different categories of PTDM

The incidences of PTDM were 39.0% at 1 year and 35.1% at 7 years after transplantation. Among the patients with E-PTDM, 40% had improved glucose metabolism over time (T-PTDM). Among the patients who did not develop PTDM within 1 year after transplantation, 19.1% developed L-PTDM. Figure 1 shows the different

Table 2—*Logistic regression analyses for risk factors associated with the various categories of PTDM compared with N-PTDM$_7$*

		P-PTDM		L-PTDM		T-PTDM	
Variables	No. of patients	Crude OR*	Adjusted OR†	Crude OR*	Adjusted OR†	Crude OR*	Adjusted OR†
n		18		9		12	
Age (years) at transplantation							
<40	51	1.0	1.0	1.0	1.0	1.0	1.0
≥40	26	7.5 (2.1–26.2)	6.9 (1.9–25.7)	1.9 (0.4–9.2)	1.9 (0.4–9.3)	1.3 (0.3–5.7)	1.3 (0.3–6.1)
Sex							
Male	50	1.0	1.0	1.0	1.0	1.0	1.0
Female	27	4.4 (1.3–14.5)	3.9 (1.1–14.7)	0.8 (0.1–4.5)	0.8 (0.1–4.5)	1.4 (0.4–5.7)	1.4 (0.4–5.9)
Family history of diabetes‡							
No	57	1.0	1.0	1.0	1.0	1.0	1.0
Yes	20	3.0 (0.9–10.1)	3.0 (0.7–12.6)	0.5 (0.1–4.3)	0.4 (0.0–4.0)	1.3 (0.3–5.7)	1.3 (0.3–5.9)
Calcineurin inhibitor							
CsA	58	1.0	1.0	1.0	1.00	1.0	1.0
Tacrolimus	19	3.4 (0.9–12.3)	3.9 (0.8–19.1)	1.5 (0.3–9.2)	1.4 (0.2–8.6)	2.7 (0.6–11.8)	2.8 (0.6–13.0)
BMI (kg/m^2) at 1 year							
<25	63	1.0	1.0	1.0	1.0	1.0	1.0
≥25	14	4.3 (1.0–17.7)	2.1 (0.4–10.8)	6.8 (1.3–36.3)	7.4 (1.2–46.7)	NA	NA
FPG (mmol/l) at 1 year							
<5.6	48	1.0	1.0	1.0	1.0	1.0	1.0
≥5.6	29	18.7 (4.5–76.6)	32.1 (4.6–223.2)	6.7 (1.4–32.3)	6.3 (1.3–31.5)	2.7 (0.6–11.8)	2.6 (0.6–11.6)

Data are expressed as OR (95% CI). Three logistic regression analyses included patients with P-PTDM vs. N-PTDM$_7$ (n = 56), L-PTDM vs. N-PTDM$_7$ (n = 47), and T-PTDM vs. N-PTDM$_7$ (n = 50), respectively. *Unadjusted, univariate logistic regression analysis, †age- and sex-adjusted logistic regression analysis, ‡family history of diabetes in a first-degree relative. NA, not applicable.

courses of PTDM and the incidences for each category.

Risk factors associated with progression of different courses of PTDM

The baseline values and clinical characteristics of recipients are shown in Table 1. We analyzed the risk factors associated with the various categories of PTDM compared with N-PTDM$_7$. Table 2 shows that female sex (odds ratio [OR] 3.9 [95% CI 1.1–14.7]) and older age of ≥40 years (6.9 [1.9–25.7]) denoted a higher risk of P-PTDM, whereas a high BMI of ≥25 kg/m^2 (7.4 [1.2–46.7]) and impaired FPG of ≥5.6 mmol/l (6.3 [1.3–31.5]) denoted a higher risk of L-PTDM. A positive family history of diabetes or use of CsA versus tacrolimus did not show any significant difference among the groups. There were no significant differences for acute rejection or use of combination therapy including MMF among the groups (Table 1).

Changes in insulin sensitivity and secretion for different courses of PTDM

Before kidney transplantation, there were no differences in insulin secretory function (Secr$_{1PH}$, Secr$_{2PH}$, and SecrAUC) and insulin sensitivity (ISI$_{TX}$) among the different categories of PTDM (Fig. 2). The indexes of insulin secretory function in all of the PTDM groups were decreased at 1 year after transplantation compared with values before transplantation, but those of N-PTDM$_7$ and T-PTDM were improved to values before transplantation within 7 years after transplantation. The insulin secretory function of the P-PTDM group was significantly lower at 1 year after transplantation compared with that of the N-PTDM$_7$ group, and it did not improve over time, remaining lower at 7 years after transplantation. In patients with L-PTDM, insulin secretory function was significantly lower than in the N-PTDM$_7$ group at 7 years after transplantation. Figure 2*E* reveals that Δ SecrAUC was significantly associated with the development of P-PTDM (P = 0.007) and L-PTDM (P = 0.012).

Similar to insulin secretion, the insulin sensitivity (ISI$_{TX}$) of all of the PTDM groups was decreased overall at 1 year after transplantation. The ISI$_{TX}$ became significantly lower in the P-PTDM group at 1 year after transplantation and in the L-PTDM group at 7 years after transplantation compared with ISI$_{TX}$ values for the N-PTDM$_7$ group for each time point. However, there were no significant differences in Δ ISI$_{TX}$ values among PTDM groups at 1 and 7 years after transplantation (Fig. 2*F*).

CONCLUSIONS — In this long-term study, the incidences of PTDM were 39 and 35.1% at 1 and 7 years after transplantation, respectively. We categorized the different courses of PTDM according to onset time and persistence of hyperglycemia after kidney transplantation. Among the potential risk factors for PTDM, old age was associated with a higher risk of P-PTDM, whereas a high BMI and IFG at 1 year after transplantation was associated with a higher risk of L-PTDM. We also showed that impaired insulin secretion was the main pathogenic mechanism of PTDM.

In the current study, the 39% incidence of PTDM at 1 year was very high and was even higher than the 23.7% we reported in our previous CsA-based study (6). In the previous study, we used the World Health Organization (WHO) criteria to define NGT (both FPG and 2-h postload glucose <7.8 mmol/l) and PTDM (FPG ≥7.8 mmol/l or 2-h postload glucose ≥11.0 mmol/l), whereas, in the current study, we defined NGT and PTDM according to American Diabetes Association criteria (8). If the members of

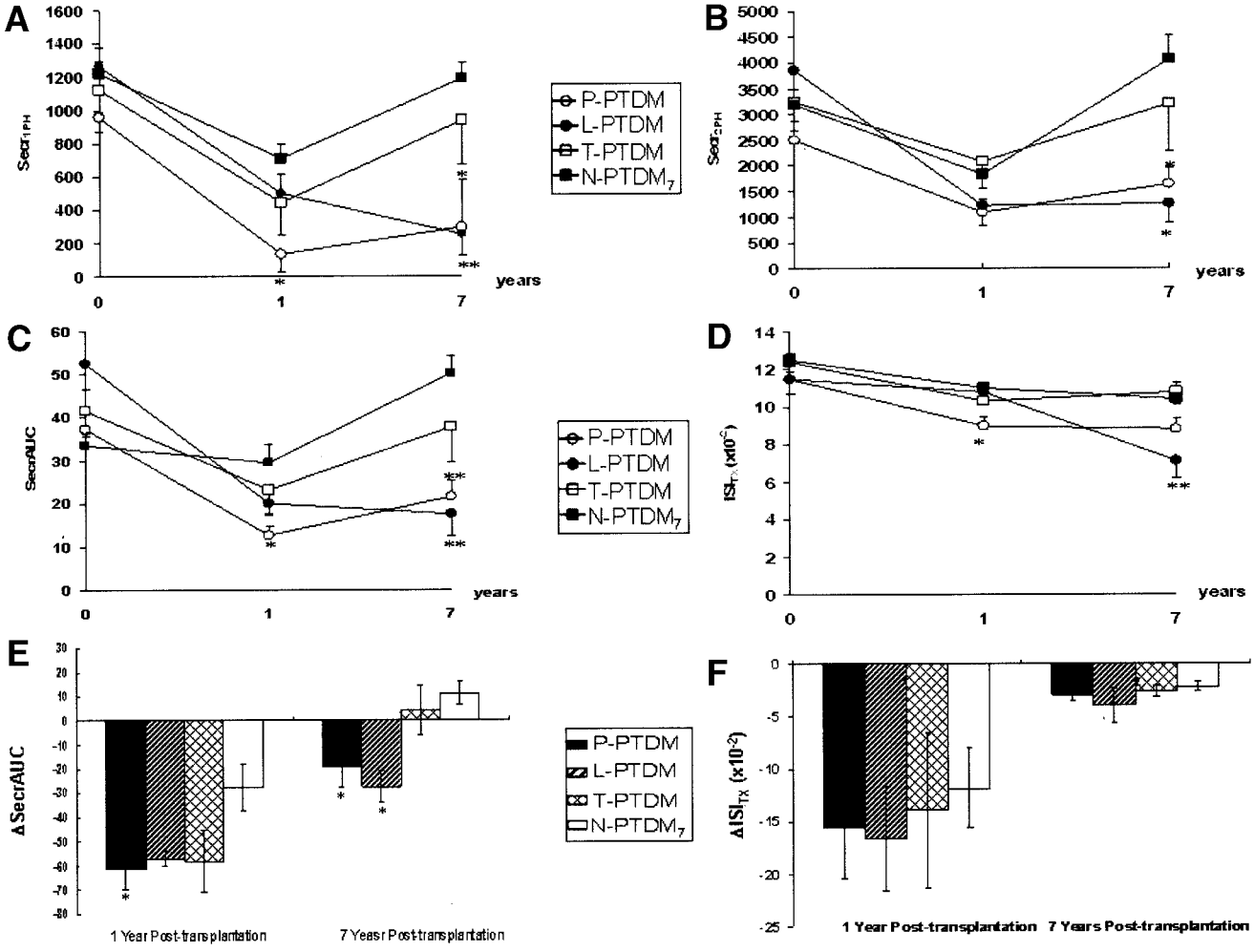

Figure 2—*Serial changes in insulin secretion and insulin sensitivity.* A: $Secr_{1PH}$. B: $Secr_{2PH}$. C: *SecrAUC*. D: ISI_{TX}. E: Δ *SecrAUC* (*SecrAUC [at year 1 or 7] − SecrAUC [before transplantation]*. F: Δ ISI_{TX} (*ISI [at year 1 or 7] − ISI [before transplantation]*. *P < 0.05 and **P < 0.001, *compared with N-PTDM$_7$ at each time point by the Kruskal-Wallis test. Data are expressed as means ± SE. See equations in text for additional details.*

the cohort in this study were reanalyzed according to WHO criteria, an incidence of 18.2% (14 of 77) would be obtained. Although the current cohort included the patients treated with tacrolimus, the numbers were so small that the current incidence of PTDM at 1 year (22.2%) was similar to the previous incidence (23.7%) according to WHO criteria. Thus, the higher incidence of PTDM in the current study appeared to result largely from more stringent diagnostic criteria for both NGT and PTDM.

Old age appeared to be an important contributing factor to the development of P-PTDM as reported previously (19–22). Further, Hjelmesaeth et al. (23) reported that older age is an important determinant of β-cell dysfunction after renal transplantation, and Chiu et al. (24) reported that the aging of β-cells has been characterized by a reduction in mass and disturbances in different insulin secretory patterns. Accordingly, older patients are likely to be more susceptible than younger patients to equal doses of immunosuppressive agents.

Our results indicated that women were more likely to develop P-PTDM, even after adjustment for age (Table 2). Our study did not have a large enough number of patients to discriminate differences between sexes, and, thus, a future study with a larger number of patients would be necessary to confirm this result.

In the present study, patients with a BMI ≥25 kg/m^2 at 1 year after transplantation had a higher risk for developing L-PTDM. Many previous studies have reported that body weight is one of the risk factors for the development of PTDM (1,11,25–27), whereas some studies have reported that the associations between PTDM and body weight or BMI are weak (5,20). As BMI is included in the equation for the dependent parameter ISI_{TX}, a higher BMI is likely to be related to a greater reduction in insulin sensitivity.

As shown in Table 2, patients with FPG ≥5.6 mmol/l at 1 year after transplantation had a higher risk of developing L-PTDM (OR 6.3 [95% CI 1.3–31.5]). The incidences of L-PTDM in individuals with IFG and NGT were 45.5 and 11.1%, respectively ($P = 0.023$). Thus, IFG at 1 year after transplantation appeared to be an important risk factor for PTDM.

Glucocorticoids (9,11,18,25,28–35), as well as calcineurin inhibitors (9,36), predispose patients to diabetes through various mechanisms such as β-cell toxicity, inhibition of insulin synthesis or release, and decreased peripheral insulin sensitivity. However, our results indicated that neither a transiently high dose of glucocorticoids, in the case of acute rejection, nor combination therapy, including MMF, had any significant association with the progression of PTDM, perhaps

due to the small numbers of patients in each group (Table 1). Although both CsA and tacrolimus have been reported to increase the risk of PTDM, clinical studies indicate that tacrolimus is up to five times more diabetogenic than CsA (25,37–39). Although the present study also demonstrated that the incidence of PTDM with tacrolimus treatment was higher (57.9% at 1 year and 68.4% at 7 years) than that with CsA (32.8% at 1 year and 44.8% at 7 years), the number of patients taking tacrolimus does not seem to be enough to determine statistical significance among the groups (Table 2).

There were limitations to this study in that the numbers of patients in each group were insufficient to discriminate between any possible independent risk factors of PTDM, as described above. Although we analyzed each potential risk factor using age- and sex-adjusted logistic regression analysis, the statistical power appeared to be weak. Despite such limitations, we believe that this result would be valuable in the analysis of the risk factors associated with the onset and progression of PTDM.

Similar to type 2 diabetes, impaired insulin secretion and insulin resistance are the two major components of PTDM. Consistent with our results, in a previous 6-year prospective study, Hagen et al. (14) reported that impaired insulin secretion was the dominant mechanism in the development of PTDM. They did not perform an OGTT before kidney transplantation but did so at 10 weeks and 6 years after transplantation. For our study, we strictly recruited patients with NGT after screening with a 75-g OGTT 1 week before transplantation and performed follow-up OGTTs at 1 and 7 years after transplantation to identify new-onset PTDM, mainly focusing on the different progression with contributing factors.

In summary, we performed a 7-year study to investigate the various types of onset and progression of PTDM and to determine associated risk factors. Although immunosuppressive agents have been known to be related to both insulin resistance and insulin secretion, our results indicated that an impairment of insulin secretion, rather than insulin resistance, may be the primary pathogenic mechanism for the development of PTDM. Furthermore, older age at the time of transplantation seemed to be associated with the development of P-PTDM, whereas high BMI and IFG at 1 year after transplantation were associated with the development of L-PTDM. As PTDM is associated with a wide range of complications, early detection by regular screening with more sensitive methods and intensive control of modifiable risk factors, such as weight and plasma glucose levels, should be required for renal allograft recipients.

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