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Gene Polymorphisms Are Associated With Posttransplantation Diabetes Mellitus Among Taiwanese Renal Transplant Recipients

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ABSTRACT

Background. Genetic variations may affect posttransplantation metabolic syndrome and diabetes mellitus (PTDM), which is associated with greater morbidity and progressive impairment of both patient and graft survivals. The aim of this study was to evaluate several candidate gene polymorphisms for their association with the risk of developing PTDM.

Methods. In April 1999, we enrolled 278 renal transplant participants, including 251 subjects free of diabetes and 27 with PTDM. We studied several candidate gene polymorphisms associated with diabetes: 4G/5G polymorphism of plasminogen activator inhibitor 1 (PAI-1) at −675; C/T polymorphism of interleukin-1beta (IL-1β) at −511; G/C polymorphism of IL-6 at 174; polymorphic XbaI of Glucose transporter 1 (GLUT1); and C/T polymorphism of methylenetetrahydrofolate redutase (MTHFR) at 677.

Results. The PTDM group had an older mean age (47.6 ± 9.8 years), greater predominance of men (77.8%), higher number of chronic diseases (CDN ≥2, 96.3%), and more patients using tacrolimus-based immunosuppression (44.4%; $P < .05$). Using model A, a simple logistic regression, we observed that patients with the IL-6 G/G genotype experienced a lower risk of developing PTDM (odds ratio [OR], 0.08; 95% confidence interval [CI] 0.01–0.86), and multiple logistic regression models B and C, after adjusting for different variables, confirmed this observation (model B: OR, 0.05; 95% CI, 0.00–0.66). The IL-6 G/G genotype showed a borderline effect in model C (OR, 0.02; 95% CI, 0.00–1.16). There were no significant differences between the 2 groups in genotype variations of PAI-1, IL-1β, GLUT-1, and MTHFR.

Conclusions. The G/G genotype of IL-6 may play an important role to lower the risk for PTDM development.

THE 2%–53% incidence of posttransplantation diabetes mellitus (PTDM) may represent an underestimation owing to the short observation periods in most studies and the fact that an oral glucose tolerance test (OGTT) is usually not performed routinely.[1] PTDM threatens the outcome of kidney transplantation, not only graft but also

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patient survival.[1] A number of risk factors are known to be associated with the development of PTDM, including obesity, age, race, ethnicity, cadaver donor kidney, hepatitis C infection, metabolic syndrome, glucose intolerance, and immunosuppressive agent.[1,2] However, there are few data on the effect of genetic polymorphisms. Several candidate gene polymorphisms contributing to the risk of developing type 2 DM have been reported, including an insertion/deletion of guanine at position −675 in plasminogen activator inhibitor 1 (PAI-1) promoter (4G/5G polymorphism).[3] In addition, associations have been reported with interleukin-1beta (IL-1β) C/T or T/T polymorphism, IL-6 gene C/G and G/G polymorphism, XbaI polymorphism of glucose transporter 1 (GLUT1) gene, and the C/T genotype of methylenetetrahydrofolate reductase (MTHFR).[4–7] The aim of the present study was to evaluate whether the polymorphisms elevated the risk of developing PTDM.

MATERIALS AND METHODS

Study Design and Patients

This cross-sectional study of 278 recipients of unrelated kidney transplant, included 251 cases free of diabetes after renal transplantation and 27 cases of PTDM. The patients were prospectively followed for 12 years or until death. All participants with PTDM were diagnosed according to the 2003 international consensus guidelines for new-onset diabetes after transplantation.[1] The study was approved by our Ethics Committee before patient enrollment. Informed consent was obtained from each of the participants. The following variables were collected from the subjects: age, sex, hepatitis, chronic diseases, immunosuppressive therapy, biochemical measurements, and immunosuppressant concentrations.

Table 1. Characteristics of the Study Population, n (%)

	Non-PTDM (n = 251)	PTDM (n = 27)	*P* Value*
Age (y), mean ± SD	41.7 ± 11.5	47.6 ± 9.8	.010†
Sex			
Male	139 (55.4)	21 (77.8)	.026
Female	112 (44.6)	6 (22.2)	
Hepatitis B	28 (11.2)	3 (11.1)	1.000
Hepatitis C	58 (23.1)	8 (29.6)	.477
Hypertension	179 (71.3)	16 (59.3)	.193
Cardiovascular disease	150 (59.8)	11 (40.7)	.066
Hyperlipidemia	71 (28.3)	6 (22.2)	.652
Cancer	37 (14.7)	3 (11.1)	.778
Chronic disease number‡			
<2	107 (42.6)	1 (3.7)	.000
≥2	144 (57.4)	26 (96.3)	
Immuno-suppressant			
Tacrolimus-based	46 (18.3)	12 (44.4)	.004
Cyclosporine-based	205 (81.7)	15 (55.6)	
Mortality after 12-year follow-up	17 (6.8)	2 (7.4)	1.000

* Calculated by Fisher Exact Test.
† Calculated by independent-samples *t* test.
‡ Within 19 evaluated chronic diseases: chronic arthritis, autoimmune diseases, hypertension, diabetes mellitus, chronic heart disease, stroke, dyslipidemia, hyperuricemia, chronic obstructive pulmonary disease, asthma,mycobacterium tuberculosis, hepatitis, peptic ulcer, hemorrhoid, benign prostate hypertrophy, cancer, varicosis, vertebral degenerative joint disease, osteoarthritis.

Table 2. Laboratory Data and Cyclosporine and tacrolimus Concentrations Between the Non-PTDM and PTDM Groups, Mean ± SD

	Non-PTDM (n = 251)	PTDM (n = 27)	*P* Value*
WBC (/μL)	7,839.1 ± 3,311.5	7,371.5 ± 2,939.8	.542
HgB (mg/dL)	11.5 ± 2.2	11.9 ± 1.9	.331
Platelet ($\times 10^3/\mu$L)	229.8 ± 85.0	218.8 ± 83.0	.838
SCr (mg/dL)	1.3 ± 1.6	1.9 ± 0.9	.678
Na (mmol/L)	138.2 ± 10.8	138.8 ± 4.6	.500
K (mmol/L)	4.6 ± 1.9	4.5 ± 0.5	.109
Ca (mg/dL)	9.2 ± 0.8	9.3 ± 0.7	.505
Cyclosporine (ng/mL)†	233.5 ± 209.7	209.9 ± 183.7	.791
Tacrolimus (ng/mL)†	4.2 ± 4.1	4.8 ± 2.6	.139

* Calculated by Mann-Whitney *U* test.
† Cyclosporine and tacrolimus were calculated by average of the 3-year values before the cross-sectional study. Cyclosporine (C0.) reference: 60–200 ng/mL; tacrolimus reference: 5–15 ng/mL.

Genomic DNA Preparation and Genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells by the salting-out method. Candidate genetic polymorphisms were detected using the polymerase chain reaction–restriction

Table 3. Genotype Distribution of the PAI-1, IL-1β, IL-6, GLUT1, and MTHFR Genes in the 2 Groups, n (%)

	Non-PTDM (n = 251)	PTDM (n = 27)	*P* Value*
PAI-1 genotype			
4G/4G	91 (36.3)	6 (22.2)	.148
5G/4G	119 (47.4)	13 (48.1)	
5G/5G	41 (16.3)	8 (29.6)	
IL-1β genotype			
T/T	48 (19.3)	7 (25.9)	.379
C/T	137 (54.6)	16 (59.3)	
C/C	66 (26.1)	4 (14.8)	
IL-6 genotype			
G/G	250 (99.6)	25 (92.6)	.026
C/G or C/C	1 (0.4)	2 (7.4)	
GLUT-1 Xbal genotype			
+/+	137 (54.6)	14 (51.9)	.334
+/−	108 (43.0)	11 (40.7)	
−/−	6 (2.4)	2 (7.4)	
(GLUT-1 Xbal genotype)			
+/+ or +/−	245 (97.6)	25 (92.6)	.303
−/−	6 (2.4)	2 (7.4)	
MTHFR genotype			
A/A	132 (52.6)	16 (59.3)	.712
V/A	104 (41.4)	9 (33.3)	
V/V	15 (6.0)	2 (7.4)	
(MTHFR genotype)			
A/A or V/A	236 (94.0)	25 (92.6)	.722
V/V	15 (6.0)	2 (7.4)	

Abbreviations: PTDM, posttransplantation diabetes mellitus; PAI-1, plasminogen activator inhibitor 1; IL-1β, interleukin-1beta; IL-6, interleukin-6; GLUT1, glucose transporter 1; MTHFR, methylenetetrahydrofolate redutace (point mutation from alanine-to-valine substitution).
* Calculated by Fisher exact test.