Variants of the Adiponectin and Adiponectin Receptor-1 Genes and Posttransplantation Diabetes Mellitus in Renal Allograft Recipients

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Context: Posttransplantation diabetes mellitus (PTDM) is a major metabolic complication in renal transplant recipients. Adiponectin (*ADIPOQ*) and adiponectin receptor-1 (*ADIPOR1*) gene polymorphisms have been associated with type 2 diabetes. However, it is unknown whether these polymorphisms are also risk factors for PTDM.

Objective: We investigated the association between PTDM and single-nucleotide polymorphisms of *ADIPOQ* and *ADIPOR1* in a cohort of renal allograft recipients.

Design, Setting, and Participants: Five hundred seventy-five patients (367 men and 208 women) who received kidney transplants between 1989 and 2007, without a history of diabetes and with a pretransplant fasting glucose concentration less than 5.5 mmol/liter. Patients were followed up for a median 10 yr. Genotypes included single-nucleotide polymorphisms of the following: *ADIPOQ* rs266729, rs822395, rs822396, rs2241766, and rs1501299 and *ADIPOR1* rs2232853, rs12733285, and rs1342387.

Results: TT-homozygotes in *ADIPOQ* rs1501299 [hazard ratio (HR) = 1.70, $P = 0.032$] had greater risk of PTDM after adjusting for age, sex, amount of weight gain, and type of immunosuppressant. There was a significant interaction between sex and *ADIPOQ* rs1501299 genotype ($P = 0.037$). In men, but not in women, TT-homozygotes in *ADIPOQ* rs1501299 were more likely to develop PTDM than the wild GG-homozygotes (HR = 2.50, $P = 0.002$), whereas GT-heterozygotes had nonsignificantly elevated risk (HR = 1.41, $P = 0.128$).

Conclusion: Genetic variation in *ADIPOQ* rs1501299 is associated with PTDM in a sex-specific manner. **(*J Clin Endocrinol Metab* 97: E129–E135, 2012)**

Use of immunosuppressive medications has minimized the incidence of rejection of transplanted organs and increased patient survival. With increased transplant recipient life expectancy, however, many chronic complications of organ transplantation have emerged, the most important of which is cardiovascular disease (1). Several studies have shown that metabolic abnormalities including diabetes and dyslipidemia are important contributors

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Abbreviations: *ADIPOQ*, Adiponectin gene; *ADIPOR1*, adiponectin receptor-1 gene; FPG, fasting plasma glucose; HR, hazard ratio; PTDM, posttransplantation diabetes mellitus; SNP, single-nucleotide polymorphism.

to cardiovascular mortality in transplant recipients (2). Posttransplantation diabetes mellitus (PTDM), or new-onset diabetes after transplantation, is a common serious complication after organ transplantation and is associated with increased morbidity, cardiovascular mortality, and graft loss (1–3). The reported incidence of PTDM varies but increases with time after transplantation (3). Renal allograft recipients are at high risk for developing diabetes mellitus due to a number of factors including aging, obesity, and corticosteroid and immunosuppressive medication use. In addition, we have previously reported that genetic factors have an important role in the development of PTDM (4–6).

Adiponectin gene (*ADIPOQ*; gene identification 9370, GenBank identification NM_004797) polymorphisms have been shown to be associated with type 2 diabetes, although some controversies remain (7). Also, the polymorphisms in the adiponectin receptor-1 gene (*ADIPOR1*; gene identification 51094, GenBank identification NM_015999) have been associated with insulin resistance and diabetes mellitus (8, 9). Adiponectin concentrations in plasma and the expression of adiponectin receptor-1 are lower in patients with diabetes than in healthy subjects (10). The association of these polymorphisms with PTDM has never been examined. In this study, we evaluated single-nucleotide polymorphisms (SNP) in genes encoding adiponectin and its type 1 receptor in a large cohort of renal allograft recipients with long-term (median 10 yr) follow-up.

Materials and Methods

Subjects and measurements

Unrelated renal transplant recipients were recruited from the Severance Hospital Transplantation Center, Yonsei University Health System. PTDM was diagnosed 1 yr after transplantation as previously described (4–6), according to the International Consensus Guidelines for the diagnosis and management of PTDM (11–13). Patients who started antidiabetic medication (oral medication or insulin) after transplantation and continued the medication thereafter were included in the PTDM group. The rest of the patients were assigned to the non-PTDM group. According to our previous study (14), cases of persistent PTDM (patients who developed diabetes within 1 yr after transplantation and remained diabetic) and late PTDM (patients who developed diabetes after 1 yr after transplantation) were assigned to the PTDM group. Transient PTDM cases (patients who developed diabetes within 1 yr after transplantation but eventually recovered to normoglycemia without medication) were classified as non-PTDM. Patients were eligible to participate in the study if they were recipients of a kidney allograft with no other history of organ transplantation and were followed up for at least 1 yr. Only individuals with no previous diagnosis of diabetes and pretransplant fasting plasma glucose (FPG) concentration less than 5.5 mmol/liter were included. Patients were excluded if they had a history of diabetes before transplantation, severe metabolic or infectious disease, or FPG concentration 5.5 mmol/liter or greater.

A total of 805 unrelated transplant recipients were recruited from 1989 to 2007. Of 805 patients screened, 103 patients were excluded because they had a recorded FPG concentration 5.5 mmol/liter or greater. Thirty patients had diabetes before transplantation, 35 patients had repeated renal allograft operation, and 13 patients were younger than 18 yr. Among the remaining 624 patients, DNA samples were available for 575 (367 men and 208 women). Medical histories were obtained, anthropometric measurements were taken, and blood samples were collected after an overnight fast at the time of transplantation and again at 3, 6, and 12 months after transplantation. FPG concentration was determined by using an enzymatic colorimetric assay. The internal review board of Severance Hospital approved the study protocol, and all subjects were provided with adequate information about this study and gave informed consent.

Immunosuppressant medications

The main immunosuppressive regimens consisted of calcineurin inhibitors and glucocorticoids. Detailed medication schedule is described previously (4, 6). Calcineurin inhibitors (cyclosporin or tacrolimus) were the main immunosuppressant medications used. Prednisolone and deflazacort were the main glucocorticoid regimens used in the prevention of rejection. The usual dose of prednisolone was 10 mg/d and that of deflazacort was 12 mg/d. Because prednisolone is known to be 1.2–1.5 times more potent than deflazacort, we converted the deflazacort dose to a corresponding prednisolone dose by multiplying by 0.8.

Gene and SNP selection

The *ADIPOQ* maps to 3q27 and has more than 10 tagging SNP (15, 16) and two haplotype blocks between −2049 and −450 (17, 18). We chose four intronic SNP and one exonic SNP to genotype these two blocks. We chose to genotype rs266729 (5′ flanking region), rs822395 (intron 1), and rs822396 (intron 1) to tag block 1 and rs1501299 (intron 2) and rs2241766 (exon 2) to tag block 2 because these SNP are the five most common SNP and have been studied extensively by others as to their functionality and in relation to diabetes (7, 15, 19, 20). Also, we selected only SNP with a minimum allele frequency of 10% in Koreans.

ADIPOR1 has more than 28 SNP in two linkage disequilibrium blocks (17, 21). One block extends from the 5′ flanking region to intron 4 and the other is located at the 3′ end of the gene (17). Based on this structure, we selected five common SNP for genotyping. For block 1, we selected the following tagging SNP: rs2232853 (5′ flanking region), rs12733285 (intron 1), and rs1342387 (intron 4). For block 2, we selected rs7539542 (exon 8) and rs10920531 (3′ flanking region). However, minimum allele frequency of the two SNP in block 2 was less than 10%, so we excluded these two SNP (rs7539542 and rs10920531) from further analysis.

Genotyping and quality control

Genomic DNA was isolated from peripheral blood lymphocytes using the QIAamp DNA blood minikit (Qiagen, Valencia, CA). Genotyping was performed using a TaqMan SNP genotyping assay system (Applied Biosystems, Foster City, CA). Genotyping for all eight SNP was performed by Taq man SNP allelic discrimination by means of an ABI 7900HT (Applied Bio-

TABLE 1. Clinical characteristics of the study population

	PTDM	Non-PTDM	*P* value
n (female)	154 (58)	421 (150)	0.653[a]
Age (yr) at transplantation	42.3 ± 9.2	37.3 ± 9.4	3.04×10^{-8}
Age at transplantation older than 40 yr	92 (59.7%)	161 (38.2%)	4.25×10^{-6}
Family history of diabetes (%)	47 (32.4%)	149 (33.6%)	0.398[a]
Follow-up duration (months)	155.8 ± 62.0	143.0 ± 61.4	0.027
BW (kg) at transplantation	59.8 ± 9.6	58.8 ± 9.9	0.269
BW (kg) at 6 months after transplantation	63.0 ± 8.8	61.0 ± 9.1	0.018
Δ BW during first 6 months after transplantation	3.3 ± 5.7	2.2 ± 5.4	0.049
Baseline body mass index	21.87 ± 3.37	21.42 ± 2.91	0.155
FPG (mg/dl) at transplantation	91.6 ± 12.5	93.8 ± 13.9	0.093
FPG (mg/dl) at 3 months after transplantation	117.9 ± 43.3[b]	96.5 ± 13.9[b]	1.11×10^{-8}
FPG (mg/dl) at 6 months after transplantation	120.7 ± 50.7[b]	96.7 ± 13.9[b]	3.28×10^{-8}
FPG (mg/dl) at 12 months after transplantation	127.4 ± 46.8[b]	97.0 ± 14.6[b]	7.07×10^{-13}
Fasting plasma insulin (pmol/liter)	48.23 ± 26.15	48.44 ± 29.05	0.945
Patients with tacrolimus use, n	48 (31.2%)	83 (19.7%)	0.005[a]
Mean daily steroid dose (mg/d)	9.76 ± 1.17	9.57 ± 1.41	0.107
Serum creatinine (mg/dl) 6 months after transplantation	1.31 ± 0.43	1.32 ± 0.34	0.602
Serum creatinine (mg/dl) 12 months after transplantation	1.33 ± 0.64	1.30 ± 0.35	0.378

Data are presented as the mean ± SD or n (%) unless otherwise indicated. *P* values were calculated from *t* tests. Mean daily steroid dose is shown in prednisolone equivalent dose. BW, Body weight; Δ BW, change in body weight.

[a] *P* values were calculated from χ^2 tests.

[b] Includes patients with antidiabetic medications.

systems). The assay mix identifications were C2412786_10 for *ADIPOQ* rs266729, C2910317_10 for *ADIPOQ* rs822395, C2910316_10 for *ADIPOQ* rs822396, C26426077_10 for *ADIPOQ* rs2241766, C7497299_10 for *ADIPOQ* rs1501299, C198957_10 for *ADIPOR1* rs2232853, C26186730_10 for *ADIPOR1* rs12733285, and C37350_10 for *ADIPOR1* rs1342387. A total of 58 samples (10%) were genotyped in duplicate and showed 100% concordance. A total of 48 duplicate samples and negative controls (7.6%) were included to ensure the accuracy of the genotyping, and 100% of the duplicates replicated the original genotype.

Statistical analyses

We analyzed the 10 SNP in each of the 575 renal transplant patients. For all SNP, compliance with the Hardy-Weinberg equilibrium was assessed using the χ^2 test. The genotype frequencies were compared between the non-PTDM and PTDM groups using Pearson's χ^2 test in additive, codominant 1 (major allele homozygotes *vs.* heterozygotes), codominant 2 (major allele homozygotes *vs.* minor allele homozygotes), dominant (major allele homozygotes *vs.* minor allele homozygotes plus heterozygotes), and recessive (major allele homozygotes plus heterozygotes *vs.* minor allele homozygotes) models. The allele frequencies were also compared using Pearson's χ^2 test. All continuous variables are expressed as the mean ± SD. Student's *t* test was used to compare continuous variables and the χ^2 test was used to compare categorical variables between the PTDM and non-PTDM groups. A Cox proportional hazard model was used to identify risk factors for PTDM development and calculate the adjusted hazard ratio (HR) and 95% confidence intervals, after controlling for potential risk factors (age, sex, amount of weight gain, and type of main immunosuppressant used).

Interactions between genotype and sex were assessed using multivariate Cox models. To avoid any false-positive result due to multiple comparisons, conservative Bonferroni correction was applied. A $P < 0.00313$ [0.05 divided by 16, *i.e.* the total number of SNP studied in this study plus the number of SNP that showed significant results in previous studies (4–6)] was considered significant.

SPSS version 12.0 (SPSS Inc., Chicago, IL), StatMate version 2.00 (GraphPad, La Jolla, CA), and Prism version 5.04 (GraphPad) were used in the statistical analysis and graph construction.

Results

Clinical characteristics of patients

PTDM patients were significantly older than non-PTDM patients at the time of transplantation (Table 1). The mean follow-up time was 156 months (13 yr) for the PTDM group and 143 months (12 yr) for the non-PTDM group ($P = 0.027$). The initial body weight was not significantly different between the two groups, but PTDM patients gained more body weight than non-PTDM patients at 6 months after transplantation (Table 1). PTDM patients had greater FPG concentration than non-PTDM patients at 3 months after transplantation onward, despite the use of antidiabetic treatment (Table 1). There was no significant difference in the mean daily steroid dose between the PTDM group and the non-PTDM group (Table 1).

Genotype distribution and association between genotype and PTDM

All SNP did not deviate from the Hardy-Weinberg equilibrium. None of eight SNP was nominally associated with PTDM development in additive, codominant 1, codominant 2, dominant, or recessive models (Table 2). In addi-

TABLE 2. Comparison of genotype frequencies between PTDM patients and non-PTDM patients

						P value					
	Genotype	PTDM (n)	%	Non-PTDM (n)	%	Additive	Codominant 1	Codominant 2	Dominant	Recessive	HWE *P* value
rs266729	CC	96	62.34	225	53.44	0.087	0.057	0.597	0.057	0.597	0.901
	CG	47	30.52	171	40.62						
	GG	11	7.14	25	5.94						
rs822395	AA	128	83.12	342	81.24	0.861	0.653	0.738	0.605	0.350	0.118
	AC	24	15.58	72	17.10						
	CC	2	1.30	7	1.66						
rs822396	AA	133	86.36	350	83.14	0.509	0.478	0.344	0.350		0.055
	AG	20	12.99	64	15.20						
	GG	1	0.65	7	1.78						
rs2241766	TT	67	43.51	216	51.31	0.248	0.100	0.461	0.098	0.751	0.756
	TG	73	47.40	170	40.38						
	GG	14	9.09	35	8.31						
rs1501299	GG	70	45.45	216	51.31	0.176	0.484	0.063	0.214	0.083	0.127
	GT	62	40.26	166	39.43						
	TT	22	14.29	39	8.48						
rs2232853	CC	149	96.75	398	94.54	0.274	0.274		0.274		0.550
	CT	5	3.25	23	5.46						
	TT	0	0.00	0	0.00						
rs12733285	CC	139	90.26	361	85.75	0.227	0.120	0.485	0.155		0.700
	CT	14	9.09	59	14.01						
	TT	1	0.65	1	0.24						
rs1342387	GG	27	17.53	79	18.76	0.800	0.565	0.972	0.667	0.736	0.784
	AG	78	50.65	200	47.51						
	AA	49	31.82	142	33.73						

P values were calculated from Pearson's χ^2 test. HWE, Hardy-Weinberg equilibrium; codominant 1, major allele homozygotes *vs.* heterozygotes, codominant 2, major allele homozygotes *vs.* minor allele homozygotes; dominant, major allele homozygotes *vs.* minor allele homozygotes plus heterozygotes; recessive, major allele homozygotes plus heterozygotes *vs.* minor allele homozygotes.

tion, no significant nominal association between allele and PTDM was observed (Table 2). Haplotype information is shown in Supplemental Tables A1 and A2 and Supplemental Figs. A1 and A2, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. We used Cox proportional hazard regression test to analyze the genetic effect on PTDM development, including age, sex, amount of postoperative weight gain, type of immunosuppressant, and genotype as covariates in the regression model. As shown in Table 3, TT-homozygotes in *ADIPOQ* rs1501299 (HR 1.70, $P = 0.032$) had greater risk of PTDM after adjusting for age, sex, amount of weight gain, and type of immunosuppressant.

Multivariate logistic regression analysis for risk factors associated with PTDM

Age at transplantation was the strongest risk factor for development of PTDM (Table 4). Tacrolimus use as the main immunosuppressant was 2.5 times more likely to lead to the development of PTDM than cyclosporin use (Table 4). Preoperative baseline fasting plasma glucose was not associated with PTDM development. *ADIPOQ* rs1501299 TT genotype was significantly associated with PTDM ($P = 0.038$), whereas the TG genotype did not ($P = 0.149$). There was an interaction between *ADIPOQ* rs1501299 genotype and sex, which significantly affected the effect of this polymorphism on the development of PTDM ($P = 0.037$) (Table 4). After Bonferroni adjustment for multiple comparisons ($P < 0.05$, 16 SNP), men with the TT genotype at *ADIPOQ* rs1501299 had a significantly greater risk of PTDM than the GG homozygotes (HR 2.50, $P = 0.002$, Fig. 1, *top panel*). GT heterozygotes had nonsignificantly elevated risk (HR 1.41, $P = 0.128$, Fig. 1, *top panel*). However, among women, no such genetic effect was observed (TT: HR 0.70, $P = 0.430$ and GT: HR 1.14, $P = 0.637$) (Fig. 1, *bottom panel*). No significant interaction between *ADIPOQ* rs1501299 genotype and type of immunosuppressant was observed ($P = 0.755$).

Discussion

In this study, we analyzed the relationships of *ADIPOQ* and *ADIPOR1* polymorphisms with PTDM. We found a sex-specific association of the *ADIPOQ* rs1501299 polymorphism with the development of PTDM in renal allograft recipients, with the TT genotype conferring significantly greater risk of PTDM in men but not in women.

Likewise, Yamaguchi *et al.* (22)reported that the *T* allele in the *ADIPOQ* rs1501299 represents a risk factor for type 2 diabetes only in men, and Sun *et al.* (23) made similar observations for the *PPARGC1* gene in Chinese subjects. Because most of the female patients participating in our study were relatively young and thus still reproductively active (*i.e.* not likely to be postmenopausal), our

TABLE 3. Cox proportional hazard regression analysis of genotypes associated with PTDM

	Genotype	Adjusted HR (95% CI)	*P* value[a]
rs266729	CC	1.00	
	CG	0.64 (0.44–0.92)	0.015
	GG	1.08 (0.58–2.03)	0.804
rs822395	AA	1.00	
	AC	0.90 (0.58–1.41)	0.647
	CC	0.86 (0.21–3.51)	0.833
rs822396	AA	1.00	
	AG	0.84 (0.52–1.36)	0.488
	GG	0.62 (0.09–4.48)	0.636
rs2241766	TT	1.00	
	TG	1.34 (0.95–1.34)	0.095
	GG	1.27 (0.71–2.28)	0.423
rs1501299	GG	1.00	
	GT	1.21 (0.85–1.73)	0.283
	TT	1.70 (1.05–2.76)	0.032
rs2232853	CC	1.00	
	CT	0.42 (0.28–0.69)	0.423
rs12733285	CC	1.00	
	CT	0.77 (0.44–1.33)	0.344
	TT	0.99 (0.13–7.44)	0.994
rs1342387	GG	1.00	
	AG	1.09 (0.75–1.57)	0.665
	AA	1.03 (0.63–1.68)	0.917

[a] *P* values for each SNP were adjusted for age, sex, amount of body weight gain, and type of immunosuppressant regimen (0, cyclosporine A; 1, tacrolimus). CI, Confidence interval.

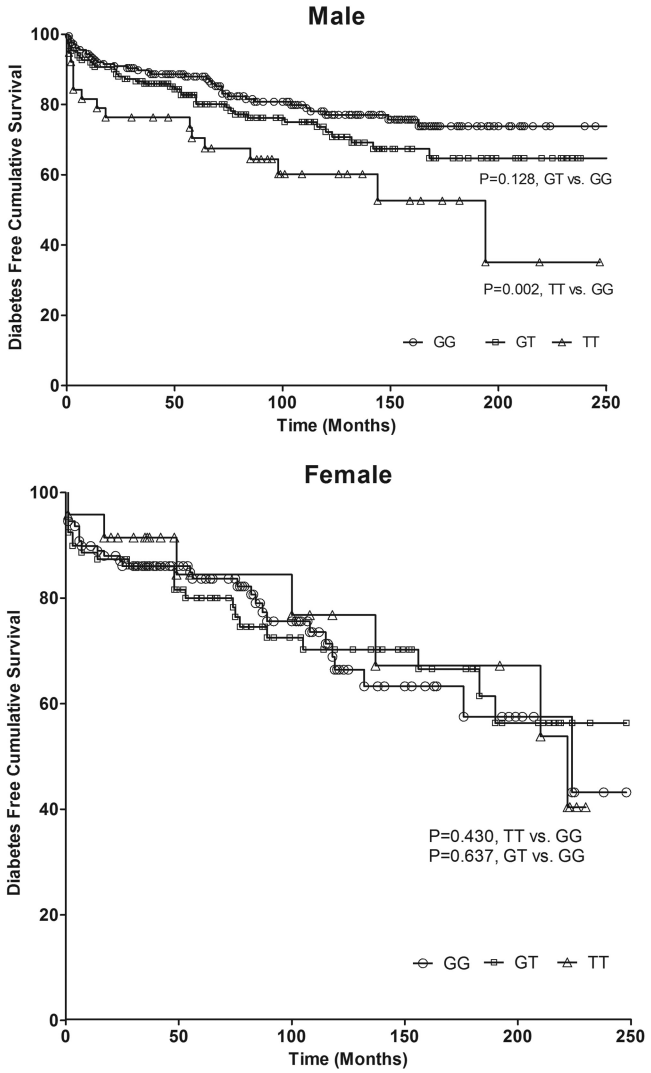

FIG. 1. Cox proportional hazard regression analysis of PTDM development and *ADIPOQ* rs1501299 according to sex. Men with the TT genotype at *ADIPOQ* rs1501299 had a significantly greater risk of PTDM development than the GG homozygotes (HR 2.50, $P = 0.002$, *top panel*). GT heterozygotes had nonsignificantly elevated risk of PTDM (HR 1.41, $P = 0.128$, *top panel*). However, among women, no such genetic effect was observed (TT: HR 0.70, $P = 0.430$ and GT: HR 1.14, $P = 0.637$, *bottom panel*).

results may reflect an interaction between estrogen availability and adiponectin. Although clinical studies on the association between estrogen replacement therapy and serum adiponectin levels are conflicting (24–26), estrogen is believed to have antidiabetic effects in skeletal muscle cells, adipocytes, and pancreatic islets (27), and estrogen receptor gene polymorphisms have been associated with circulating adiponectin concentrations (28). Whether there is cross talk between estrogen availability and adiponectin action requires further investigation.

A previous study has shown that the *ADIPOQ* rs1501299 (G276T) polymorphism is associated with type 2 diabetes mellitus, with the *G* allele conferring greater risk for diabetes, more insulin resistance, and lower plasma adiponectin concentration (15). However, similar to our results, another study performed in a large cohort reported that the *T* allele of *ADIPOQ* rs1501299 represents a risk factor for diabetes (22, 29). Although according to a metaanalysis, polymorphisms of *ADIPOQ* rs1501299 gene are not significantly associated with diabetes, with relative risks for the GT and TT genotypes being 0.98 and 0.95, respectively, when compared with the GG genotype (7). The reasons for these discrepant results between studies are not clear but could be related to different subject characteristics and/or possible differential genetic effects, depending on ethnicity. Herein we studied renal allograft recipients for the first time, whereas

TABLE 4. Multivariate logistic regression analysis for risk factors associated with PTDM

	HR (95% CI)	*P* value
Age (yr)	1.06 (1.04–1.08)	<0.001
Sex (0, male; 1, female)	0.98 (0.70–1.37)	0.905
FPG at baseline	1.01 (0.99–1.02)	0.254
Weight gain	1.02 (0.99–1.05)	0.295
Type of immunosuppressant (0, cyclosporin A; 1, tacrolimus)	2.42 (1.63–3.57)	0.001
Genotype (0, wild homozygote; 1, heterozygote)	1.29 (0.91–1.82)	0.149
Genotype (0, wild homozygote; 1, mutant homozygote)	1.67 (1.03–2.70)	0.038

CI, Confidence interval.

previous studies examined patients with diabetes not occurring in the context of renal transplantation. A number of studies on *ADIPOQ* rs1501299 reported that the *T* allele is associated with increased adiponectin concentration in plasma (20, 30). *ADIPOQ* rs1501299 is located in intron 2, and it is possible that this polymorphism is in linkage with other polymorphisms that are involved in insulin secretion or insulin resistance. Also, we cannot exclude the possibility that some of these associations may have occurred by chance. Exact mechanisms underlying our observations need to be explored in detail in the future.

Although steroid use is known to be diabetogenic, we found no association between PTDM and steroid dose. This is probably due to low dose of steroids used in our study patients and/or the overwhelming effects of other factors.

Our study has several limitations. Oral glucose tolerance tests were not routinely performed before transplantation, and preexisting diabetes or impaired glucose tolerance could have led to an overestimation of PTDM incidence. As we reported previously, there could be a phenotype change from PTDM to non-PTDM mainly due to steroid pulse therapy to treat acute rejection. To minimize the effect of phenotype change and avoid this possible confounding, we included only renal allograft patients who were followed up more than 1 yr and determined the PTDM phenotype at 1 yr after transplantation. Another limitation is the lack of measurements of plasma adiponectin concentration before transplantation due to lack of samples. However, it has been shown that patients with end stage renal disease have elevated plasma adiponectin concentration and plasma adiponectin does not correlate with insulin sensitivity (31, 32). Finally, the relatively small sample size precluded the study of gene-gene interactions. However, our study included a unique cohort of diabetic patients and over a relatively long-term observational period (median of 10 yr). Although it would be desirable to have confirmed our results in another smaller cohort of transplant patients, this was not feasible in this study. Larger studies are therefore required to confirm our results in different populations and ethnicities and evaluate the prognostic significance of our findings.

In conclusion, our results suggest that genetic variation in *ADIPOQ* is associated with PTDM. Variants of the *ADIPOQ* rs1501299 are linked to PTDM development only in male but not in female renal allograft recipients. This indicates a possible sex-specific effect of adiponectin on the development of PTDM in this population.

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