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Pilot Study: Association of Traditional and Genetic Risk Factors and New-Onset Diabetes Mellitus Following Kidney Transplantation

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Abstract

Introduction—New-onset diabetes mellitus, which occurs after kidney transplant and type 2 diabetes mellitus (T2DM), shares common risk factors and antecedents in impaired insulin secretion and action. Several genetic polymorphisms have been shown to be associated with T2DM. We hypothesized that transplant recipients who carry risk alleles for T2DM are "tipped over" to develop diabetes mellitus in the posttransplant milieu.

Methods—We investigated the association of genetic and traditional risk factors present before transplantation and the development of new-onset diabetes mellitus after kidney transplantation (NODAT). Markers in 8 known T2DM-linked genes were genotyped using either the iPLEX assay or allelic discrimination (AD)-PCR in the study cohort testing for association with NODAT. We used univariate and multivariate logistic regression models for the association of pretransplant nongenetic and genetic variables with the development of NODAT.

Results—The study cohort included 91 kidney transplant recipients with at least 1 year posttransplant follow-up, including 22 who developed NODAT. We observed that increased age, family history of T2DM, pretransplant obesity, and triglyceridemia were associated with NODAT development. In addition, we observed positive trends, although statistically not significant, for association between T2DM-associated genes and NODAT.

Conclusions—These findings demonstrated an increased NODAT risk among patient with a positive family history for T2DM, which, in conjunction with the observed positive predictive trends of known T2DM-associated genetic polymorphisms with NODAT, was suggestive of a genetic predisposition to NODAT.

New-onset diabetes mellitus is a common complication of kidney transplantation (NODAT), with a widely dispersed reported incidence between 2% to 50%.[1] The lack of uniformity in the reported incidence is due to variations in the studied populations, varying immunosuppressive regimens, and the different definitions for diabetes ranging from the American Diabetes Association definition to diabetes being defined after institution of therapy. NODAT is associated with decreased allograft and patient survival.[2–4] Risk factors for the development of NODAT include traditional ones, such as age,[5,6] obesity,[3,7] ethnicity

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(African American[3,6,8] and Hispanic ethnicity,[3,9] family history of diabetes, presence of hepatitis C, and receipt of a deceased donor transplant.[6,8] Additionally, various diabetogenic immunosuppressants (corticosteroids,[10,11] calcineurin inhibitors,[3,12–14] sirolimus[15]) contribute to the development of NODAT. The diabetogenic effect of glucocorticoids is primarily caused by insulin resistance followed by enhanced gluconeogenesis in the liver and decreased glucose uptake and glycogen synthesis in skeletal muscle cells.[16,17] The pathogenesis of the diabetogenic effect of calcineurin inhibitors is attributed to both impaired insulin sensitivity and inhibition of insulin production by beta cells.[18–25]

Mechanistically, NODAT and type 2 diabetes mellitus (T2DM) have common antecedents in impaired insulin secretion and insulin action; both diseases share many of the same risk factors. It has also been shown that first-degree relatives of individuals with T2DM have up to 3.5-fold greater risk for NODAT development compared to the general population.[26] Key genes previously shown to be involved in T2DM susceptibility include transcription factor 7-like 2 (*TCF7L2*), peroxisome proliferator-activated receptor gamma (*PPARG*), potassium inwardly-rectifying channel, subfamily J, member 11 (*KCNJ11*), solute carrier family 30 (zinc transporter), member 8 (*SLC30A8*), cyclin-dependent kinase inhibitors *CDKN2A/CDKN2B,* the insulin-like growth factor 2 mRNA binding protein 2 (*IGF2BP2*), and others.[27–35] Interestingly, it has been observed that many of the genes influence diabetes risk by affecting insulin secretion.[36–38] More over, recent studies have shown that the risk allele in a SNP in *SLC30A8* associated with T2DM in multiple studies was also linked with increased risk of NODAT in renal allograft patients.[39]

Type 2 diabetes mellitus is thought to be a complex polygenic disease. Because transplant-associated diabetes shares a similar clinical behavior and presentation as does T2DM, it is possible that similar nongenetic and genetic variants that increase susceptibility to T2DM may also influence NODAT development in kidney transplant recipients. We hypothesized that, in addition to risk conferred by traditional risk factors measured before transplantation, genes with known effects on T2DM susceptibility may also contribute to increased risk in the development of NODAT.

SUBJECTS AND METHODS

Study Participants

The study cohort consisted of a random sample of all patients above 18 years of age undergoing first kidney transplantations between 2003 and 2006. Patients eligible for inclusion were all those who had no diagnosis of T2DM prior to transplant (normal fasting glucose and Hb A_{1c} < 6.0 pretransplant and not on therapy for T2DM pretransplant) and with at least 1 year of posttransplant follow-up. Informed consent was obtained and the study was approved by our Institutional Review Board. NODAT was defined as the ongoing requirement for insulin therapy or oral diabetogenic agents beyond 1 month after transplant. We chose this time point because several factors, including the stress of surgery and introduction of immunosuppressive therapy, produce transient hyperglycemia during the first month posttransplant, which could potentially confound a NODAT diagnosis.

Single Nucleotide Polymorphism (SNP) Genotyping

Genomic DNA was extracted from saliva specimens using the Oragene kit according to the manufacturer's specifications (DNA Genotek, Ottawa, Ontario), and hydrated in TE (pH = 8.0). The DNA concentration was measured by the NanoDrop 1000 spectrophotometer (NanoDrop Technologies, Wilmington, Del), with an average yield of 13.3 μg DNA. The DNA quality was assessed using A260/A280 absorbance measurements and agarose gel electrophoresis; no visible product degradation was observed. We used this DNA to

genotype variants in genes previously shown to be associated with T2DM across multiple populations including TCF7L2, PPARG, KCNJ11, SLC30A8, CDKN2A/CDKN2B, IGF2BP2, and others. All markers except *KCNJ11* rs5219 and *IGF2BP2* rs1470579 were genotyped using both the iPLEX assay in conjunction with the MassARRAY platform (Sequenom, La Jolla, Calif). In this method, primers and multiplex conditions were designed using the Assay Design v4.0 software, and DNA amplification and iPLEX primer extension were performed according to the manufacturer's protocol (Sequenom). Markers rs5219 and rs1470579 were genotyped by AD-PCR using TaqMan SNP Genotyping Assays and 7000 Sequence Detection System according to the manufacturer's protocol (Applied Biosystems). The observed genotype frequency for each SNP was assessed for deviation from that expected under Hardy-Weinberg equilibrium (HWE) using chi-square analysis, and 14 duplicate samples were used to assess data quality. Assays were considered successful and genotype data subsequently analyzed if (1) a minimum of 90% of all genotyping calls were obtained, (2) markers did not deviate significantly ($P \leq .05$) from HWE, and (3) genotyping error results were <3%.

The sample call rate per SNP ranged from 96.88% to 100%, and the rate of successful SNPs genotyped per individual ranged from 73.33% to 100%, with an average call rate of 98.89%. Of the 16 markers selected for genotyping, only rs7903146, located in the *TCF7L2* gene, failed multiple times owing to >10% missing calls. Therefore, our overall SNP success rate was 93.75%.

Data Analysis

Descriptive analyses of continuous variables were performed using Student *t* tests for continuous variables and chi-square to compare proportions. The extent to which observed genotype frequencies for each SNP deviated from that expected under the HWE was assessed; none of the markers varied significantly from the HWE. In addition, encrypted samples were used to assess data quality.

We used a logistic regression model to measure univariate and multivariate associations of baseline nongenetic variables with development of NODAT. The statistical evidence for the association and the strength of association between genotypes and affection status (NODAT) was determined by the odds ratio (OR) and its corresponding 95% confidence interval (CI), as calculated by the logistic model. For these analyses, an additive model was used in which the genotype was coded as a numeric variable representing the number of risk alleles; thus, the OR designates the odds for NODAT associated with each copy of the risk allele. In these analyses we tested for disease association with 15 previously identified variants in 8 genes associated with T2DM. These included rs12255372 and rs7901695 in *TCF7L2,* rs5219 and rs5215 in *KCNJ11,* rs1801282 in *PPARG,* rs13266634 in *SLC30A8,* rs10811661 and rs564398 in *CDKN2A/CDKN2B,* rs4402960 and rs1470579 in *IGF2BP2,* rs10946398, rs7756992, and rs7754840 in *CDKAL1,* and rs1111875 and rs5015480 in *HHEX.*

Given the different allele frequencies and linkage disequilibrium patterns among different ethnic groups, we conducted a logistic regression analysis adjusting for age, gender, and ethnicity (as determined by self-report). We additionally adjusted in a stepwise fashion for variables that were significant in the unilateral analyses. To augment power to detect an association, we assumed that most of these alleles modestly affect the risk of disease, and therefore we conducted a “multiallelic” analysis with the number of “representative” risk alleles; the SNP with the strongest association for each locus was chosen as representative of the locus. The number of representative risk alleles carried by each individual was defined as the sum of the risk alleles for each gene described in prior studies. The association of the number of risk alleles with NODAT was analyzed in a fashion analogous to the individual

SNPs. All statistical analyses were conducted using STATA statistical software, version 8.0 (StataCorp LP, College Station, Texas).

RESULTS

Baseline characteristics of individuals comprising the study sample are shown in Table 1. The sample consisted of 22 individuals who developed NODAT within 1 year of transplantation (cases) and 69 others who remained unaffected (controls). The majority of cases diagnosed with NODAT were within 6 months' posttransplant except for 5 cases diagnosed at 14, 24, 36, 40, and 60 months posttransplant. In this study sample, cases were older than controls (57.0 ± 10.4 vs 46.4 ± 15.9 years) and were more likely to be female (59% vs 46%) and Caucasian (90% vs 68%). A positive family history of T2DM was more common in cases (41% vs 19%), as was higher pretransplant body mass index (BMI) (30.6 ± 5.9 vs 25.8 ± 5.3 kg/m^2) and a history of hepatitis C virus infection (13.6% vs 4.3%). A majority of patients (n = 76, 84%) were on tacrolimus. Approximately 50% (46 patients) were on a quick steroid withdrawal immunosuppression protocol; specifically a 5-day quick tapering course of glucocorticoids (methylprednisolone IV 500 mg on day 1, 250 mg on day 2, and 125 mg on day 3, followed by oral prednisone 60 mg on day 4 and 30 mg on day 5. The remainder of patients were placed on a slow taper of glucocorticoids to 5 mg by day 90 posttransplant.

We first examined previously identified traits as potential risk factors for NODAT development in the study cohort. As shown in Table 1, both univariate and multivariate analyses identified older age, presence of family history of T2DM, pretransplant obesity, and pretransplant hypertriglyceridemia as significant predictors of NODAT development. Difference in gender, race and ethnicity, hepatitis C seropositivity, trough tacrolimus level, and institution of steroid withdrawal immunosuppression did not confer significant risk toward development of future NODAT.

To investigate the impact of variants previously associated with T2DM, we selected 15 markers from 8 previously identified susceptibility genes. These genes were selected based on the strength of prior association in well-powered study samples, as well as validation in at least 2 independent study samples. Given the different allele frequencies and linkage disequilibrium patterns among different ethnic groups we conducted multivariate logistic regression analyses adjusting for age, gender, and ethnicity (Table 2). As shown in Table 2, no statistically significant evidence for association with NODAT was observed for any of the markers, including the *SLC30A8* variant which previously was found to confer resistance against NODAT in renal allograft patients. However, all of the relationships, although not reaching the level of statistical significance, did show an odds ratio (OR) in the same direction as earlier studies for T2DM association. To further investigate associations between these markers and NODAT, we adjusted for traditional risk factors that were significant in the univariate model (ie, age, family history of T2DM, triglyceride concentration, and BMI) in a step-wise manner, but did not find results that were substantially different from those presented in Table 2 (data not shown).

Because many of the investigated markers were selected from studies originally conducted in study samples comprised of individuals of Northern European ancestry, we conducted a subgroup analysis restricted to patients of Caucasian ethnicity. Results of these analyses were similar to those obtained from analysis of all subjects.

DISCUSSION

New-onset diabetes mellitus after kidney transplantation is a well-recognized complication of renal replacement with negative consequences on both patient and allograft survival.[2–4] Prior studies have demonstrated the impact of traditional risk factors for T2DM on the development of NODAT.[5–9] Given the known correlation of increased NODAT risk with the presence of a positive family history for T2DM,[6] we postulated that predisposition to NODAT may also be governed by genetic variants known to increase risk for T2DM development. As of today, there has been a paucity of studies in the literature investigating the possibility of genetic predisposition to NODAT. The present study is the first to investigate this possibility by examining a comprehensive set of T2DM-associated markers in the context of increased susceptibility to NODAT development.

The current study confirmed the association of traditional risk factors prior to transplantation including age, a family history of T2DM, presence of pretransplant obesity, and pretransplant elevated triglyceride concentration in the development of NODAT. Knowledge of these risk factors pretransplant may provide the basis for assertive prophylactic modalities including lifestyle and immunosuppression modifications to delay or prevent the development of NODAT in those patients who may be more susceptible to develop NODAT. Several studies have demonstrated diet and lifestyle modifications to reduce the incidence of T2DM among patients at high risk to develop T2DM.[40–42]

To identify novel risk factors for NODAT, we investigated the impact of known susceptibility alleles for T2DM on the development of diabetes following kidney transplantation. Prior studies have reported associations between SNPs located in or near the following genes: TCF7L2, KCNJ11, CDKAL1, HHEX, PPARG, SLC30A8, IGF2BP2, and *CDKN2A/CDKN2B* and T2DM.[27–35, 43] In our analyses, we did not find statistically significant evidence for association between markers in any of these genes and risk of NODAT development. Previous large genetic-association studies in T2DM have typically yielded low *P* values associated with small OR values (~1.15). However, as shown in Table 3, the confidence intervals for these studies are quite narrow, which reflects, in part, the power of the study sample to detect weaker genetic effects. In contrast, the wide confidence intervals and OR fluctuations in the present study are largely reflective of the small sample size. However, the fact that results from the current study are consistent with effects from the T2DM studies with respect to the direction and magnitude of the OR provides support that T2DM susceptibility alleles may indeed play a role in risk of NODAT development, and larger studies will be necessary to determine whether genetic variants have similar effects to those reported of T2DM.

In conclusion, in addition to traditional risk factors, we identified positive predictive trends with known genetic risk factors for T2DM in NODAT patients, which support the possibility of genetic predisposition to diabetes susceptibility following kidney transplantation. Although the present study comprised only 91 individuals and did not have adequate power to detect genetic effects, it does provide the justification for conducting larger-scale studies to assess the effects of T2DM susceptibility alleles on predisposition to NODAT. The possibility that similar genetic factors are shared between T2DM and NODAT may lead to an enhanced understanding of the molecular mechanisms by which the 2 diseases develop and ultimately to improved methods of diagnosis and treatment in affected individuals.

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Table 1

Unadjusted and Adjusted Traditional Risk Factors Associated With NODAT

Risk Factor	Odds Ratio (95% CI) Univariate Analyses	Odds Ratio (95% CI) Multivariate Analyses*
Age per 1-year increase	1.05 (1.01–1.10)	1.11 (1.04–1.18)
Family history of T2DM	2.98 (1.05–8.45)	6.89 (1.32–35.8)
BMI pretransplant (increase by 1 kg/m^2)	1.16 (1.06–1.28)	1.16 (1.02–1.33)
Pretransplant triglyceride level >200 vs <200	4.90 (1.74–13.7)	7.95 (1.89–33.4)

*Adjusted for age, T2DM family history, pretransplant BMI, and pretransplant triglyceride levels.

Table 2

Association Analyses of T2DM Susceptibility Genes With NODAT

Gene	SNP	Alleles*	Frequency of High-Risk Allele		Odds Ratio (95% CI)†	Odds Ratio (95% CI)‡
			Cases (%)	Controls (%)		
TCF7L2	rs12255372	G/**T**	20.4	18.8	1.10 (0.48–2.52)	0.98 (0.41–2.30)
TCF7L2	rs7901695	T/**C**	27.3	24.6	1.12 (0.54–2.32)	0.98 (0.45–2.14)
KCNJ11	rs5219	C/**T**	36.3	35.5	1.03 (0.52–2.01)	0.93 (0.45–1.94)
KCNJ11	rs5215	C/**T**	63.6	62.3	1.05 (0.54–2.02)	1.15 (0.56–2.36)
PPARG	rs1801282	G/**C**	86.3	86.9	0.96 (0.39–2.34)	1.02 (0.36–2.85)
SLC30A8	rs13266634	T/**C**	77.2	73.9	1.19 (0.54–2.57)	1.17 (0.48–2.84)
CDKN2A/CDKN2B	rs10811661	C/**T**	79.5	80.4	0.95 (0.435–2.13)	1.42 (0.55–3.58)
CDKN2A/CDKN2B	rs564398	G/**A**	63.6	66	0.91 (0.45–1.81)	1.20 (0.54–2.66)
IGF2BP2	rs4402960	G/**T**	31.8	24.6	1.44 (0.67–3.07)	1.16 (0.51–2.63)
IGF2BP2	rs1470579	A/**C**	36.3	29.7	1.31 (0.66–2.59)	1.21 (0.56–2.60)
CDKAL1	rs10946398	A/**C**	34.1	27.5	1.38 (0.65–2.91)	1.84 (0.79–4.28)
CDKAL1	rs7756992	A/**G**	31.8	26.1	1.39 (0.61–3.17)	2.06 (0.81–5.28)
CDKAL1	rs7754840	G/**C**	34.1	30.4	1.19 (0.57–2.50)	1.69 (0.72–3.95)
HHEX	rs1111857	A/**G**	63.6	60.8	1.11 (0.57–2.16)	1.33 (0.66–2.69)
HHEX	rs5015480	T/**C**	61.4	57.2	1.14 (0.61–2.15)	1.32 (0.67–2.58)
Multiallelic risk					1.10 (0.89–1.35)	1.06 (0.82–1.38)

*Underlined and bold alleles are diabetes-associated alleles as described in prior studies.

†Odds ratio (unadjusted) per copy of the risk allele.

‡Odds ratio: adjusted (age, gender, race) per copy of the risk allele.

Table 3

Reported Data on Association Analyses of T2DM Susceptibility Genes[43] Compared to Our Results on Genetic Association With PTDM

Gene	SNP	Alleles*	Frequency of High-Risk Allele in Controls		Odds Ratio (95% CI)†	
			Prior Studies	Our Study	Prior Studies	Our Study
TCF7L2	rs7901695	T/**C**	27.3	24.6	1.37 (1.31–1.43)	1.12 (0.54–2.32)
KCNJ11	rs5219	C/**T**	46	35.5	1.14 (1.10–1.19)	1.03 (0.52–2.01)
PPARG	rs1801282	G/**C**	82	86.9	1.14 (1.08–1.20)	0.96 (0.39–2.34)
SLC30A8	rs13266634	T/**C**	61	73.9	1.12 (1.07–1.16)	1.19 (0.54–2.57)
CDKN2A/CDKN2B	rs10811661	C/**T**	85	80.4	1.20 (1.14–1.25)	0.95 (0.43–2.13)
IGF2BP2	rs4402960	G/**T**	30	24.6	1.14 (1.11–1.18)	1.44 (0.67–3.07)
CDKAL1	rs7754840	G/**C**	36	30.4	1.12 (1.08–1.16)	1.19 (0.57–2.50)
HHEX	rs1111875	A/**G**	52	60.8	1.13 (1.09–1.17)	1.11 (0.57–2.16)

*Underlined and bold alleles are diabetes-associated alleles as described in prior studies.

†Odds ratio: Unadjusted model per copy of the risk allele.