TCF7L2 (rs7903146) But Not CDKAL1 (rs7754840) Gene Polymorphisms Increase the Risk of New-Onset Diabetes After Kidney Transplant

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Abstract

Objectives: **Incidence of new-onset diabetes after transplant negatively affects graft and patient survival. Obesity, impaired fasting glucose before transplant, and a history of diabetes in first-degree relatives are well-defined risk factors. TCF7L2 and CDKAL1 gene polymorphisms have been implicated in the pathogenesis. We investigated the effect of single gene polymorphisms of TCF7L2 (rs7903146) and CDKAL1 (rs7754840) on new-onset diabetes in renal transplant recipients.**

Materials and Methods: **We evaluated 239 renal transplant recipients. TCF7L2 and CDKAL1 gene polymorphisms were assessed by polymerase chain reaction.**

Results: **Mean patient age was 43 ± 13 years. There were 148 male patients (61.9%), and 91 were female (38.1%). New-onset diabetes was detected in 55 patients (23%). In 20 cases (36%), the glycemic disorder was transient; 61% of patients required insulin therapy. In terms of CDKAL1, 108 patients had the wild-type allele, 112 had a single-allele mutation, and 19 had a 2-allele mutation (45.2%, 46.9%, and 7.9%, respectively). In terms of TCF7L2, 163 of the patients had the wild-type allele, 49 had a single-allele mutation, and 27 had a 2-allele mutation (68%, 20%, and 11%, respectively). New-onset diabetes-related factors were age at transplant, body mass index after transplant (calculated as weight in kilograms divided by height in meters squared), tacrolimus, mycophenolate, and TCF7L2 polymorphism but not CDKAL1 polymorphism. After multiple regression analysis, the effect of TCF7L2 polymorphism persisted. A single allelic change resulted in a risk factor 1.4 times higher for new-onset diabetes after transplant (*P* = .043; 95% CI, 1.142-1.874) and a double allelic change was 2.7 times higher (*P* < .01; 95% CI, 1.310-4.073)**

Conclusions: **TCF7L2 (rs7903146) gene polymorphism is an independent risk factor for new-onset diabetes in Turkish renal transplant patients. This study is the first in Turkey to show the distribution and effect of these genes in kidney transplant patients.**

Key words: *Diabetes mellitus, Posttransplant diabetes mellitus, Renal transplant*

Introduction

Renal transplant is the preferred treatment for end-stage renal disease.[1] New-onset diabetes after transplant (NODAT) is an important and frequent complication in kidney transplant recipients. New-onset diabetes after transplant is associated with reductions in patient and organ survival. The prevalence has been reported to range from 10% to 40% in series, dependent on the definition of diabetes.[2-4] The risk factors are age over 40 years, obesity, impaired fasting glucose before transplant, hepatitis C virus (HCV) seropositivity, ethnicity (Black or Hispanic), and family history.[5-8] Furthermore, glucocorticoids, calcineurin inhibitors, and rapamycin also increase risk.[2,9,10]

In the past 3 decades, science has witnessed the discovery of numerous genes related to type 2 diabetes. More recently, genome-wide-association studies revealed the association between several single-nucleotide polymorphisms (SNP) and diabetes, one of the most important of which is the transcription factor 7 like 2 (TCF7L2).[11] In 2008, Kang and colleagues proved the close relation between TCF7L2 SNPs and NODAT for the first time.[12]

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Many other polymorphisms are also associated with NODAT to some extent. In a recent meta-analysis, Benson and colleagues evaluated 18 single-gene polymorphisms of 12 genes and found 3 SNPs invariably associated with NODAT.[13] These were TCF7L2 rs7903146, CDK5 regulatory subunit associated protein 1 like 1 (CDKAL1) rs10946398, and potassium voltage-gated channel subfamily Q member 1 (KCNQ1) rs2237892 gene polymorphisms.

TCF7L2 protein functions as a transcription factor encoded by the gene of the same name. The TCF7L2 gene is located on chromosome 10q and is inherited via autosomal dominant fashion. It affects various biological pathways, including the Wnt signaling pathway and insulin metabolism. The β cells of the pancreas extensively express TCF7L2.[14] Individuals with gene polymorphisms have a higher risk of diabetes, NODAT, gestational diabetes, and obesity.[15] These may also increase the risk of coronary artery disease and hyperlipidemia. TCF7L2 rs7903146 C-to-T is the most common polymorphism.

The CDKAL1 gene encodes the protein of the same name. This protein is a methylthiotransferase with a function that is not clearly understood. It is thought to cause susceptibility to diabetes by disruption of insulin secretion. CDKAL1 rs7754840 G-to-C is the most common polymorphism.[16]

Several studies demonstrated the association between TCF7L2 rs7903146 and diabetes and obesity in nontransplanted Turkish patients.[17-19] To our knowledge, no data on CDKAL1 rs7754840 SNP in a Turkish population cohort exist. KCNQ1 rs2237892 SNP has been extensively studied in Asian populations, and its association with diabetes and NODAT in the Caucasian population is questionable.[13,20]

In this study, we investigated the association between TCF7L2 rs7903146 and CDKAL1 rs10946398 polymorphisms with NODAT risk in our kidney transplant recipients.

Materials and Methods

Study population and ethical statement

This study was conducted in our Nephrology and Transplantation department. Kidney transplant recipients who were older than >18 years of age and agreed to participate were included in the study. We recruited 239 recipients of living or deceased donor organs. Patients received transplants between 1990 and 2016. Informed consent was obtained from all patients to be included in the study. Patients who did not want to give informed consent, those who were followed up for less than 2 years, and patients with a diagnosis of pretransplant diabetes were excluded. The clinical features of the patients such as age, sex, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), primary kidney disease, transplant type, dialysis duration, and modality before transplant and comorbid conditions were recorded. Previous and current medical treatments regarding immunosuppression and NODAT were also noted. Creatinine levels and glomerular filtration rates (GFR) of the patients in the first and the last years after transplant were noted. We used the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) to estimate GFR.

This study protocol conformed to ethical guidelines of the Declaration of Helsinki, and all participants gave written informed consent and willingness to participate. The ethics committee of Zekai Tahir Burak Research and Training Hospital approved the study protocol.

Definition of new-onset diabetes after transplant

American Association of Endocrinology 2016 criteria were used for diagnosis, as follows: (1) fasting plasma glucose ≥126 mg/dL, or (2) incidental plasma glucose + diabetes symptoms ≥200 mg/dL, or (3) oral glucose tolerance test 2-hour plasma glucose = 200 mg/dL, or (4) hemoglobin A1c (HbA1c) ≥6.5%.

The treatments the patients received for NODAT were recorded as diet alone, oral anti-diabetes drug, insulin, and insulin plus oral anti-diabetes drug. Hemoglobin A1c values of patients with NODAT were recorded.

Genotyping and single-gene polymorphism analysis

We prepared genomic DNA extracts from whole blood samples containing EDTA with the automated magnetic dead method (MagPurix, kit ZP02001; Zinexts) according to the manufacturer's instructions; samples were stored at -80 °C until analysis. TCF7L2 rs7903146 and CDKAL1 rs10946398 polymorphisms were genotyped by real-time polymerase chain reaction (PCR) with specific oligonucleotide primers, which are shown in Table 1 and Table 2.

Table 1. DNA Isolation and Primer Design

Primer	Sequence (5′-3′)	Polymorphism	Amplicon Size, bp
CDKAL1_SNP1_F	CAAATTGTCCAGATTTGAGAGTGAGC	SNP1	213
CDKAL1_SNP1_R	CATCAGGCACTATTCTAGAGACCAAGG		
TCF7L2_SNP1_F	GTCAGATGGTAATGCAGATGTGATGAG	SNP1	238
TCF7L2_SNP1_R	CATTGACTAAGTTACTTGCCTTCCCTG		

Abbreviations: PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism

One researcher (SG) performed all the tests. DNA isolation was performed with an automated system by magnetic bead method (MagPurix Blood DNA Extraction Kit 200; catalog No. ZP02001; Zinexts). A pair of PCR primers were designed for each polymorphism to be studied.

Table 2. Polymerase Chain Reaction Conditions

Content	Amount per Reaction, µL
Distilled H_2O	15
5× Buffer (ThermoFisher)	5
dNTP mix, 10 mM each	0.5
Advanced primer (5 µM)	1
Back primer (5 µM)	1
Phire Hot Start II DNA polymerase (ThermoFisher)	0.5
Template DNA (20-50 ng/µL)	2
Total	25

Abbreviations: dNTP, deoxynucleoside triphosphate; PCR, polymerase chain reaction

PCR amplification of the polymorphism regions to be studied was performed using designed primers. Reaction results were visualized with 2% agarose gel electrophoresis. PCR products obtained for each sample were mixed so that each sample was approximately equally represented, considering the reaction efficiency. PCR pools created for each sample were purified by an appropriate method (NucleoFast 96 PCR 96-well ultrafiltration kit, Macherey-Nagel). Purified PCR pools were measured with a spectrophotometer (NanoDrop 1000, ThermoFisher). The measured PCR pools were standardized to 0.2 ng/µL in accordance with the sequencing kit. New-generation sequencing was performed with the MiSeq platform (Illumina), and data were analyzed with MiSeq Reporter software (Illumina) and IGV 2.3 Integrative Genomics Viewer software (Broad Institute). Samples were analyzed, and the genotypes of each sample were extracted.

The PCR pools generated for each sample were purified with the NucleoFast 96 PCR 96-well ultrafiltration kit (Macherey-Nagel). Purified samples were measured with a NanoDrop 1000 spectrophotometer (ThermoFisher). New-generation sequencing was performed on the MiSeq platform (Illumina) with the v2 300 cycle sequencing kit. Single-nucleotide polymorphisms were finally determined by with MiSeq Reporter software (Illumina) and IGV 2.[3] Integrative Genomics Viewer software (Broad Institute).

Statistical analyses

Continuous variables are expressed as means and SD, and categorical variables are expressed as frequency and percentage. The normal distribution pattern was tested with the Kolmogorov-Smirnov test. Independent samples *t* tests and Mann-Whitney U tests detected differences between groups when appropriate. The compliance of the genetic distribution to the Hardy-Weinberg balance was analyzed with the chi-square test. The variations of genotypic distributions between patients with and without NODAT were evaluated with the Fisher exact test. Multivariate logistic regression analysis was used to identify possible risk factors for NODAT. A *P* value of less than .05 was considered statistically significant. All statistical analyses were performed with SSPS software for personal computers (version 20.0)

Results

There were 239 renal transplant recipients included in the study; 148 of the patients were male (61.9%), and 91 were female (38.1%). The mean age at transplant was 32 ± 13 years. The mean follow-up was 10.3 ± 5.6 years. A preemptive transplant was received by 33 patients (13%). The remainder underwent either hemodialysis, peritoneal dialysis, or a combination of both. The mean dialysis vintage was 43 ± 53 months.

There were 184 patients (76%) who had living donors, and 55 patients (23%) who had deceased donors. Of 184 living transplants, 87 donations were from first-degree relatives (47%), 83 were from second-degree relatives (45%), and 14 were from third-degree relatives (7%).

New-onset diabetes after transplant was detected in 55 of the patients (23%). Thirty-four of these 55 patients (61%) required insulin (Table 3). Mean HbA1c was 7.1 ± 1.2.

Patients with NODAT had a higher age at transplant. TCF7L2 mutations to CC and CT were higher in the NODAT group. Sex, preemptive transplant rates, modality, vintage of renal replacement, donor type, second transplant, and HCV infection rates were similar between those with and without NODAT (Table 4).

Posttransplant BMI was higher in patients who developed diabetes. For the first and last year

posttransplant, GFR values were lower in the NODAT group. These patients had a higher rate of tacrolimus use and a lower rate of mycophenolate use. Cytomegalovirus infection was similar between the 2 groups. Patients without NODAT were less likely to have hypertension and coronary artery disease (Table 5).

Age, tacrolimus, BMI, and TCF7L2 polymorphism were risk factors for NODAT in univariate analysis. In multivariate analysis, all parameters except BMI remained significant. Mycophenolate was protective of NODAT (Table 6).

Table 3. New-Onset Diabetes After Transplant and Treatment

Modality	Number of Patients	% of NODAT
Diet alone	4	7.3
OAD	17	30.9
OAD + insulin	27	49.1
Insulin	7	12.7
Total	55	100

Abbreviations: NODAT, new-onset diabetes after transplant; OAD, oral antidiabetes drug

Table 4. Characteristics of Transplant Recipients

	Total (N = 239)[a]	NODAT Absent (n = 184)[b]	NODAT Present (n = 55)[b]	*P*
Age at transplant, mean ± SD, y	32 ± 13	30 ± 12	40 ± 13	<.001
Sex, No. of patients (%)				.53
Male	148 (61%)[a]	116 (78%)[b]	32 (21%)[b]	
Female	91 (38%)	68 (74%)	23 (25%)	
Dialysis vintage, mean ± SD, mo	40 ± 53	41 ± 57	39 ± 50	.52
Preemptive transplant, No. of patients (%)				.49
Yes	33 (13%)	26 (78%)	7 (21%)	
No	206 (87%)	158 (76%)	48 (23%)	
Dialysis modality, No. of patients (%)				.81
HD	164 (79%)	126 (76%)	38 (23%)	
PD	23 (11%)	16 (69%)	7 (31%)	
HD + PD	16 (8%)	13 (81%)	3 (18%)	
HCV infection, No. of patients (%)				.45
No	227 (94%)	174 (76%)	53 (23%)	
Yes	12 (5%)	10 (83%)	2 (16%)	
Donor, No. of patients (%)				.48
Living	184 (76%)	141 (76%)	43 (23%)	
Deceased	55 (23%)	43 (78%)	12 (21%)	
CDKAL1, No. of patients (%)				
GG	110 (46%)	83 (45%)[c]	27 (45%)[c]	.727
GC	110 (46%)	85 (46%)	25 (49%)	
CC	19 (7%)	16 (9%)	3 (6%)	
TCF7L2, No. of patients (%)				
CC	163	136 (74%)[c]	27 (49%)[c]	.001
CT	49	33 (18%)	16 (42%)	
TT	27	15 (8%)	12 (22%)	

Abbreviations: HCV, hepatis C virus; HD, hemodialysis; NODAT, new-onset diabetes after transplant; PD, peritoneal dialysis
[a]Column percentage. [b]Row percentage. [c]Column percentage. Note: additive values may not sum 100 because of rounding.

Table 5. Posttransplant Follow-up Characteristics of Transplant Recipients

	Total (N = 239)	NODAT Absent (n = 184)	NODAT Present (n = 55)	*P*
Follow-up, mean ± SD, y	10.3 ± 5.5	10.5 ± 5.6	9.6 ± 5.1	.295
Posttransplant BMI, mean ± SD,	26 ± 3	25 ± 4	27 ± 3	.018
First year posttransplant				
Creatinine, mean ± SD, mg/dL	1.11 ± 0.32	1.09 ± 0.30	1.16 ± 0.38	.131
GFR, mean ± SD, mL/min	83 ± 23	86 ± 23	74 ± 21	.001
Last year posttransplant				
Creatinine, mean ± SD, mg/dL	1.36 ± 0.84	1.36 ± 0.84	1.36 ± 0.54	.998
GFR, mean ± SD, mL/min	71 ± 26	73 ± 26	62 ± 22	.004
Corticosteroids, No. of patients (%)				.45
Present	226 (94%)[a]	174 (76%)[b]	52 (23%)	
Absent	13 (5%)	10 (76%)	3 (23%)	
Tacrolimus, No. of patients (%)				.002
Present	178 (74%)	146 (82%)	32 (17%)	
Absent	61 (26%)	38 (62%)	23 (37%)	
Mycophenolate, No. of patients (%)				.004
Present	166 (69%)	143 (86%)	23 (13%)	
Absent	73 (31%)	41 (56%)	32 (43%)	
CMV infection, No. of patients (%)				.55
Yes	218 (91%)	168 (77%)	50 (22%)	
No	21 (9%)	16 (76%)	5 (23%)	
Hypertension, No. of patients (%)				.009
Yes	153 (64%)	110 (71%)	43 (28%)	
No	86 (35%)	74 (86%)	12 (13%)	
Coronary artery disease, No. of patients (%)				.001
Yes	222 (92%)	177 (79%)	45 (20%)	
No	17 (7%)	7 (41%)	10 (58%)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CMV, cytomegalovirus; GFR, glomerular filtration rate; NODAT, new-onset diabetes after transplant
[a]Column percentage. [b]Row percentage. Note: additive values may not sum 100 because of rounding.

Table 6. Risk Factors for New-Onset Diabetes After Transplant

	Univariate Logistic Regression		Multivariate Logistic Regression	
	P	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)
TCF7L2 rs7903146				
CT	.031	1.442 (1.182-1.547)	.043	1.413 (1.142-1.874)
TT	<.01	2.868 (1.698-4.030)	<.01	2.758 (1.310-4.073)
Age at transplant	<.01	1.112 (1.059-1.105)	<.01	1.077 (1.046-1.109)
Posttransplant BMI	.02	1.200 (1.003-1.196)	.052	1.093 (0.987-1.284)
Tacrolimus	<.01	2.097 (1.337-3.289)	.013	1.378 (1.175-1.815)
Mycophenolate	<.01	0.784 (0.644-0.854)	.02	0.841 (0.631-0.943)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared)

Discussion

Our study, conducted in 239 patients, showed that the rs7903146 polymorphism of TCF7L2 was an independent risk factor for NODAT in Turkish renal transplant recipients.

Single-center studies from Turkey have reported NODAT prevalence to be between 15% and 26%.[21-24] Our prevalence of 23.3% complies with these studies.

Common variants in TCF7L2 stand out as the leading polymorphisms associated with type 2 diabetes in the general population in most genome-wide studies performed to date.[25] A meta-analysis by Benson and colleagues also proved the association of rs7903146 with NODAT in different communities with a homogeneous distribution.[13] Our study showed that a C-to-T change of a single allele increases the relative risk of NODAT by 1.4 times; with the change of 2 alleles, the risk increases by 2.7 times. TCF7L2 rs7903146 has been associated with diabetes and obesity in Turkish patients.[17-19] In this respect, our findings are compatible with both global and local literature.

We did not find an association between CDKAL1 rs10946398 G-to-C polymorphisms and NODAT. Kang and colleagues reported CDKAL1 rs10946398 to be a significant risk factor in Korean patients.[26] The statistical power of their study reflects its influence on the review from Benson and colleagues.[13] However, other studies have disagreed with their results.[27,28] Interestingly, another study from the Korean transplant database, published in 2019,[29] did not replicate the results of Kang and colleagues. Genetic differences between the populations may explain this phenomenon. Overall, our results are not discordant with current literature. Knowledge of CDKAL1 SNPs in the Turkish people does not exist; hence, it is not possible to comment on local data.

According to our data, the presence, duration, and type of dialysis treatment before transplant do not affect NODAT. This subject has not been well elucidated. A single study from Poland reported peritoneal dialysis to be a risk factor for NODAT,[30] whereas 2 other studies did not.[31,32] Studies with prospective cohorts may help resolve these conflicting reports. The current literature does not include sex as a major risk factor for NODAT; our study has yielded similar results.[33]

Age at the time of transplant, posttransplant BMI, and tacrolimus use are associated with the risk of NODAT. In multivariate regression, the interaction between NODAT and BMI lost its significance. Obesity increases NODAT risk; however, depending on the definition of obesity and statistical technique, the odds ratio may be between 1.04 and 1.7.[9,34,35] Age is a well-known and repeatable risk factor.[7] In this respect, our findings are compatible with the literature.

Tacrolimus and cyclosporine disrupt insulin secretion by interference with the nuclear factor of active T cell signaling in pancreatic β islets. This toxicity is more severe for tacrolimus.[36] Several studies have repeatedly proved that tacrolimus is a potent diabetogenic and independent risk factor for NODAT.[4,37]

Corticosteroids trigger diabetes via multiple mechanisms[10]; however, in our study, we were unable to establish an association between steroid use and NODAT. In our clinic, we do not have "steroid-free regimens." Therefore, the total number of patients who were not on corticosteroids was only 13, which may have interfered with statistics.

Retrospective data have suggested that mycophenolate (sodium or mofetil) might reduce the risk of diabetes by about 15% to 25%.[7] This finding has not been validated in a prospective setting. It remains uncertain whether this effect of mycophenolate is the result of a metabolic pathway or the result of its strong immunosuppressive properties that allow lower doses of diabetogenic drugs. Nonetheless, our findings agree with current knowledge.

Cytomegalovirus and HCV infection do not increase the risk of NODAT according to our work. Data for cytomegalovirus infection are variable.[38,39] Hepatitis C virus is expected to be associated with diabetes.[37] However, we had few patients seropositive for HCV (only 12), and their tests were positive for anti-HCV IgG but negative for HCV RNA, ie, without active hepatitis. No patient received anti-HCV treatment after transplant. These characteristics might explain why we failed to demonstrate an association between HCV and NODAT.

Our study also revealed the coexistence of NODAT with hypertension and coronary artery disease. This association is well known.[2,7,23,33] In addition, patients with NODAT had lower GFR both in the first year and in the last year of follow-up. Because we did not recruit patients with failed grafts, it is impossible to comment on the effect of NODAT on renal survival. Nevertheless, given the mentioned interactions, NODAT diagnosis should be warning for premature mortality risk.

Our study is cross-sectional, and this is a limitation. The family history, pretransplant BMI, and glycemic status are notable risk factors for

NODAT.[3,4] Unfortunately, we were not able to analyze these because of a lack of data.

Conclusions

New-onset diabetes after transplant is a prevalent complication associated with hypertension and coronary artery disease. This study proves TCF7L2 (rs7903146) to be an independent and significant risk factor for NODAT in Turkish renal transplant recipients.

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