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Analysis of glucocorticoid receptor gene polymorphisms in kidney recipients with post-transplant diabetes

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ABSTRACT

Introduction: Post-transplant diabetes mellitus (PTDM) is a severe and common metabolic problem after transplantation. Glucocorticoid receptor (GR) is encoded by the NR3C1 gene and it seems that polymorphisms in this gene lead to altering insulin sensitivity.

Objectives: This study aimed to evaluate the frequency of four common polymorphisms in the NR3C1 gene of renal recipients with and without PTDM.

Patients and Methods: Blood samples were collected from 32 PTDM and 59 non-diabetic renal-transplanted patients. After DNA extraction, DNA fragments were amplified and directly sequenced using specific primers. Data analysis was performed with SPSS 22.0 software.

Results: There was no significant correlation between diabetes incidence and the four investigated polymorphisms of the GR gene. Nevertheless, diabetic patients' age was higher than non-diabetic patients. Additionally, transplant acute rejection (AR) in diabetic patients was found to be more than non-diabetic patients.

Conclusion: Based on gathered information in this research, none of the studied polymorphisms affected the development of PTDM. Further investigations should be conducted in a large sample size.

Original

Implication for health policy/practice/research/medical education:
Predisposing genetic factors are involved in the development of post-transplant diabetes mellitus (PTDM) as a severe and common metabolic problem after transplantation. No significant association was observed between ER22/23EK, A3669G, BclI, and N363S polymorphisms of NR3C1 gene and PTDM. In addition, glucocorticoid receptor (GR) gene polymorphisms were not involved in the pathogenesis of post-transplant diabetes mellitus in kidney recipients of living donors.

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Introduction

Post-transplant diabetes mellitus (PTDM) is a severe and common metabolic problem that is frequently occurred after successful solid organ transplantation, with about 2% to 50% incidence rate (1). PTDM rigorously endanger graft survival and life quality by increasing the risk of cardiovascular diseases, allograft dysfunction, chronic rejection, severe infections, graft failure and mortality. PTDM is developed within the first year after transplantation, suggesting that the risk factors are present or develop prior or even at the time of transplantation (2).

PTDM is a complex disease triggered by the interaction of different modifiable and non- modifiable factors (3). Numerous clinical risk factors have been informed in the literature, including a family history of diabetes, older age, viral infection (hepatitis B, C and cytomegalovirus), polycystic kidney disease, acute rejection (AR), hypertension (4) and other risk factors; yet, there still are controversies. Moreover, a variation of the composition of gut microbiota is also connected to the glycemic status after renal transplantation (5). However, administration of the immunosuppressive medications such as glucocorticoids (GCs) and calcineurin inhibitors especially tacrolimus (4) has a key role in the development and pathogenesis

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of PTDM (6, 7). Therefore, the clinical consequences of these factors deserve great attention.

Objectives

At present, predisposing genetic factors are also involved in the development of PTDM and carriers of several predisposing single nucleotide polymorphisms (SNPs) have a higher risk of PTDM (8). Candidate genetic factors connected with type 2 diabetes (T2D), genes that encode enzymes involved in the metabolism of glucose, drugs and glucose transporters, genes encoding cytokines, transcription factors, as well as genes involved in beta-cell function have been studied (2). Unfortunately, the results between different populations are inconclusive and the clinic needs to identify the carriers of pharmacogenetics variants and the genetic risk factors involved in the development of PTDM.

Most of GCs functions are triggered by a glucocorticoid receptor (GR) encoded by the NR3C1 gene. GR binds to GC response elements on the promoter of anti-inflammatory, immunosuppressive, lipid and glucose metabolism and other related genes as a transcription factor to suppress or activates their expression. This study aimed to evaluate the associations of NR3C1 gene polymorphisms with PTDM. Therefore, ER22/23EK, A3669G, BclI, and N363S polymorphisms of NR3C1 gene were studied in a group of Iranian kidney transplant recipients with and without PTDM.

Patients and Methods

Study design

The present retrospective study recruited 369 renal kidney transplants from the transplantation ward of Imam Reza hospital (Tabriz, Iran) between July 2012 to 2017. Inclusion criteria were patients over 18 years old from both genders (male/female), after at least three months of kidney transplantation, patients treated with the same treatment protocol, and fasting blood sugar of ≤99 mg/dL before transplantation. Exclusion criteria were patients with active BK and cytomegalovirus infections and patients with pre-transplant diabetes. During this study, thirty-two PTDM cases and fifty-nine non-diabetic kidney transplant patients (as a control group) were included. AR was also evaluated in the patients during the post-transplant period.

Genotyping

Blood samples were taken from all subjects in normal and non-fasting condition and kept in CBC tubes at -20°C. Genomic DNA was extracted from whole blood samples (2 mL) according to the previously reported protocol. Four variants in the NR3C1 gene including A3669G, ER22/23EK (rs6189/6190), N363S (rs6195) and BclI (rs41423247) polymorphisms were identified by polymerase chain reaction (PCR) using the designed primers (Table 1). Then, the direct sequencing of the amplified fragments was performed.

Statistical analysis

For variables with a skewed distribution, medians with interquartile ranges were employed, while continuous variables with a normal distribution were expressed as means ± standard deviations (SD). Categorical variables were presented as percentages. Analysis of the variances between qualitative variables was completed with Fisher's exact or Pearson's χ^2 tests. The IBM SPSS Statistics package version 22 (IBM Corporation, NY, USA) applied for statistical analysis. In all tests, $P<0.05$ was considered as a significance level.

Results

Patients characteristics

During July 2013-2018, 369 kidney transplantation conducted in our transplantation ward (Figure 1). In this retrospective study, 91 eligible kidney recipients were divided into two groups based on the development of diabetes after kidney transplantation; 32 PTDM patients and 59 non-diabetic patients (controls). None of the patients had a history of diabetes before kidney transplantation.

Among people with PTDM, the incidence rate of diabetes was the same in both men and women ($P=0.229$). There was a statistically significant difference in age between PTDM and control groups ($P<0.0001$). Therefore, the mean age of diabetics was higher than the mean age of non-diabetics. Furthermore, no significant difference existed between the two groups regarding body mass index (BMI) level ($P=0.501$). It was observed that the duration of dialysis was significantly different between PTDM and control groups ($P=0.001$). In the study of the two groups with the chi-square test, no statistically significant correlation was observed between the type of dialysis (hemodialysis and peritoneal dialysis) and the onset of diabetes in the PTDM group ($P=0.856$; Table 2).

The tests of between-subjects effects showed that the intragroup changes of creatinine in diabetic patients in different measurements (at discharge, three months and six months later) were statistically significant ($P=0.013$),

Table 1. The primer sequences used in the present study

Polymorphisms	Forward/ Reverse	Primers sequences
rs41423247 (BclI)	F	TCTGGAGGACAGATGTACCA
	R	CTTGCAGGAACATTTGAACGTA
rs6195 (N363S)	F	TCTGGAGGACAGATGTACCA
	R	CTTGCAGGAACATTTGAACGTA
rs6189/rs6190 (ER22/23EK)	F	AATGTGGCATGCTGAATGGG
	R	ACCCAGAAGAAAACTCCAAATCC
rs6198 (A3669G)	F	TTCCAGTTTCACCTAAGTCTCAT
	R	TGATGTTTCTCCATATTTGGCATTG

F: Forward, R: Reverse.

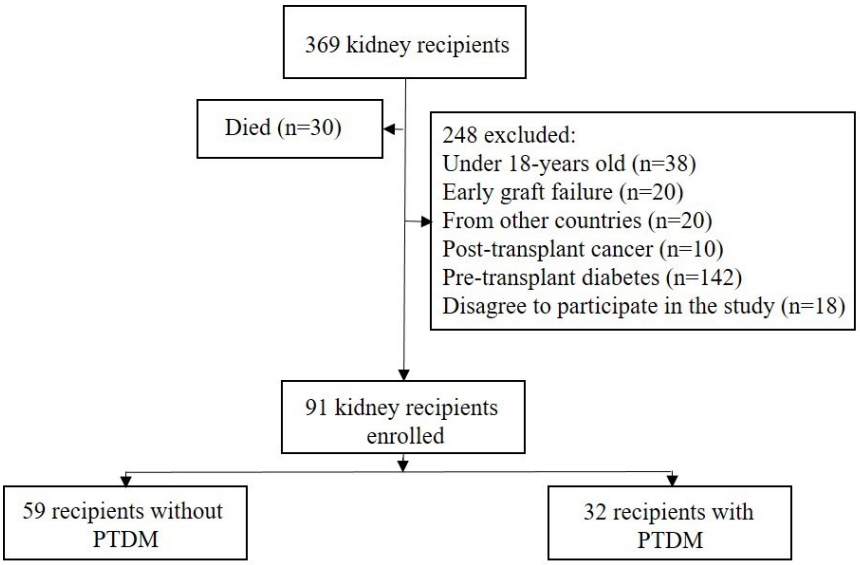

Figure 1. Patient selection flowchart of renal transplanted recipients during this study. PTDM; Post-transplant diabetes mellitus.

since the creatinine levels showed a significant increase over time. In the intergroup comparison of creatinine, no significant difference was seen between PTDM and control groups ($P=0.077$). On the other hand, the results of creatinine level analysis between PTDM and non-diabetic groups showed that the levels of creatinine at the baseline ($P=0.063$) and three months after transplantation (P= 0.538) were not statistically significant. However, the difference in serum creatinine levels between the two groups after six months of kidney transplantation was statistically significant ($P=0.023$). The mean cholesterol level in diabetic patients was higher than in the non-diabetic patients ($P=0.246$). It was also found that the mean triglyceride level in the PTDM group was higher than controls, while it was not statistically significant ($P=0.069$).

Among the subjects in both groups, 12 recipients received allografts from cadaver donors, four of which (33.3%) were positive for diabetes while no significant correlation between the living or cadaveric allografts and the risk of diabetes was detected (Fisher's exact test; $P=1$). Among the studied 91 recipients, three patients had an episode of AR that all of them developed PTDM. Consequently, a significant relationship was observed between AR and PTDM ($P=0.017$). Among patients with a family history of diabetes, twelve (60%) recipients did not develop PTDM, while eight (40%) recipients developed diabetes. The diabetic rate was 33.8% in patients without a history of diabetes (n = 24). Therefore, no significant correlation was observed between family history of diabetes and PTDM ($P=0.608$).

Likewise, there was not a significant association between the PTDM and types of administrated drugs including tacrolimus, cyclosporine and sirolimus in the studied kidney recipients (Fisher's exact test, $P=0.67$). In addition, no significant association was observed between steroids pulse administrations and PTDM while we had four (40%) non-diabetics versus six (60%) diabetics

Table 2. Basic characteristics of the studied recipients

Variables	PTDM recipients	Non-PTDM recipients	*P* value
Numbers	32	59	
Gender (female/male)	11/21	28/31	0.22
Age (years)	51.59±11.14	40.44±10.63	**<0.0001**
BMI (kg/m^2)	26.6±3.88	30.08±30.89	0.501
Cholesterol (mg/dL)	176.66±45.02	166.19±38.42	0.246
TG (mg/dL)	213.34±139.03	159.76±81.69	0.069
Creatinine (mg/dL)	1.38±0.36	1.23±0.3	0.063
Creatinine after 3 month (mg/dL)	1.4±0.44	1.33±0.38	0.538
Creatinine after 6 month (mg/dL)	1.49±041	1.3±0.35	**0.023**
Dialysis length (months)	25.5(18)	15(18)	**0.001**[a]

TG; triglycerides, BMI; body mass index, PTDM; Post-transplant diabetes mellitus. The quantity data are expressed as mean ± SD.
[a] Median (interquartile range) is presented, *P* value is based on Mann-Whitney U test.

recipients ($P=0.157$).

In the study of PTDM patients, no significant correlation between renal failure (RF) causes including polycystic kidney disease, glomerulonephritis, hypertension, urological problems and unknown causes and the onset of diabetes was seen ($P=0.269$). No significant correlation was found between the anti-thymocyte globulin (ATG) drug usage and risk of PTDM ($P=0.99$).

Associations of NR3C1 gene polymorphisms and PTDM

Among the patients included in this study, only one case with ER22 / 23EK polymorphism (rs6189 /rs6190) was observed, since this patient was negative in terms of diabetes risk. Therefore, no statistically significant correlation was observed between this polymorphism and diabetes ($P=1$). Among all patients, two cases (28.6%) with A3669G polymorphism (rs6198) were positive for diabetes and no statistically significant correlation existed between this polymorphism and diabetes ($P=1$). Eight patients (88.9%) with BclI polymorphism (rs41423247) had a negative diabetes outcome while no significant association was observed between PTDM carrier of BclI and diabetes ($P=0.152$). Additionally, regarding tacrolimus and cyclosporine consumers, no statistically significant link was detected between the studied polymorphisms and PTDM (Table 3).

The correlation between the studied polymorphisms and the incidence of diabetes was examined in transplant patients. Based on the results, the correlation coefficient between exacerbating polymorphism (A3669G) and diabetes (Phi=-0.04) indicated no significant correlation ($P=0.704$). In addition, the correlation coefficient (Phi=-0.167) showed that there was no significant correlation between the BclI polymorphism and diabetes ($P = 0.111$; Table 4).

Table 3. The results of the studied polymorphisms in kidney transplants

Polymorphisms	Diabetic patients	Non-diabetic patients	*P* value
rs41423247 (BclI)	1	8	0.152
rs6195 (N363S)	0	0	
rs6189/rs6190 (ER22/23EK)	0	1	1
rs6198 (A3669G)	2	5	1

Table 4. The correlations between the studied polymorphisms and PTDM

Polymorphisms	PTDM	*P* value
BclI	Phi= -0.04	0.704
A3669G	Phi= -0.04	0.704
N363S	Phi= -0.167	0.111

PTDM; Post-transplant diabetes mellitus.

Discussion

This study explored the associations of GR gene polymorphisms with the incidence of PTDM. We found that the four common GR gene variants were not significantly associated with PTDM.

The PTDM pathophysiology has not obviously been defined and similar to T2D, may be characterized by principally defective insulin secretion or insulin resistance, or both. High doses and long-duration of GCs therapy can cause insulin resistance and steroid diabetes (hyperglycemia) (9). A dose-dependent manner of GCs-induced insulin resistance is associated with an elevated appetite, weight gain and redistribution of body fat (10) and a grade of resistance to hypoglycemic agents (6).

The efficacy and response to GCs are highly variable between people, signifying genetic factors to have a role in GC receptor (GR) sensitivity; consequently, this sensitivity may play an essential role in the development of GC-induced PTDM. In an earlier study, about half of kidney allograft recipients cured with high-dose prednisone could develop PTDM within one-year post-transplantation (11). The GCs' diabetogenic effect is dose-dependent and a dose reduction of prednisolone from a daily mean of 16 to 9 mg could significantly elevate the sensitivity index of insulin (12). However, the exact GC-induced insulin resistance mechanisms are not fully understood. GCs can decrease the glucose transporter 2 and glucokinase expression leading to a reduction in uptake and phosphorylation of glucose, synthesis of adenosine triphosphate and influx of Ca^{2+} and consequently, reduce the secretion of insulin. On the other hand, GCs by inducing the transcription of serum and GC inducible kinase-1, upregulate the K^+ channel activity that decreases the entry of Ca^{2+} and insulin release. Additionally, GCs reduce the cyclic adenosine monophosphate and activity of protein kinase A and insulin release by increasing the expression of α_2-adrenergic receptors. Furthermore, GCs may induce cell apoptosis and decrease the islet mass, reviewed comprehensively (13).

It is reported that different polymorphisms in the NR3C1 gene are related to glucose homeostasis and different GCs sensitivity (14). A relationship between the glucose metabolism, metabolic syndrome manifestations and GR gene polymorphisms had been raveled, where homozygous carriers of GR BclI variant had higher total body fatness that contributes to elevated insulin resistance. This result indicates that even a GR genetic variation altering the GC sensitivity can exert metabolic effects (15). A statistically significant link was also found between BclI polymorphism and reduced glucose metabolism in Addison's disease cases (16). Likewise, among carriers of the BclI homozygous variant, a statistically significant rise was observed in fasting plasma glucose, insulin, BMI, body weight, and abdominal obesity in men in a study with a 5-year follow-up (17). In renal recipients with the Bcl1 G allele, as a risk factor, the prevalence of dyslipidemia was significantly higher than carriers of the CC genotype (18). In our patients, no significant association was

observed between Bcl1 polymorphism and PTDM. In Turkish patients, BclI GG genotypes were associated with metabolic syndrome (19). None of the NR3C1 gene polymorphisms was linked to insulin sensitivity among German and Dutch volunteers (20). Likewise, in our study, no significant relationship was found between the studied polymorphism and the development of diabetes after transplantation.

N363S variant is another well-studied polymorphism of the NR3C1 gene located in exon 2 (codon 363) that results from asparagine substitution by serine. N363S polymorphism is linked with a higher plasma glucose level, insulin response to dexamethasone and sensitivity to GCs (21) and N363S carriers had significantly higher BMI (22). However, some other studies recommended that the N363S variant is not associated with T2D (23), which is in agreement with our findings.

In the transactivation domain of the NR3C1 gene, the ER22/23EK polymorphism is located and the SNPs are identified in both of 22 and 23 codons. These SNPs are reported to be connected with relative GC resistance and reduced levels of insulin resistance (21). Male carriers of ER22/23EK had an increased insulin sensitivity, lower C-reactive protein, total and low-density lipoprotein cholesterol levels, and also fasting insulin (24). Collectively, in contrast to the others, ER22/23EK polymorphism is connected with a beneficial metabolic profile, it lowers insulin resistance level, decreases cardiovascular risk and prolongs the lifetime (21).

The A3669G allele located in the end of exon 9 beta (β) by increasing the stability of GR-β mRNA and its protein expression, inhibits the transcriptional activity of GRα, resulting in GC insensitivity. The A3669G polymorphism might lessen the adverse effects of GCs on lipid metabolism and fat distribution (25). In patients with Cushing's syndrome, it is reported that the A3669G polymorphism has a protective role; reducing the effects of excess GC on glucose metabolism by reducing the diabetes risk (26). In this study, only one non-diabetic recipient carried this allele and the presence of this polymorphism was not associated with PTDM.

Beyond inhibiting the PTDM development, the effective treatments may prevent graft rejection, cardiovascular complications and improve allograft survival. This study could not find any statistically significant association between the NR3C1 gene polymorphisms and PTDM in renal transplant recipients.

Conclusion

In conclusion, taking into account that pharmacogenetics can help the clinic to develop the personalized treatment, we studied the polymorphisms of the GR gene in a group of kidney transplant recipients who developed PTDM and those who did not. These results suggested that the GR polymorphisms were not associated with PTDM. Moreover, there was a significant association between PTDM and AR.

Limitations of the study

It is important to identify the carriers of genetic factors that predispose recipients to develop PTDM and to decide the proper immunosuppressive therapy. Further studies are needed to confirm the results. Identification of the predisposing genetic factors is needed to identify the recipients with a higher risk to develop diabetes after transplantation.

Authors' contribution

JE and SA developed the idea, selected and followed up the cases, and designed the study. TM and BN performed the sampling. SZV, RM and MJN prepared the draft of the manuscript and revised it. All authors read and revised the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study was approved by the Tabriz University of Medical Sciences, Tabriz, Iran (Ethics committee code: IR.TBZMED.REC.1397.219). Written informed consent forms were signed by all participants. This study was extracted from Fellowship thesis of Taraneh Majidi at the Kidney Research Center at this university (Thesis # 59597). Additionally, the authors completely have observed the ethical issues including data fabrication, falsification, plagiarism, double publication misconduct, or submission and redundancy.

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