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Importance of Gene Polymorphisms in Renal Transplant Patients to Prevent Post Transplant Diabetes

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Abstract

Objective: Post transplantation diabetes mellitus (PTDM) is a major complication associated with kidney transplantation due to the immunosuppressive therapy. Defects in insulin secretion play a pivotal role in the pathogenesis of PTDM and zinc also playsan important role in all process of insulin trafficking, i.e. synthesis, storage and secretion. Gene polymorphisms in the transcription factor 7-like 2 (TCF7L2) and zinc transporter protein member 8(SLC30A8) was reported to be associated with type 2 diabetes, possibly associated with an insulin secretion defect. The aim of this study was to investigate the association between genetic variations in TCF7L2, SLC30A8 and PTDM in renal allograft recipients.

Method: PCR and RFLP based genotyping of TCF7L2 (rs#7903146) and SLC30A8 (rs#13266634) polymorphisms were carried out in 364 individuals which included patients who had undergone renal transplant (n=140), 42 of which developed post-transplant diabetes mellitus and healthy control volunteers (n=224). DNA was isolated from peripheral blood and TCF7L2 and SLC30A8 gene analysis was carried out for genotypes and alleles.

Results: In the present study the genotype distribution of TCF7L2 TT genotype (26.1%) was high in cases when compare to Controls (8.2%) and the incidence of PTDM was significantly higher in patients with T allele and TT genotype (OR 2.315, 95% CI=1.466-3.656, p=0.0003 and OR 2.403, 95%, CI=1.212-4.766, p=0.01) respectively. Whereas SLC30A8 TT genotype (14.2%) distribution was also higher in patients when compared to controls (4.2%), PTDM incidence also showed significant association with T allele and TT (OR 3.057, 95%, CI=1.89-4.941, p<0.0001 and OR=3.929, 95%, CI=2.085-7.612, p<0.0001).

Discussion: TCF7L2 and SLC30A8 polymorphisms could be used as biomarkers to identify individuals at high risk of developing PTDM, it would be a valuable asset in selecting appropriate immunosuppressive regimens for individuals undergoing transplant. Present study shows that importance of these polymorphisms in increasing the risk of PTDM in patients with ESRD belonging to the Asian Indian population.

Keywords: Diabetes; Renal transplant; PTDM; TCF7L2, SLC30A8; Gene polymorphism

Introduction

India has the greatest number of diabetic individuals in any single country. Prevalence of Type 2 diabetes (T2DM) is reaching epidemic proportions and other types of diabetes like Post transplantation diabetes mellitus (PTDM) add to this load. It has been reported that the gene polymorphisms associated with complex diseases in Indians may be different from that reported for other ethnic groups [1].

Post transplantation diabetes mellitus (PTDM) is an important metabolic complication after transplant which is associated with the use of immunosuppressive therapy. The incidence of PTDM ranges from 2 to 53% [2]. Various risk factors for the development of PTDM have been described which include obesity, family history of T2DM, polycystic kidney disease, corticosteroid dose and type of immunosuppressant therapy followed after organ transplantation [3]. Immunosuppressive drugs contribute to the risk for NODAT by causing insulin resistance (corticosteroids) and reducing insulin secretion (mainly tacrolimus) [4]. Identifying individuals at high risk of any form of diabetes is beneficial for preventing and improving long-term patient outcome by allowing personalized management [5].

Hence in the present study two gene polymorphisms were evaluated in renal transplant individuals with or with Post transplant diabetes mellitus and compared with healthy controls. The candidate genes selected for the study were TCF7L2 and SLC30A8 polymorphisms in these two genes are known to be associated with T2DM.

TCF7L2 protein is a member of a T-cell transcription factor family that plays a critical role in the regulation of cell proliferation and differentiation through the Wnt signaling pathway. TCF7L2 is also implicated in the development and maturation of the pancreas, including the islets of Langerhans. It has also been discovered that TCF7L2 exerts its influence through an impairment of insulin secretion. This impairment was reportedly due to a functional defect in the glucagon-like peptide-1 (GLP-1) signaling in β-cells and not due to defective/failing GLP-1 secretion [6]. TCF7L2 might also impact β-cell function both directly through modulating β-cell response to glucose and indirectly by modulating insulin action or secretion [7]. The variants of TCF7L2 that have been observed to be associated with type 2 diabetes [8].

A genome-wide association study identified the SLC30A8 rs13266634 polymorphism encoding an Arg325Trp polymorphism in

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the zinc transporter protein member 8 (ZnT-8) to be associated with T2DM [9]. SLC30A8 gene is expressed predominantly in pancreatic β-cell and transports zinc from cytoplasm into insulin secretary vesicles [10], in which insulin is stored as a solid hexamer bound with two Zn^{2+} ions before secretion [11-13]. Zinc plays an important role in all processes of insulin trafficking, i.e. synthesis, storage, and secretion [14], the variations in SLC30A8 may affect these processes.

The aim of the study was to evaluate the association of TCF7L2 (rs7903146) and SLC30A8 (rs13266634) polymorphisms in renal transplant individuals with (diabetic) or without PTDM (non-diabetic) in an Asian Indian population.

Methodology

Subjects

The present study was carried out in 364 Asian Indian individuals from a cosmopolitan city Hyderabad, located in South India.

140 unrelated non-diabetic end stage renal disease (ESRD) patients who had undergone renal transplant and were on immunosuppressive therapy (Cyclosporine (CsA) and Tacrolimus (Tac)) for more than three months, the patients were on routine follow up and were monitored by senior nephrologists periodically for renal function as per the hospital protocol. 42 of the renal transplant recipients whom developed PTDM based on the American Diabetes Association (ADA) were selected. Clinical data, personal and family history were recorded in a well-designed proforma. The demographic profiles of the renal transplant recipients are given in Table 1.

The control group (n=224) consisted of healthy volunteers, above the age of 40 years without either type 1 and 2 diabetes and who had a normal FBS and had no history or renal disease. The study was approved by the Institutional Ethics Committees.

Sample

2 ml of peripheral blood was obtained from all the individuals included in the study. Detailed clinical and family history, along with a three generation pedigree was collected in a well-designed proforma.

S.No	Demographic details	No of individuals (Range in years)
	TCF7L2 Gene	**SLC30A8 Gene**
1	Renal Transplant recipients	140
2	Males/Females	105/35
3	Age (years) : a) Males : Mean ± SD b) Females : Mean ± SD	 40.09 ± 10.7 (13 – 63) 40.52 ± 9.59 (21- 63)
4	Weight (Kgs) : a) Males : Mean ± SD b) Females : Mean ± SD	 65.1 ± 13.01 (36 – 108) 67.06 ± 12.09 (38 – 90)
5	Sample collected after Transplant (months) :Mean ± SD	20.4 ± 15.3 (03 – 36)
6	Immunosuppressive therapy: a) CsA b) Tac	 80 (57.1%) 60 (42.9%)
7	Diabetes status a) PTDM b) Non PTDM	 42 (30%) 98 (70%)

Table 1: Demographic profile of patients with ESRD-T.

Isolation of DNA and genotype analysis

Genomic DNA was isolated from the peripheral blood of individuals according to the method routinely used in our group (Chava et al. 2011). DNA was stored at −80°C until processed. Genotyping for the TCF7L2 and SLC30A8 polymorphisms were performed by Polymerase chain reaction (PCR) using a thermal cycler (Applied biosystem, USA). In brief, a 50 µl PCR reaction containing, 5 µl of 10X tris buffer (cat#105878, Banglore Gene, Banglore, India), 4 µl l of $Mgcl_2$ (Conc: 25 mM, cat#METB5 Banglore Gene, Banglore, India), 1 µl of each dNTP (Conc: 10 mM, cat# Fermentas, Hannover, MD, USA), 1 µl of forward and reverse primers at a final conc of 10 pmol each primer (Table 2). The primers were synthesized by Bioserve biotechnology, (Hyderabad, India), 2.5 units of Taq polymerase (cat# MME27, Banglore Gene, Banglore, India) and were based on published paper.

A three step PCR for TCF7L2 gene was carried out with slight modifications of the method published by us [15]. Initial denaturation at 94°C for 5 minutes was followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds for TCF7L2 gene and 52°C for 30 seconds for SLC30A8 gene, extension at 72°C for 45 seconds, final extension at 72°C for 5 minutes. The amplified PCR products of TCF7L2 gene was digested with RsaI (cat# ER 1121, MBI Fermentas, Hannover, MD, USA), for detecting the rs7903146 (C/T) and Hpa II (cat# FD 0514, MBI Fermentas, Hannover, MD, USA), enzyme is used for digesting the PCR products of SLC30A8 rs13266634 (C/T) polymorphisms in a total volume of 20 µl for 2 hours at 37°C, and subsequently digested samples were loaded on 2% Agarose gel followed by horizontal electrophoresis. Later Bands were analyzed and imaged by gel documentation system along with the DNA Ladder (UV I Tech documentation system, Cambridge, UK).

Statistics

Genotype and allele frequencies were calculated for the described SNPs. The groups were compared using the $\chi 2$ test to analyze the statistical significance of the difference in allelic distribution of various polymorphisms in patients and controls. Values of $p<0.05$ were considered statistically significant. Odds ratio was performed using MedCalc for Windows, version 7.4.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

A total of 364 include 224 healthy controls and 140 ESRD individuals were included in the study. These ESRD patients' clinical characteristics are given in Table 1. The mean age of ESRD male patients were 40.09 ± 10.7 years (age group 18-63 years) and 40.52 ± 9.59 years for female ESRD patients are in the age group between 21-63 years. Patients with ESRD received the RT and were on immunosuppressive drugs, 80 (57.1%) of them were on cyclosporine (CsA) medication and 60 (42.9%) of them were on Tacrolimus (Tac). The mean weight of the males at the time of transplant was 65.1 ± 13.01 kgs and females were 67.06 ± 12.09 kgs. Samples were collected between 3-36 months after transplant i.e. at

Gene	Snp	Rs no	Forward primer	Reverse primer	Fragment Pcr product	Annealing temp	Enzyme
TCF7L2	INTRON 3	rs7903146	CCTAGTTAT CTGACATTGACT	GAGAGCTA AGCACTTTTTAGGTA	188bp	60°C	RsaI
SLC30A8	EXON 8	rs13266634	GAAGTTGGA GTCAGAGCAGTC	TGGCCTGTC AAATTTGGGAA	256bp	52°C	HpaII

Table 2: List of Primer Sequence, Region Amplified, Amplicon Size, Detection Method and Annealing Temperature.

a mean time of 20.4 ± 15.3 months. Subsequently some of the patients developed Post Transplant Diabetes Mellitus (PTDM), these were categorized based on ADA criteria. When the renal transplant patients were categorized as PTDM and Non-PTDM based on diabetes status by biochemical tests, it was observed that 30% of the renal transplant recipients developed PTDM [15].

TCF7L2 rs7903146

The 188bp PCR product obtained on digesting with RsaI restriction enzyme gave fragments of 158/30bp indicating CC, 188/158/30bp indicating CT and 188bp indicating TT genotype of the TCF7L2 polymorphism.

TCF7L2 genotypes distribution was (31% of CC, 42.8% CT and 26.1% TT) in cases with PTDM which was significantly different from controls (51.8% of CC, 39.8% CT and 8.2% TT) (Table 3). The TT genotype was high in PTDM cases (26.1%), when compared to controls (8.2%). PTDM showed a significant association with TT genotype and T allele (OR=2.403, 95% CI 1.211-4.766, p=0.012 & OR=2.315, 95% CI 1.466 – 3.656, p=0.0003) (Table 3a), respectively.

SLC30A8 rs13466632

256bp PCR product of SLC30A8 was digested with HpaII restriction enzyme to give 176/80bp indicating CC, 256/176/80bp indicating CT and 256bp indicating TT genotypes.

The overall genotype frequency in PTDM was CC, 38%, CT, 47.6% and TT, 14.2% (Table 3). The TT genotype was found to be more in PTDM (20.4%). The genotype distribution in PTDM T allele (p<0.0001, OR-3.0574, (95%CI=1. 98-4.94) and when we compared the TT+CT Vs CC (p<0.0001, OR-3.9295, (95%CI=2.08-7.61) (Table 3b), the TT genotype was found to significantly associated when compared with the controls.

Discussion

Diabetes can be defined as a state of chronic hyperglycemia sufficient to cause long-term damage to specific tissues, notably the retina, kidneys, nerves and arteries [16]. It is the result of decreased insulin signaling and the inability of insulin sensitive cells to take up glucose. Therefore, hyperglycemia (non-fasting plasma glucose levels greater or equal to 200 mg/dl or 11.1 mmol/L) [17] is one of the criteria used in the diagnosis of diabetes.

	TCF7L2 Gene					SLC30A8 Gene				
	CC	CT	TT	C	T	CC	CT	TT	C	T
Controls N=376	195 (51.8)	150 (39.8)	31 (8.2)	540 (71.8)	212 (28.1)	266 (70.7)	94 (25)	16 (4.2)	626 (83.2)	126 (16.8)
PTDM N=42	13 (31)	18 (42.8)	11 (26.1)	44 (52.3)	40 (47.6)	16 (38)	20 (47.6)	06 (14.2)	52 (61.9)	32 (38)

Table 3: Genotype and allele frequency distribution of TCF7L2, SLC30A8.

S.No	Genotypes	PTDM
1	CC+ CT Vs TT	OR=0.253, 95% CI=0.116-0.552, p=0.002.
2	CT Vs CC + TT	OR=1.13, 95% CI=0.593-2.154, p=0.71
3	TT+CT Vs CC	OR=2.4033, 95% CI=1.212-4.766, p=0.01
4	T Vs C	OR=2.3156, 95% CI=1.4666-3.656, p=0.0003

Table 3a: Statistical Analysis for TCF7l2 Gene.

S.No	Genotypes	PTDM
1	CC+ CT Vs TT	OR=0.267, 95% CI=0.098-0.724, p=0.001
2	CT Vs CC + TT	OR=2.727, 95% CI=1.425-5.219, p=0.001
3	TT+CT Vs CC	OR=3.929, 95% CI=2.085-7.6122, p<0.0001
4	T Vs C	OR=3.0574, 95% CI=1.8916-4.9418, p<0.0001

Table 3b: Statistical Analysis for SLC30A8 Gene.

India has the greatest number of people with diabetes mellitus in the world [18]. Although the association of variants of the TCF7L2 gene and T2DM has been investigated in several studies including those from India, there are no studies of this TCF7L2 variant in relation to PTDM from Indian population best of our knowledge.

TCF7L2 is a novel T2DM susceptibility gene that confers up to a ~2 fold increase in the risk of developing diabetes. The TCF7L2 polymorphism is considered to be the most powerfully associated polymorphism with diabetes to date [19,20]. Our data suggest that TCF7L2 (rs#7903146) polymorphism plays an important role in the development of PTDM.

TCF7L2 gene is expressed in human pancreas, suggesting direct effects on normal β-cell insulin secretion or, more likely, β-cell growth and differentiation from the precursor cells [21]. A report suggests that this genetic variation increases TCF7L2 expression in the β-cell, reducing insulin secretion and predisposing the subject to diabetes [22].

Florez et al. reported that rs 7903146 polymorphism in the TCF7L2 gene was associated with an increased risk of developing T2DM [23]. Subsequent studies confirmed the association of this polymorphism in multi ethnic groups [19-21,24,25]. A large meta-analysis from 35 studies concerning the IVS3C>T polymorphism which include 33,135 cases of T2DM and 36,316 controls, showed a notable association of this polymorphism with T2DM with the CT heterozygotes carrying just over a 1.4-fold increased risk of T2DM, and TT homozygous variants a 2.0-fold increase in T2DM risk when compared with CC homozygotes [26].

Various risk factors for the development of PTDM have been studied, but there are few reports on its genetic risks. Many recent studies have suggested that TCF7L2 may play a role in insulin secretion [24]. Therefore, we investigated the genetic influence of the *TCF7L2* polymorphism on the development of PTDM in a renal transplant cohort and showed that this variant is associated with the risk of PTDM. A study from Korea [27] assessed the role of TCF7L2 variants in causing PTDM in renal allograft recipients. Of the three variants evaluated rs7903146 genetic variation was associated with an increased risk of PTDM. The TT genotype was completely absent in the cases and controls, however in our study 36.3% of the PTDM showed the TT genotype.

Evidence from GWAS implicates SLC30A8, located at chromosome position 8q24.11, in T2DM predisposition. Replication studies from different ethnic backgrounds have confirmed this association. SLC30A8 encodes a zinc transporter expressed solely in the secretary vesicles of beta-cells and is thus implicated in the final stages of insulin biosynthesis, which involve co crystallization with zinc. Over expression of SLC30A8 in insulinoma (INS- 1E) cells enhanced glucose-induced insulin secretion.

The above two studies are done in the North Indian samples. But in our study South Asian Indian samples were included and to the best of our knowledge this is the first study from India to study in all different forms of diabetes.

It has been reported that the genetic polymorphism of SLC30A8 was associated with impaired proinsulin conversion involved in the production and secretion pathway. Fu et al., found that reduced ZnT-8 expression in cultured pancreatic β cells gives rise to reduced insulin

response to hyperglycemia and that SLC30A8 polymorphism could affect insulin secretion and glycemic response. Another two studies indicate that patients with the rs13266634 C allele showed decreased first-phase insulin release following an intravenously administered glucose load. Furthermore, it has been found that the C alleles of rs13266634 at SLC30A8 were associated with increased FPG and decreased insulin during the oral glucose tolerance test. An investigation also showed SNP rs13266634 increased the risk for T2DM by 1.24-fold in Chinese Han population. Qiong Huang et al. studies showed that SLC30A8 rs13266634 and rs16889462 polymorphisms were associated with repaglinide therapeutic efficacy in Chinese T2DM patients.

A study from Korea published a paper on SLC30A8 gene polymorphism studies in PTDM in Renal allograft recipients in which they had included 624 Renal allograft recipients among them 174 patients developed PTDM. The prevalence of PTDM was 33.8% in patients carrying the R/R genotype, 26.8% in patients with the R/W genotype, and 19.8% in patients with the W/W genotype. These data provide evidence that the SLC30A8 rs13266634 gene variation is associated with protection from the development of PTDM in renal allograft recipients [28].

Conclusion

In conclusion, our study suggests that TCF7L2 and SLC30A8 gene polymorphisms are associated with PTDM in South Indian Asians. Both these genes involved in β-cell dysfunction. These polymorphisms are important susceptibility markers for assessing risk of diabetes status in renal transplant individuals.

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