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Original Article

Association of GLUT-1 (XbaI) Gene Polymorphism in Type 2 Diabetes Mellitus and Diabetes Nephropathy Patients of North Indian Population

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ABSTRACT: Diabetic nephropathy (DN) is a chronic complication of both type 1 and type 2 diabetes. However, there is still inadequate understanding of the exact mechanism related to progressive diabetic renal disease. The GLUT-1 XbaI gene polymorphism in the glucose transporter has been suggested in the development of DN. However, its association with T2DM and DN is controversial and has not been established in different ethnic populations. To enhance the understanding of GLUT-1 XbaI gene polymorphism in the context of T2DM and DN. We investigated the possible genetic association of GLUT-1 XbaI polymorphism with T2DM and DN in North Indian population. 100 T2DM patients and 100 patients of DN with 100 healthy controls were included in the study. GLUT-1 XbaI polymorphism was determined by PCR (polymerase chain reaction) and RFLP (restriction fragment length polymorphism). The obtained data showed no significant association between GLUT-1 XbaI gene polymorphism with T2DM and DN leading us to conclude that GLUT-1 XbaI gene polymorphism may not have major effects on T2DM and DN in North Indian population.

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INTRODUCTION

Approximately, 150 million people are globally affected by type-2 diabetes mellitus (T2DM), and this number is expected to double in the coming next 20 years. Until recently, T2DM was considered to be a disease confined to adulthood, rarely observed in persons under the age of 50, but clinically based reports and regional studies suggests that T2DM in children and adolescents, although still rare, is more frequently being diagnosed [1]. Diabetic nephropathy (DN) is a most important long term chronic microangiopathic problems of diabetes mellitus, leading to end-stage renal disease [2].

It is defined by episode of albuminuria and/or proteinuria in a diabetic patient with no evidence of nondiabetic renal conditions [3]. It is considered also by increased arterial blood pressure, decrease in glomerular filtration rate (GFR), and high risk of cardiovascular morbidity and mortality [4].

Glucose transporter 1 (GLUT-1) is the most important facilitative glucose transporter in glomerular mesangial cells [5]. Glucose transporters (GLUTs) a family of facilitative transporters classified into three classes [6]. GLUT-1 is a member of class 1 and it is extremely expressed in the glomeruli, mesangial, endothelial cells and podocytes [7].

GLUT-1 gene (SLC2A1) (rs841853) is situated on chromosome 1p34.2, and it contains 10 exons and 9 introns [8, 9]. GLUT-1 play a vital role in DN pathogenesis because up stream expression of GLUT-1 in glomerular mesangial cells is expected to augment the basal glucose uptake [10], and trigger the cellular pathways involved in cellular growth and in accumulation of the extracellular matrix [11]. The expression and activity of mesangial GLUT-1 in diabetic patients comprise large individual variability attributed mainly to genetic causes. This viewpoint it becomes clear why only a definite group of diabetics are prone to the development of DN, and could also elucidate the cause for the weak correlation between glycemic control and progression of nephropathy in a subset of diabetics [12].

Therefore, the present study was carried out to investigate the GLUT-1 gene polymorphism in T2DM and Diabetic nephropathy patients of North Indian Population.

MATERIALS AND METHODS

In present study, we recruited 300 Subjects.200 patients with type 2 diabetes mellitus with nephropathy and without nephropathy and 100 healthy controls for the study. Decisive factors such as age, body mass index (BMI), HbA1c, fasting blood sugar (FBS) and post prandial blood glucose (PPBS) level, urea level, serum creatinine, lipid profiles, Uric Acid, total protein, albumin protein and urine albumin test. All the control subjects were recruited based on the absence of any history of kidney disease and the presence of normal serum urea, serum creatinine level, blood glucose profile, Serum lipid Profile, Uric Acid total protein, albumin protein and urine albumin test. To determine the profile, 4–5 ml of blood was collected.

All biochemical analyses were carried out using the Vitros 250 Autoanalyser (Johnson & Johnson, Germany) using kits. The study protocol was approved by the institutional ethics committee of King George's Medical University, (KGMU) Lucknow, India.

GLUT-1 Genotyping:

Peripheral blood for genotyping was collected in EDTA vials and DNA was extracted by using the salting-out method. The genomic DNA samples were amplified by polymerase chain reaction (PCR). For PCR amplification a forward primer 5'-TGTGCAACCCATGAGCTAA – 3' and reverse primer 5'-CCTGGTCTCATCTGGATTCT - 3' were applied. A 1.1 kb DNA fragment of GLUT-1 gene was obtained. To PCR product were generated in the final volume of 10 µl containing 1 µl genomic DNA, 5 µl PCR master mix and 4 µl H_2O was used to obtain PCR products. The PCR protocol was: 940 C for 4 min followed by 35 cycles of 94^0C for 35 sec, 57 ^{0}C for 35 sec 72 ^{0}C for 35 sec and final extension at 72 ^{0}C for 7 min. The PCR products were digested with XbaI restriction enzyme (New England Biolabs Inc, Ipswich, MA, USA) and electrophoresed on a 2% agarose gel. RFLP of XbaI was detected by ethidium bromide staining. A 1.1 kb band corresponded to the XbaI (-) allele, and a 0.9 and 0.2 kb bands corresponded to the XbaI (+) allele (Figure 1).

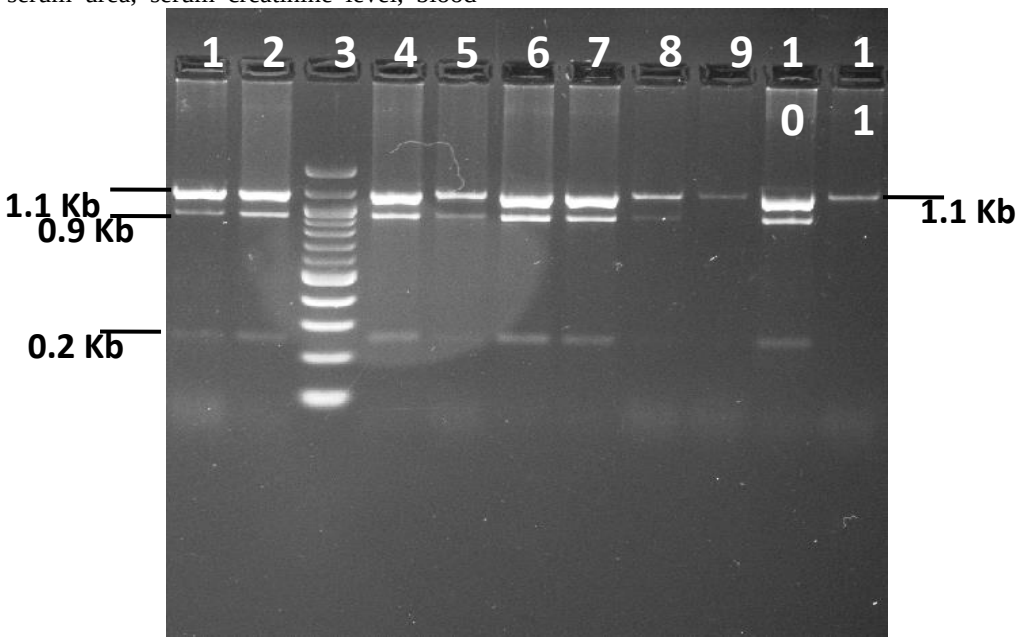

Figure 1: XbaI polymorphism of human GLUT-1 gene detected by PCR- RFLP

Lanes 1, 2,4,5,6,7,8 and 10 are the XbaI (+/-) genotype and Lane 9 and 11 are the XbaI (--)

Statistical analysis:

Demographic and clinical data are reported as mean ± standard deviation (SD). Statistical comparisons between group means were done by the unpaired student t- test. Glut-1 genotype and allele frequencies of the T2DM and DN patients were compared to the respective frequencies of the control groups using the chi-square test. The odds ratios (ORs), together with the 95% confidence interval (CI), comparing the allelic distribution in the study groups were also calculated. Two-tailed P-value <0.05 were considered significant.

RESULTS

The baseline characteristics of Type-2 diabetes, diabetic nephropathy and healthy controls are presented in table 1. In this study, we observed significantly age in diabetic nephropathy patients compared with controls.

Table 1: Demographic data and biochemical parameter of study subjects

Variable	Control	DM	DN
Age (Years)	50.82±10.12	53.46±9.44	57.74±9.60*
BMI (kg/mt^2)	26.14±4.41	24.11±5.69*	21.93±4.03*
Duration (Years)	00	9.408±3.29	11.27±6.74*
HbA1C (%)	5.41±0.59	9.72±3.08**	8.36±2.49**
Fasting Sugar (mg/dl)	94.60±8.93	176.22±85.2**	186.52±74.6**
PPBS (mg/dl)	136.7±13.9	312.6±124.4	271.06±158.3
Cholesterol (mg/dl)	148.12±29.93	147.38±47.24	142.48±44.97
TG (mg/dl)	132.7±44.40	202.2±149.3**	164.73±113.6**
HDL (mg/dl)	43.51±13.82	39.30±25.74	36.90±23.97*
LDL (mg/dl)	88.46±33.40	79.39±36.51	71.21±41.0**
VLDL (mg/dl)	26.88±9.64	35.97±27.090 ***	32.29±22.06 *
Urea (mg/dl)	31.47±17.44	34.10±23.96	118.58±63.39***
Creatinine (mg/dl)	0.816±0.127	0.726±0.184**	4.61±3.51**
Total Protein (gm/dl)	7.17±0.74	6.71±1.06***	6.40±0.84***
Albumin (gm/dl)	4.02±0.569	3.57±0.689**	3.37±3.15*
Uric Acid (mg/dl)	4.49±0.985	4.83±1.05*	7.46±2.31**
Urine Protein (mg/day)		7.85±6.8	155.26±83.50

All data are shown as mean ± SD; p< 0.05 is considered statistically significant.

Fasting sugar, RBS, HbA1C, TG and Uric acid were significantly higher level found in T2DM and Diabetic nephropathy patients when compared with controls. Moreover, Creatinine was also found significantly increased level in diabetic nephropathy patents and decrease level in T2DM patients compared with controls. Meanwhile, LDL, HDL and albumin level were significantly decrease in diabetic nephropathy patients compared with controls and these levels also lower in T2DM patients but did not reach any significantly level (Table 1). The distribution of genotypes and alleles of GLUT-1 gene polymorphism in Type-2 diabetes (Patients) and healthy population (controls) is shown in table 2. Digestion of the amplification products with the restriction endonuclease Xba-I yielded fragments of either 1.1 kb or 0.9 and 0.2 kb in the presence of the polymorphic Xba-I restriction site, and these generated GLUT1 genotypes of 1.1 0.9/0.2 1.1 or 0.9/0.2, as previously described [11]. We did not observe any ++ genotype in the studied population neither in healthy controls and both patients' groups (T2DM and D N) The frequencies of XbaI (-/-) genotype were 12% and 6% found healthy controls and Type-2 diabetes (Patients). The distribution of XbaI (+/-) genotypes were 6% and 94 % in healthy controls and T2DM, respectively and they did not reach statistically significant. (p<0.2, OR=2.136, 95% CI: 0.7685-5.939). The allele frequency of XbaI – were 112 (56%) and 106 (53%) in controls and T2DM, respectively, while allele frequency of + were 88 (44%) and 94 (47%) controls and T2DM, respectively. These alleles frequency found statistically not significant. (P<0. 0.6, OR=1.129, 95% 0.7612-1.673) (Table 2).

Table 2: Genotype and allele frequency of XbaI polymorphism of GLUT1 in healthy controls and T2DM patients

Genotype	Control N=100 (%)	T2DM N=100 (%)	OR (95% CI)	P- Value
--	12 (12%)	06 (06%)	1	-
+-	88 (88%)	94 (94%)	2.136 (0.7685-5.939)	0.2
++	00 (0%)	00 (0%)	-	-
Allele				
-	112 (56%)	106 (53%)	1	-
+	88 (44%)	94 (47%)	1.129 (0.7612-1.673)	0.6

All data are shown as mean ± SD; p< 0.05 is considered statistically significant

The distribution of genotypes and alleles of GLUT-1 gene polymorphism in Diabetic nephropathy (Patients) and healthy population (controls) is shown in table 3. The distribution of XbaI (-/-) genotype were 12% and 11% found healthy controls and diabetic nephropathy (Patients). The distributions of XbaI (+/-) genotype were 88% and 89% respectively, in healthy controls and diabetic nephropathy (Patients), respectively. The genotypes distribution did not show statistically significant. (p<0.8, OR=1.103, 95% CI: 0.4623-2.633). The allele frequency of XbaI – and + are similar in Diabetic nephropathy (Patients) and healthy controls. We analyzed the studied demographic data and biochemical parameters according to genotypes of XbaI polymorphism in type 2 diabetics and diabetic nephropathy patients but no significant difference was observed (Table 4, 5).

Table 3: Genotype and allele frequency of XbaI polymorphism of GLUT1 in healthy controls and DN patients.

Genotype	Control N=100 (%)	DN N=100 (%)	OR (95% CI)	P- Value
--	12 (12%)	11 (11%)	1	-
+-	88 (88%)	89 (89%)	1.103 (0.4623-2.633)	0.8
++	00 (0%)	00 (0%)	-	-
Allele				
-	112 (56%)	111 (55.5%)	1	-
+	88 (44%)	89 (44.5%)	1.020 (0.6877-1.514)	0.9

All data are shown as mean ± SD; p< 0.05 is considered statistically significant

Table 4: Demographic data and biochemical parameters according to genotypes of XbaI polymorphism in T2DM.

Variables	-/- (N=6)	+/-(N=94)	+/+(N=0)	p value
Age (Years)	52.02±10.38	53.90±8.83		0.347
Duration (Years)	9.27±3.63	9.42±3.14		0.873
BMI (kg/mt^2)	23.98±5.65	24.07±5.82		0.599
HbA1C (%)	9.51±2.64	9.81±3.28		0.640
FBS (mg/dl)	168.5±76.1	182.4±91.4		0.666
PPBS (mg/dl)	253.8±91.7	271.5±115.2		0.692
HDL (mg/dl)	38.59±27.61	39.59±25.08		0.768
LDL (mg/dl)	84.22±42.57	75.42±32.09		0.390
VLDL (mg/dl)	34.73±29.8	35.94±27.7		0.579
TG (mg/dl)	200.4±152.8	200.8±148.3		0.751
Cholesterol (mg/dl)	153.05±54.05	142.4±42.30		0.366
Urea (mg/dl)	29.89±15.5	35.89±25.67		0.0573
Creatinine (mg/dl)	0.727±0.181	0.728±0.189		0.877
Uric Acid (mg/dl)	4.60±1.75	4.98±0.940		0.207
Total Protein (gm/dl)	6.63±1.05	6.65±0.972		0.810
Albumin Protein (gm/dl)	3.66±0.714	3.53±0.672		0.407
Urine Protein(mg/day)	8.70±5.55	11.83±7.91		

All data are shown as mean ± SD; p< 0.05 is considered statistically significant

Table 5: Demographic data and biochemical parameters according to genotypes of XbaI polymorphism in DN

Variables	-/ (N=11)	+/-(N=89)	+/+(N=00)	p value
Age (Years)	57.53±8.32	57.53±10.09		0.357
Duration (Years)	11.23±7.48	11.14±5.42		0.816
BMI (kg/mt^2)	21.48±4.14	22.63±3.97		0.381
HbA1C (%)	8.45±2.60	8.33±2.39		0.672
FBS (mg/dl)	195.8±81.28	171.2±62.18		0.290
PPBS (mg/dl)	263.9±93.6	234.2±64.9		0.319
HDL (mg/dl)	38.9±25.8	32.46±20.1		0.499
LDL (mg/dl)	71.8±44.8	68.3±36.5		0.871
VLDL (mg/dl)	30.8±16.7	36.6±32.6		0.522
TG (mg/dl)	157.2±83.3	182.9±63.4		0.573
Cholesterol (mg/dl)	147.0±43.1	131.5±47.7		0.308
Urea (mg/dl)	128.0±66.6	100.2±58.8		0.166
Creatinine (mg/dl)	4.92±3.75	4.15±3.12		0.623
Uric Acid (mg/dl)	7.66±2.53	7.13±1.96		0.735
Total Protein (gm/dl)	6.35±0.866	6.48±0.820		0.713
Albumin Protein (gm/dl)	3.50±3.92	4.91±9.46		0.597
Urine Protein (mg/day)	134.3±79.4	147.5±81.8		0.007**

All data are shown as mean ± SD; p< 0.05 is considered statistically significant

DISCUSSION

The glucose transporter GLUT-1 is the most important representative of the family of facilitative glucose transporters in glomerular mesangial cells. Its expression on the cell surface is possibly pivotal in raising intracellular glucose levels in diabetes mellitus [5, 7].

In mesangial cells, elevated intracellular glucose as a consequence of diabetes mellitus is thought to affect a number of cellular pathways known to be implicated in cellular growth and in the

accumulation of the extracellular matrix [13-14]. Exactly these pathological changes are key factors in the pathogenesis of diabetic nephropathy. From this perspective, it becomes clear that the activity of glucose transporter GLUT-1 on the cell surface of the mesangial cells may be rate limiting for the development of the pathological changes in diabetic nephropathy. In this study, we observed lack of association of GLUT-1 genotype in T2DM and Diabetic nephropathy patients.

In our present study, GLUT-1 XbaI polymorphism was not associated with T2DM and DN. Our results are in agreement with the findings of Alcolad and Baroni, 1992 [15], who found no association with GLUT-1 and T2DM. Elbein, et al. [16] is also found no association between familial NIDDM and GLUT-1 gene polymorphism. These results are accordance with our present study. Ramadan et al 2016 [17] were confirmed no association between GLUT-1 gene polymorphism with diabetic nephropathy. Another study in Danish population showed no association with type 1 DM and DN with XbaI polymorphism with was reported [18]. Furthermore, some contrasting results have also been reported. Liu et al [19] are reported significant association of diabetic nephropathy and non-insulin-dependent diabetes mellitus with GLUT-1 gene polymorphism.

Makni et al [20] confirmed GLUT-1 gene is susceptibility to DN in type 2 diabetes patients in the Tunisian population. Pontiroli et al [21] reported that GLUT-1 polymorphism may contribute to susceptibility to T2DM in few populations especially in overweight/ obese women. In present study we did not find any ++ genotype in T2DM and diabetic nephropathy patients and as well as healthy controls. Our findings are accordance with previous study of Ramadan et al 2016 [17] and he was not found any homozygous (GG) genotype in the studied population. A meta-analysis conducted by Cui et al. [22] found negative outcome in the assessment for the influence of XbaI or Enh2-2 SNP on the pathogenesis and progression of DN. There may be number of possible reasons for these discrepancies including allelic heterogeneity between different ethnicity, population admixture in the studies, small or insufficient sample size and linkage disequilibrium or environmental factors which may mask the genetic effects.

In summary, we have carried out a study to investigate the association between GLUT-1 gene polymorphism with T2DM and diabetic nephropathy patients in North Indian population. Our observations suggested that there was no significant association between Glut-1 gene polymorphism and T2DM and diabetic nephropathy patients in North Indian population leading us to conclude that GLUT-1 gene polymorphism may not have major effects on in T2DM and diabetic nephropathy patients of North Indian population.

The present research however, has some limitations in as it was carried out in only ethnically homogenous North Indian population who visited diabetes clinic for health examination. Therefore, further studies are needed for population from the general population and other ethnic groups of India.

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Conflict of Interest: The authors declare that they have no conflict of interests.

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