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Original Research

ACE Gene (I/D) Polymorphism: Understanding the Genetic basis of Nephropathic Predisposition in Type 2 Diabetics

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Abstract

Introduction: About 20-40% of Type 2 Diabetic patients are affected by Diabetic nephropathy, a microvascular complication of Diabetes Mellitus.To prevent the disease, it is requisite to identify the individuals at higher risk of development of Diabetic nephropathy. Glomerular hypertension instigated by increased activity of Renin angiotensin System assumed to contributes majorly for the development of Diabetic nephropathy.287 bpAlu repeats either inserted or deleted in the 16th intron of ACE gene, which causes 3 genotypes of ACE insertion/deletion gene polymorphism; II, ID andDD.

Aim: The present study was designed to detect the association of ACE gene polymorphism and Diabetic nephropathy

Materials and methods: A total of 100 Type 2 DM patients, who have diabetes for at least 10 years were recruited in this study and divided in two groups; without nephropathy (n=42) and with nephropathy (n=58). ACE genotyping was performed from the DNA extracted from WBCs, which is amplified by PCR and distinguished by gel electrophoresis. Genotypes described as I/I-490 bp, I/D-490+190 bp, and D/D-190 bp on electrophoresis.

Result: 50% (n=29) of DN patients compared to 23.80% (n=10) ofnon-nephropathic patients had DD genotype. Univariate analysis showed significant association of ACE DD homozygote with diabetic nephropathy. Odd ratio in the development of diabetic nephropathy with DD genotype was 3.20.

Conclusion: Study showed association of I/D polymorphism of ACE gene with Diabetic nephropathy in Type 2 Diabetes Mellitus patients. The risk of development of nephropathy increases with DD genotype in comparison with ID and II genotype.

Key Words: ACE gene polymorphism, Diabetic Nephropathy, Type 2 Diabetes Mellitus

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Introduction:

Diabetes mellitus (DM) define as metabolic disordercomprising the phenotype of hyperglycemia with chronic complications affecting many organ systems which causes majority of morbidity and mortality relatedto the disease. The development of diabetes specific complication in the retina, renal glomerulus andperipheral nerves leads to retinopathy, nephropathy and neuropathy. Diabetes mellitus is classified on the bases of etiology of the disease, where insulin deficiency is categorized as Type 1 DM and insulin resistance is categorized as Type 2 DM. In India diabetes is growing as a substantial epidemic as not less than 62 million diabetic patients are currently diagnosed with the disease and the cases will increase up to 79.4 million by the year 2030. [1]

Diabetic nephropathy (DN) is a chronic microvascular complication of Diabetes mellitus affecting 20-40% of Type 2 DM patients. In India, the age-adjusted incidence rate of end-stage renal disease (ESRD) is 229 per million population. Approximately 152,000 new ESRD patients require renal replacement therapy (RRT) annually. Diabetic nephropathy accounts for 41% of ESRD cases.[2]. The required healthcare personnel and infrastructure to take care of this large case load is currently not available in the country, therefore, identification of risk factors and the patients having higher risk for the development of DN required to prevent the disease.

The pathogenesis of this severe complication iscomplexandcompriseshemodynamic alterations, metabolic abnormalities,genetic factors andvarious

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growth factors. In experimental studies, it was found that Glomerular hypertension instigated by altered activity of Renin angiotensin System contributes majorly for the development of Diabetic nephropathy. [3]Angiotensin II shows hyperactivity in high glucose conditions which causes hypertrophy of various renal cells and increases vascular pressure bycausing contraction of arteriolar smooth muscles.[4]Another major contributing factor for DN is poor glycemic control, butsome DM patients having good glycemic control also suffers from DN, while many patients with poor glycemic control do not suffer from DN. Studies found a strong genetic predisposition to the onset and progression of Diabetic nephropathy and, ACE gene was shown to be highly associated amid all genes.

The human ACE geneis 21 kb long and made located on the long arm of chromosome 17q23 and made up of 26 exons and 25.[5].287 bpAlu repeats either inserted or deleted in the 16th intron of ACE gene, which causes 3 genotypes of ACE insertion/deletion gene polymorphism; II, ID andDD.[6]Association of ACE gene polymorphism with DN was demonstrated byJeffers BW et al [7], Ohno T et al[8],Movva S et al[9], and refuted by Schmidt S et al[10], Jayapalan JJ et al[11]. Keeping in view the different outcomes of earlier researchers, the aim of the present study was to examine the associations between the ACE gene I/D polymorphisms and susceptibility to Diabetic nephropathyin patients of Type 2 diabetes mellitus (T2DM).

Materials and Methods

A case control study was conducted from period of August 2017 to July 2018 and was reviewed and approved by Human Ethics Committee of Government Medical College, Bhavnagar, Gujarat, India. 100 unrelated adultpatients with more than 10 years duration of Type 2 Diabetes Mellitus, being treated and followed up in the Medicine OPD at Sir Takhtsinhji General Hospital, Bhavnagar were included.Patients suffering from diseases causing proteinuria other than diabetic nephropathy were excluded.

We documented the medical history (both present and past) for all cases, paying special attention to smoking history, medication use, and any systemic illnesses, particularly hypertension. Additionally, we measured anthropometric parameters such as weight (in kilograms) and height (in meters) for all patients. Using these measurements, we calculated the Body Mass Index (BMI) by dividing weight by height squared (Kg/m^2).

After an overnight fast of 12 hours, venous blood sampling was donefor biochemical determinations and isolation of DNA in Plain and EDTA vacutainer and urine sample was collected for analysis of albumin excretion rate (AER). After centrifugation of blood samples, separated serum was analyzed for following biochemical parameters. Glucose (Glucose oxidase method[12], CV%: 4.8), Creatinine (Modified Jaffe's method[13], CV%: 6.8), Cholesterol (Cholesterol oxidase method[14], CV%: 4.7) , Triglycerides (Enzymatic method[15], CV%: 3.6), HDL-C (Immunoinhibition method[16], CV%: 8.5), LDL-C (Enzyme selective protection method[17], CV%: 4.5), HbA1c (Immunoturbidimetric method[18], CV%: 4.9)The urine samples are tested for AER by immunoturbidimetric assay[19]. Patients with AER ≥30 mg/daywere considered as cases and all others were considered as controls.[20] All biochemical investigations carried out were in the scope of accreditation for ISO 15189:2012 and analysis was performed on fully auto chemistry analyzer I-Lab 650at Clinical Biochemistry Section, Laboratory Services Sir Takhtsinhji General Hospital,Bhavnagar.

Peripheral blood leukocytes were used for genomic DNA extractionby commercially available HiPurA™ Blood Genomic DNA Miniprep Purification Kit from HiMedia based on the selective binding of DNA to silica-based membrane in the presence of chaotropic salts [21] amplified by PCR.

Oligonucleotide primers used for DNA amplification, forward: 5'-CTG GAG AGC CAC TCC CAT CCT TTC T-3' and reverse: 5'-GGG ACG TGG CCA TCA CAT TCG TCA G-3' were designed according to the flanking sequences of the I/D region on the intron 16 of ACE gene.[22]. DNA amplification was carried out in a Thermal Cycler Bio-Rad T100 using HiMedia 2XPCR TaqMixturein a final reaction volume of 50 µl containing 3 µl of eluted DNA (50ng/µl), 1 µl each of forward and reverse primers (100ng/µl), 25 µl of 2XPCR Taq Mixture and 20 µl of Nuclease free water. The thermocycling profile used for DNA amplificationcomprised the initial denaturation at 94°C for 1 minute which was followed by 30 cycles of amplification by denaturation at 95°C for 30 seconds, annealing at 58°C for 1 minute and extension at 72°C for 2 minutes. The final extension was done at 72°C for 5 minutes.

Amplified products were separated and identified using agarose gel (2%) electrophoresis withethidium bromide as fluorescent tag, under UV (ultra-violet) light in Bio-Rad Gel Document system as a 190 bp fragment in the absence of an Alu repeat insertion and a 490 bp fragment in the presence of the insertion (genotypes described as I/I-490 bp, I/D-490+190 bp, and D/D-190 bp).

Result:

Results of the present study were analysed by using GraphPadinStat version 3.0. Data were expressed asmean ± SD (continuous variables), or as percentages oftotal (categorical variables). Two-group comparisons were made using Chi-square (χ^2) for categorical variables and unpaired t-tests for continuous variables.

All the patients were divided in two groups. Group I: Diabetic patients without nephropathy (Normoalbuminuric-Controls). Group II: Diabetic

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patients with nephropathy (Microalbuminuric or Macroalbuminuric-Cases).

The mean age for Group I was 57.95 ± 5.13 years and Group II was 58.32 ± 5.90years. Female (n=53) participants were more than male (n=47).27 patients were hypertensive in Group I while 40 patients were hypertensive in Group II. 13 patients were smoker in Group I while 18 patients were smoker in Group II. Means for duration of diabetes and BMI were12.83 ± 1.48 and 26.36 ± 2.09 respectively for Group I and 12.91 ± 1.51 and 27.14 ± 2.07 for Group II. Mean of HbA1c levels for Group I was7.69 ± 0.90 and Group II was 7.72 ± 1.10. Mean of S. Creatinine for Group II was 1.07 ± 0.29 vs.0.9 ± 0.10 for Group I (Table 1). As shown in table 2 Group I distribution of ACE genotypes II was 08 (19.04%), ID was 24 (57.14%) and DD was 10 (23.80%) and in Group II distribution of ACE genotypes II was 09 (15.51%), ID was20 (34.48%) and DD were 29 (50.00%).

Table 1: Comparison of Control Group I & Study Group II

Parameters	Group I- Diabetic patients without nephropathy (Control) (n=42)	Group II- Diabetic patients with Nephropathy (Case) (n=58)	Significance
	Mean ± SD	Mean ± SD	
Age (years)	57.95 ± 5.1	58.32 ± 5.9	p= 0.74#
Sex Males, n (%) Females, n (%)	 21 (50%) 21 (50%)	 27 (47%) 31 (53%)	p= 0.84 #
Hypertensive, n (%)	27 (64.3%)	40 (68.9%)	p= 0.67 #
Smoker, n (%)	13 (30.9%)	18 (31.0%)	p= 1.00 #
Duration of Diabetes (years)	12.83 ± 1.5	12.91 ± 1.5	p= 0.79#
BMI (Kg/m^2)	26.36 ± 2.1	27.14 ± 2.1	p= 0.06#
HbA1C (%)	7.69 ± 0.9	7.72 ± 1.1	p= 0.87#
S. Creatinine (mg/dl)	0.9 ± 0.1	1.07 ± 0.3	p= 0.0004*
S. Total Cholesterol (mg/dl)	187 ± 35	181 ± 43	p= 0.40#
S. Triglycerides (mg/dl)	173 ± 52	162 ± 58	p= 0.30#
S. HDL – C (mg/dl)	48.97 ± 8.9	48.03 ± 6.4	p= 0.54#
S. LDL – C (mg/dl)	111.2 ± 25.5	110.0 ± 32.6	p= 0.83#

*p < 0.05 – significant, **p < 0.001 – highly significant, #p ≥0.05 – not significant

Table 2: Genotype distribution of ACE I/D polymorphism in Diabetic patients without nephropathy (Group I) and Diabetic patients with nephropathy (Group II)

Genotype	Group I (n = 42)	Group II (n = 58)	X^2 d.f. - 2	P value d.f. - 2	P value d.f. - 1	OR	OR (95% of CI)	
							Lower Bound	Upper Bound
II	08	09	7.306	0.026	0.84#	0.78	0.27	2.23
ID	24	20			0.08#	0.39	0.17	0.89
DD	10	29			0.01*	3.20	1.33	7.69
Total D alleles (ID +DD)	34	49			0.78#	1.28	0.44	3.65

d.f. – Degree of freedom, OR – Odd Ratio, CI – Confidence Interval
II- Insertion/ Insertion, ID- Insertion/Deletion, DD- Deletion/Deletion
*p < 0.05 – significant, **p < 0.001 – highly significant, #p ≥0.05 – not significant

Discussion

We analyzed the genotypic and the allelic distributions of the ACE I/D polymorphism amongnormoalbuminuric controls and DN patients.Genotype data showed frequency of DD genotype was found to be significantly higher in

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Diabetic nephropathy than in normoalbuminuric participants. (p< 0.05). Odd ratio related to the association of prevalence of DD genotype in diabetic nephropathy was 3.20 (95% CI 1.33 – 7.69).Results of the present study were in accordance with some of the previous studies like Jeffers BW et al (1997)[7]Hsieh et al (2000)[23], Vishwanathan et al(2002)[24]Ha SN et al (2003)[25] but differed with studies like Gutierrez et al (1997)[26], Hadjadj S et al (2003)[27], Arfa I et al (2008)[28].Meta-analysis studies (Ng DP et al (2005){29} and Wang et al (2012)[30]) concluded that ethnicity of the study population is the major determining factor in association of ACE gene polymorphism and susceptibility of Diabetic nephropathy.Patients of Both groups wereclosely matched for potentially confoundingvariables like age, sex, hypertension, Glycemic control, Dyslipidemia and BMIwhich made it easier to compare association of ACE genotypes with DN.Although prevalence of hypertension is more in the Group II [n- 40(69%)] versus Group I [n-27(64%)] patients, the difference was not statistically significant (p= 0.67). No statistically significant difference was observed in duration of diabetes (p - 0.7917) between the two groups.There is no significant difference in HbA1c levels (p = 0.8787) between two groups. This finding is consistent with Viswanathan V et al[22]as their finding showed no significant association between HbA1c levels and DN (p = 0.69). Our results differ from Stoler M et al[31]as they reported that the mean HbA1c in patients with microalbuminuria was higher than in those with normal urinary albumin excretion. S. Creatinine is significantly high in DN patients than without DN patients(p = 0.0004), it suggests that high levels of S. Creatinine associated with renal injury in DN patients. This finding is in accordance with Prasad P. et al[32]No statistically significant difference was observed between Group I & Group II in the lipid profile,it differs from Cardoso CR et al[33]. The difference is due to comparable number of patients who were receiving lipidlowering drugs.As indicated in table 2, the frequency of the D allele was higher in the Group II (n=49) than Group I (n=34), but the difference is not statistically significant (p - 0.7883). Further it was observed that the DDgenotype (vs. other genotype) increased therisk of nephropathy in Type 2 diabetes patients up to 3.20 fold [OR 3.20 (95% CI: 1.33 – 7.69)] and these resultsare similar to the outcomes ofOhno et al[8] (OR=2.6) and Yoshida et al[34](OR=4.6), whereas the ID genotype did notalter the risk significantly [0.395 (95% CI: 0.174 – 0.893)], This data suggests that Dallele increases risk of DN only in recessive mode of inheritance.

Conclusion

The present study showed the association of Insertion/Deletion polymorphism of ACE gene with Diabetic nephropathy. The risk of development of Diabetic nephropathy in type 2 Diabetic patients increased by D alleleonly in recessive mode of inheritance (DD) not in co-dominant mode (ID).On the basis of findings from the present study it is recommended that genotyping of ACE gene can be performed in Type 2 Diabetic patients in order to decrease the burden of Diabetic nephropathy in India and long term follow up on Type 2 DM cases with DD genotype using ACE inhibitor therapy and proper glycemic control, may provide us with appropriate management options.

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