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Original Research Article

Association of FTO (rs9940128) Gene Polymorphism in Type 2 Diabetes Mellitus with Chronic Nephropathy in North Indian Population

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ABSTRACT

Background: FTO, SNP rs9940128 A/G gene polymorphism has found associated with type-2-diabetes mellitus (T2DM) and chronic kidney disease (CKD). Several biochemical markers have identified which are linked directly with obesity and T2DM induced CDK such as hypertension, HbA1c, reduced glomerular filtrate rate, uric acid concentration, serum creatinine, serum urea, and vitamin D etc.

Material and methods: This study 110 cases and 110 controls were selected from North Indian population. Most of the possible biochemical parameters were considered for the study and for genome wise study DNA was isolated, amplified with PCR. Gene sequence was compared with gene sequence available with NCBI data base. The Hardy-Weinberg equilibrium, OR, CI and p-values were calculated using SPSS software version 22. The allelic frequency was estimated and found that GG genotype frequency is twice in cases than controls and has co-relation with T2MD. Similarly, elevated AA allele frequency was responsible for CKD disorder in the reported cases.

Results: In this study 110 cases and 110 controls were selected which is diagnosed with T2DM and kidney disease.

Conclusion: This study has explored the FTO SNP rs9940128 A/G gene polymorphism among the T2DM with CKD cases. This study also advocated that elevated GG allele was associated for T2DM and elevated AA allele was responsible for CKD disorder in the reported north Indian populations.

Keywords: Urinary albumin excretion, chronic kidney disease (CKD), gene polymorphism, obesity and T2DM

INTRODUCTION

Fat mass obesity FTO (fat mass and obesity) gene has been found related to T2DM which is a metabolic disorder. Globally, T2DM corresponded to 90-95% in all the diabetes cases.[1] Due to continuous hyperglycemia and increased weight problems many diseases have been associated and noticed as CKD worldwide.[2] In the studies it has been found that 20-40% of individuals with T2DM have kidney complications too.[3] But pathogenesis, characterization, and investigation of associated risk factors for the T2DM connected nephropathy are still challenging. It has also well reported that if diabetes is

not managed on time resulting hyperglycemia which has great harm to variety of vital tissues including the kidney.[4] Several genome wide studies have been conducted to find out the association between polymorphisms of FTO gene with T2DM[5], and furthermore it's linked with nephropathy.[6] The FTO gene is found on the long arm of the Chromosome 16 and its size is approximately 400 kb.[7] Furthermore, fat mass and obesity linked protein is famous as alpha-ketoglutarate-established dioxygenase, which is an enzyme encoded by means of the FTO gene. It is known that the expression of the FTO gene is concerned with food intake and energy utilization.[8-9] In the studies it has been explored that about 10 exclusive FTO SNPs in the first intron of the gene, which linked to each BMI and T2DM. In the studies it has been mentioned that FTO gene associated with obesity[10], hypertension[11], and kidney dysfunctions.[12]
In the study conducted in Brazil it has found that T2DM was due to with polymorphism of the FTO gene and this genetic modification result high levels of urinary albumin excretion.[13] Similarly, in other report of American Indians it has mentioned that due to high prevalence of obesity, T2DM, and metabolic syndrome result of hypertension and hyper-lipidemic. Addition to these disease and smoking have contributed chronic kidney disease such as albuminuria and decreased glomerular filtration rate.[14] At the state of severe T2DM many other diseases such as diabetic retinopathy, myocardial infarction, stroke, kidney failure, and even sudden death had been reported.[15] The prevalence of T2DM nephropathy in India is found around 8.9% in Tamil Nadu and its prevalence in Asian population is quite high (22.3%).[16] Several risk factors of the diabetic nephropathy have been reported such as poor glycemic control, long lasting diabetes and high systolic blood pressure.[17] In the genome-wide studies on susceptibility variants associated with kidney diseases and its functions have been identified in the UMOD and PRKAG2 genes[18] but the association of FTO (rs9940128) gene polymorphism with T2DM and CKD in the Indian population is still unknown.
This study has the primary objective to evaluate whether the FTO gene polymorphism (rs9940128) is associated with nephropathy in the individuals of T2DM and to find out related conditions in the Indian population. This study has hypothesis whether this polymorphism would influence early CKD conditions either directly or indirectly. As the T2DM linked CKD conditions are painstaking and in particular ruled through an amalgamation of genetic and environmental factors. Genetic elements are gambling which may be an important function in the pathogenesis of these diseases.

MATERIALS AND METHODS

This study was carried out at the department of Biochemistry at Shri Balaji Institute of Medical sciences and Maa Padmavati Institute of Medical Sciences in Association with Department of Urology, DKS Hospital and Research Centre, Raipur, Chhattisgarh, India. The reagents and chemicals were procured from the standard vendors such as Sigma Aldrich, Fermentas and Quaigen. Total of 220 samples (110 cases no history of ketoacidosis and 110 controls) were considered. Standard questionnaire and written consent for participation was got from each cases and controls. The entire protocol was approved by the ethical committee. Clinically diagnosed cases of T2DM (as per ADA criteria) were taken as cases who were urinary albumin excretion less than 200 μg/min, absence of urinary tract infection or other renal diseases, and normal healthy persons were considered as control. Many parameters were compared such as age, sex, glycemic record, and nephropathological conditions etc.
Body weight and height of the participants were obtained using an anthropometric scale; Body mass index (kg/m2) was calculated as weight (kilograms) divided by height (meters) squared.
The formula for calculating BMI was:

$$\text{BMI (Kg/m2)} = \frac{\text{Weight (Kg)}}{\text{Height (m) 2}}$$

Waist circumference was measured midway between the margin of the lowest rib and the iliac crest, near the umbilicus, using a flexible, non-stretch fiberglass tape. Central obesity was defined by a waist circumference 94 cm for men and ≥80 cm for women.[19] Blood pressure was measured through the standard protocol

using a mercury sphygmomanometer with a constant deflation valve. Cuffs were preferred to appropriately fit each patient arm. After 10 minutes of rest, applicants were their blood pressure considered in the supine position, followed in sitting and then standing positions.

Measurements were performed before starting the graded exercise test. The multiple dimensions were also available, systolic and diastolic blood pressures which were calculated as an average of the measurement.[20] During the study the presence of CKD was estimated as described by American Diabetes Association.[21]

Based on 24 h urinary albumin excretion results, the cases were classified as normoalbuminuria (urinary albumin excretion < 20 μg/min) or microalbuminuria (urinary albumin excretion > 20-199 μg/min). Microalbuminuria was confirmed in second urine sample.[22] The estimated glomerular filtration rate was estimated by using the CKD-Epidemiology Collaboration formula, and recorded creatinine levels accordingly.[23] Urinary albumin excretion was estimated by an immune-turbidimetric method (Microalb, NY) using urine samples with albumin concentrations of 30 and 100 mg/L.

The intra-assay and inter-assay coefficients of variation were estimated as laboratory standard.[24]

Genotyping for FTO Polymorphism:

Single nucleotide polymorphisms (SNP) from intron 1 FTO (rs9940128) was known to be linked with obesity/T2DM were chosen.

SNP (rs9940128) was chosen from the database (NCBI) to confirm its purity. Fresh blood (2 ml) was collected to isolate DNA by using Quaigen kit with standard protocol. DNA purity was checked on 1% agarose gel.

Primers were synthesized from Chromous Biotech Pvt. Ltd, Bengaluru. DNA were amplified by PCR (Bio-RAD) and the PCR products were digested with the restriction endonuclease (Msp1 rs9940128) New England Bio labs, Inc. Beverly, MA.

Genotypes were determined by fragment by running 1% agarose gel to check the size of the digested product by RFLP.[25]

Gel photographs were observed in gel documentation system (Bio-RAD). For biochemical parameters blood samples were obtained after 12-hours of fasting. Glycated hemoglobin (HbA1c) was determined by ion-exchange high-performance liquid chromatography (Merck-Hitachi L-9100 glycated hemoglobin analyzer.[26]

Fasting plasma glucose, two hours post plasma glucose, fasting plasma insulin, serum creatinine, serum uric acid, serum urea were performed using standard laboratory assay.[27]

Statistical analyses were carried out using SPSS software version 22.

Statistical power of the study was estimated under log-additive model, assuming 10% population risk by Quanto. Hardy-Weinberg equilibrium for genotyping was checked by v2 analysis.[28] Obesity and T2DM was calculated by logistic regression analysis. Association of variants with T2DM, obesity and quantitative traits was carried out by mixing the data for two study population and adjusting for study population.

Allele frequency for cases and controls of two study population was compared by equality of proportions Z test. Entire data analyses were adjusted for age, sex and BMI.

The odds ratio (OR) and 95% confidence interval (CI) was calculated in respect to minor alleles in the study.[29]

RESULTS

In this study 110 cases and 110 controls were selected which is diagnosed with T2DM and kidney disease.

Data are expressed as- mean (±) SD, p value has statistical significance ($p < 0.05$), UAE= urinary albumin excretion, eGFR = estimated glomerular filtration rate, HbA1c= glycated hemoglobin. Several clinical parameters were selected as mention in Table-1 in the relation of diabetic nephropathy. There was a good categorization of sample size, sex and age group selected among the diagnosed cases of T2DM.

Table-1: Clinical parameter of the participants (diabetic with chronic kidney diseases)

S.N.	Characteristics		Case	Control	P value
1.	No. of participants		110	110	-
2.	M/F		65/45	60/50	-
3.	Age (year)		61.4±5.1	58.3±6.7	0.008
4.	BMI (kg/m^2)		22.87 ± 2.1	21.25 ± 1.5	0.251
5.	Diabetes record duration		10.2 ± 8.6	-	-
6.	Central obesity, *n* (%)		90 (81.5)	93 (84.6)	0.471
7.	HbA1c, %		7.6±1.7	7.3± 1.8	< 0.001
8.	Diabetes treatment, *n* (%)	Diet only	9 (8.18)	-	0.07
		Oral antidiabetic medicine	36 (32.72)	-	
		Insulin	29 (26.36)	-	
		Insulin + oral antidiabetic medicine	36 (32.72)	-	
9.	Hypertension, *n* (%)		62 (56.36)	33 (30.0)	< 0.001
10.	Total cholesterol (nmol/l)		79.2±97.2	78.3 ± 66.6	0.0001
11.	UAE (µg/min)		57.4±6.8	3.5±4.3	< 0.001
12.	eGFR (mL/min per 1.73 m^2)		82.9±4.8	84.5±5.0	0.001
13.	Chronic kidney disease (%)		76.00	1.00	0.001
14.	Urea (g/L)		9.44±8.6	4.23±6.7	< 0.001
15.	Creatinine (micromoles/L)		139.70 ± 8.4	64.81±7.5	< 0.001

Body weight and height of the cases and controls were obtained using an anthropometric scale. BMI (kg/m2) was calculated as weight (kilograms) divided by height (meters) squared. Waist circumference was measured midway between the margin of the lowest rib and the iliac crest, near the umbilicus, using a flexible, non-stretch fiberglass tape. Central obesity was defined by a waist circumference 94 cm for men and ≥80 cm for women. All the required biochemical parameters like fasting plasma glucose, two hours plasma glucose, fasting plasma insulin, serum creatinine, serum uric acid, serum urea, eGFR and chronic kidney disease were recorded whenever required. Participated cases and controls were demonstrated poor glycemic control indices (mean HbA1c > 7%) with $p < 0.001$. Older cases had found higher rates of hypertension with $p < 0.001$. Similarly, the renal function; eGFR, creatinine, urea, and total cholesterol values were recorded higher in cases than in controls and their p value was found < 0.001. But the BMI have found no significant association (p= 0.251) between cases and controls. The drug used for the treatment of T2DM was 32.72% cases oral antihyperglycemic agents, 26.36% cases used only insulin, 32.72% cases used insulin+ oral antihyperglycemic agents while 8.18% cases-controlled sugar level only on diet management.

During this study, it found that 88.18% cases of overweight were diabetic while 7.27% persons were pre-diabetic. Thus, most of the cases with abnormal BMI were either pre-diabetic or likely to diabetic and belonged to high risk group population.

In this study, involvement of FTO gene polymorphisms with T2DM with CKD cases was tested. To achieve this goal DNA was isolated and amplified with the use of primers (Table-2). The genotype and allele frequencies of the selected FTO SNP (rs9940128) were analyzed. The genotype frequencies of the FTO gene in cases of T2DM with CKD had been located in Hardy-Weinberg equilibrium. The rs9940128 A/G gene polymorphism of the FTO gene become recorded good-sized involvement in T2DM with CKD cases, and the AG genotype changed into cited considerably better in T2DM with CKD cases (Table-3). The frequency of the GG alleles changed into higher appreciably in T2DM with CKD cases ($P<0.0001$). Logistic regression analysis was implemented for AG and GG genotypes with respect to AA genotypes, which was considered a reference genotype. Association of FTO gene polymorphisms with obesity was validated the genotype and allele frequencies ($P<0.0001$).

To estimate the effect of the genotypes on the disease, logistic regression evaluation was done. The assessment between the AG and GG genotypes won an unadjusted OR of one. Sixty-nine became statistically sizeable (0.021), furthermore significance was retained after adjusting for age, intercourse, diabetes & nephropathy. While we compared the AA genotype with the GG genotype, the OR remained great, conferring 1.50 instances better chance in the direction of obesity, even after adjusting for age, sex, diabetes and nephropathy.

Hence genotype and allele frequencies of the rs9940128 A/G polymorphisms were found extensively better in T2DM with CKD cases which indicated that obese cases have suffered from disease in comparison to non-obese.

Table-2: List of primers used for DNA amplification

S.N.	Primer Sequence	Tm (ºC)
1.	Forward 5'ACTGAGATAAGAAAACTGAGGACGA-3'	55.5
2.	Backward 5'-TGCCATGGAAAATCTGGCTCATGGT-3'	60.0

Table-3: Genotypes of FTO gene and their frequencies of alleles in the study populations of in T2DM with CKD cases.

S.N	Genotype	Frequency of alleles (%)	p-value	Adjusted OR value	CI (95%) value
1.	AA	38.50	<0.0001	Reference	Reference
2.	AG	48.41	0.021	1.69	1.38-2.06
3.	GG	13.09	<0.0001	2.41	1.79-3.21

ACTGAGATAAGAAAACTGAGGACGAAGCAG
GTCTGGGGTGAATCAGGTGCTATCCCTTTGG
ACAGTCACATGACTGGTGTCTGTTCAGCACC
CAAGGGACCATCAAAGAGGCTGTTGTGGAGA
GGGAATCCGAAGGTCAGGGCCAGAGATAGA
AATCTGGGGAGTCATCCACTATATAGGTGAT
GGGTTAAAGCCTTAGAACTCTTCTTTTCATGA
ATCATTGTTGTTCTTTAGGTTGTAATGAAGTT
TTAGGCCTCAGCTTCCCTGAACTGGAGTGTTT
TTCCTTCACCTTTTCCGGTCTCTGGGTTGCAT
CGCCAGACTGTCTCTAAGCCCAACAAACGCG
TTCCTTCCAGGCAAAAGCAGGAGATGACACA
CACCATGAGCCAGATTTTCCATGGCA

Table-4: Comparison of obtained genotypes of FTO gene with the previous reports for the study of T2DM with CKD cases

S.N.	SNP	Gene	Effective allele	Minor Allele Frequency	p-Value	(95% CI)	OR	Reference
1.	rs2206136	*PLCB4*	G	0.42	0.198	0.86 (0.85-0.86)	1.12	[30]
2.	rs56094641	FTO	G	0.252	0.08	1.22 (1.21-1.23)	1.23	[31]
3.	rs10011025	*GLRA3*	G	0.16	0.073	0.64 (0.63-0.65)	-	[32]
4.	rs7588550	*ERBB4*	G	0.052	0.132	1.92 (1.86-1.97)	0.66	[33]
5.	rs9940128 Present study	*FTO*	G	13.09	<0.0001	2.46 (1.79-3.21)	2.41	[34]

Figure-1: Isolated DNA

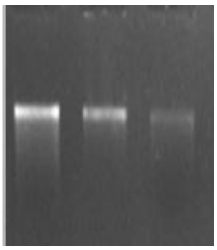
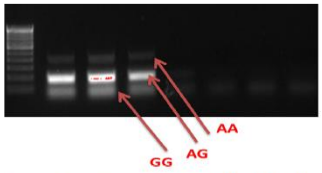


Figure-2: FTO gene amplification with PCR and genotype



During the study, we compared our finding of minor allele frequency with the other available reports of T2DM with CKD. In majority of reports, we have found significant differences between the allele frequencies of SNPs studied in T2DM with CKD cases (Table-4) but we found effective allele G in all the reports.

DISCUSSION

In this study, FTO gene SNP (rs9940128) polymorphism was studied in the cases of T2DM with CKD which is a noble study. FTO gene is located on the long arm of the chromosome 16 and its size is approximately 400 kb. Several related studies have mentioned strong association of the FTO gene with obesity and T2DM[30-35] in north Indian population. But only one study has explored the relation of FTO gene with T2DM and CKD cases by the working of SNP rs2501391.[36] In the previous studies, obesity has been identified as an important risk factor for CKD and T2DM.[37] In this study, we have selected SNP (rs9940128) and wanted to know whether this SNP of FTO gene has any association with T2DM and CKD in north Indian population. T2DM nephropathy is common microvascular complications and found in 20-40% of the individuals.[38-39] The FTO gene was chosen for this study because Naaz et al., 2019[40] and Taira et al., 2018[41] have explored that this gene is responsible for T2DM and T2DM induced nephropathy.[42] In the same way, SNP rs9940128 has been mentioned by way of Scuteri et al. 2007[43] about the great association with T2DM and obesity. In contrast, we have identified an association of T2DM and CKD with SNP rs9940128 by study of 110 cases and 110 controls of north Indian population. In this finding, BMI has not shown any association by SNP rs9940128 with T2DM and CKD, it indicated that this SNP has participated in susceptibility to T2DM and CKD via the mechanism other than raising BMI. Thus, this study might not be able to understand the role of BMI in the co-relation with susceptibility of T2DM and CKD. The similar finding has been reported by Osman et al., 2023.[36] In this study, many biochemical effects which involved in the development of T2DM and CKD in cases have been investigated such as hypertension and dyslipidemia with raised cholesterol, HDL and LDL level.

There may be independent association of lipid accumulation in tubular epithelial cells of T2DM and CKD cases. The result might be reducing glomerular filtration rate, increased uric acid & creatinine for the development of nephropathological disorders in T2DM cases. Similar findings have been mentioned in the previous study.[44-45] In addition to above mentioned factors several other unknown factors might play roles in the development of nephropathological disorders. In this study, it has explored that the risk allele of obesity has significant associated with the T2DM and CKD disease. The obtained GG genotype has indicated two-fold higher risk of T2DM and CKD disease. By the adjustment of age, sex, and BMI the GG genotype frequency was noticed elevated. Thus, this finding has explored a strong relationship between the FTO SNP rs9940128 polymorphism with T2DM and CKD cases. In this study, we also found that elevated AA allele (risk allele) among participants of CKD. Furthermore, it is also estimated that the FTO SNP rs9940128 alone have not played significant roles on the renal phenotype. This finding is partially supported by Yusuf et al., 2023[46] in which FTO gene polymorphism and GG genotype has been responsible for T2DM in Pakistani population. Similarly, the elevated AA allele has been reported risk factor for CDK in the populations by Marchetti et al., 2021.[47] Thus, this study analysis has not found very direct significant effect of the FTO gene SNP rs9940128 on T2DM and CKD cases. However, we have explored an indirect effect governed by the central fat mass obesity, blood pressure, glomerular filtration rate, and urea concentration etc. associated biomarkers for the renal function.[48] In the literature, FTO gene has been found associated with the central obesity which is a direct risk factor for deterioration of the renal functions[49] and influences poor glycemic and blood-pressure control.[50] From this study, we have noticed that obesity due to changed lifestyle is the root cause of T2DM and CKD. To control obesity and blood pressure may be important factors in the treatment of T2DM and CKD in cases. Since our study was focus in North Indian population with the limitation of small sample size.

CONCLUSIONS

This study has explored the FTO SNP rs9940128 A/G gene polymorphism among the T2DM with CKD cases. Many risk factors have identified for these disorders such as central obesity, hypertension, reduced glomerular flow rate and uric acid concentration. This study also advocated that elevated GG allele was associated for T2DM and elevated AA allele was responsible for CKD disorder in the reported north Indian populations.

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