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The Fto Gene Polymorphism (Rs9939609) As Predictor for Hypertension in Iraqi Type 2 Diabetic Patients

KEYWORDS: Diabetes Mellitus (T2DM), World Health Organization (WHO), Multinomial Logistic Regression, VLDL cholesterol and TG

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ABSTRACT *Background : Type 2 diabetes mellitus (T2DM) and hypertension are major health problems worldwide, associated with increased prevalence of obesity and excess morbidity and mortality. FTO gene is primarily expressed in the hypothalamus and encodes a 2- oxoglutarate-dependent nucleic acid demethylase*
Method : A case-control study conducted to find the association between SNP rs9939609 in T2DM with and without hypertension in AL-Najaf Governorate, Iraq. The study included 188 T2DM patients with hypertension randomly selected based on World Health Organization (WHO) guideline AND 148 T2DM patients without hypertension as a control group. DNA was extracted from blood and genotyped by PCR-RFLP by using (ScaI) enzyme. Multinominal logistic regression was applied to compare the proportions of genotypes and alleles. The odds ratio for risk of developing hypertension in T2DM was calculated with and without adjustment for age, sex and BMI.
Results : FTO gene rs9939609 polymorphism (heterozygous AT, and homozygous AA genotype was exhibited to have a protective role against the development of hypertension in type 2 diabetic patients, after the adjustment for age, sex and BMI.
Conclusion : The SNP of FTO rs9939609 gene have a protective role against the occurrence of hypertension in type 2 diabetic patients in Al-Najaf Governorate, Iraq, and changes of the serum lipid concentration as well as Rseistin levels may be taken place independent on the types of the investigated genotypes. BMI is seemed to be independent on the genotype of the investigated gene (FTO rs9939609).

Introduction

Background

Hypertension is a chronic medical condition in which the blood pressure is elevated (Anthea M.et al.1993)**.** Type 2 diabetes mellitus (T2DM) and hypertension are major health problems worldwide, associated with increased prevalence of obesity and excess morbidity and mortality. Furthermore, patients with hypertension having diabetes mellitus or obesity are more likely predisposed to target organ damage (Chobanian AV.et al 2003, Whiteworth JA. et al. 2003, Olsen MH.et al 2010 and Ogihara T. et al 2009).

FTO gene in human encompasses a large genomic region on chromosome 16 with more than 400 000 base pairs and nine exons .FTO gene is primarily expressed in the hypothalamus and encodes a 2- oxoglutarate-dependent nucleic acid demethylase. It has homology with the AlkB family of DNA repairing enzymes. (Gerken *et al.* 2007). Although the variants in FTO were strongly associated with T2DM, the association was abolished when adjusted for BMI, indicating that the association was mediated through obesity.(Frayling T.M. *et al.2007)*

METHODS

Study design

A case–control study of 336 individuals included two groups (188 type 2 diabetic patients T2DM with hypertension and 148 type 2 diabetic patients T2DM without hypertension) randomly selected was conducted to assess the association of SNP(rs9939609) of FTO gene.

The study was performed on 336 type 2 diabetic patients (184 male and 152 female).the patients included two groups {188 type 2 diabetic patients with hypertension (98 male and 90 female),the patients ages ranged between 34-65 years with mean ± SD (48.25 ± 6.31)}and {148 type 2 diabetic patients T2DM without hypertension (86 male and 62 female), the patients ages ranged between 38-66 years with mean ± SD (48.58 ± 6.38) } were included as a control group. The patient population who attended the diabetes center at AL-Sader Medical City, Najaf, Iraq from September 2014 to January 2015. All patients were diagnosed by specialist physicians as having type 2 diabetes, and based on WHO guidelines.

Phenotype measurements

We collected clinical data, such as weight, height, and other data. The BMI was calculated as weight (in kg) divided by the square of height (in m).serum cholesterol, triglyceride, high-density lipoprotein cholesterol and low- density lipoprotein cholesterol were measured. Total serum Resistin was estimated using an enzyme-linked immune sorbent assay (ELISA).

Genetic analysis

Blood samples of T2DM with and without hypertension were collected in EDTA-anticoagulant tubes, and then DNA was extracted from whole-blood samples using DNA extracted kit (Favorgen,Tawan).Then DNA concentration and purity were measured by UV absorption at 260 and 280 nm (Bio Drop,U.K.).

Genotyping was performed by polymerase chain reaction- restriction fragments length polymorphism (PCR-RFLP) for FTO (rs9939609) gene using thermocycler (Biometra, Germany). The primer sequences were obtained from (Adeela Shahid et al 2013): forward 5'AACTGGCTCTTGAATGAAATAGGATTCAGA3' and reverse 5'AGAGTAACAGAGACTATCCAAGTGCAGTAC 3'. Amplification was performed in a total volume of 25 µl which contained 12.5 µl of GoTaq Hot start Green Master Mix, (promega corporation, Madison, W1), 1.5 µl of

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each primer (1Mm final concentration) (One Alpha,U.S.A.), 3.5 µl Nuclease free water, and 6 µl of DNA template. Cycling condition were 95 ° c for 4 min followed by 35 cycles of 94 ° c for 30$_s$ min, 58 ° c for 30$_s$, 72 ° c for 1min and final extention of 72 ° c for 10 min. Amplification product of FTO (rs9939609) gene was 182 bp.The product was digested with 10 U of restriction enzyme (ScaI)(Promega) and ran on 2% agarose gels.

Statistical analysis

Student T test and ANOVA test were used to compare phenotypic data between with and without hypertension in T2DM patients using SPSS windows software (spss Inc.,Chicago,IL). Genotype frequencies were tested for Hardy-Weinberg Equilibrium by x^2 test using online software web-Assotest (www.ekstoem.com). Genetic power was calculated using the online software OSSE (OSSE.bii.a-star.edu.sg). Genotype and allele frequencies in with and without hypertension in T2DM patients were tested by multinomial logistic regression analysis with and without adjustment for age, sex and BMI using SPSS.

Results

Anthropometric and biochemical characteristics of study individuals are presented in table 1. Results of digestion with restriction enzyme (ScaI) for FTO gene rs9939609 included 182bp band for wild type (TT) genotype, for heterozygous genotype (AT) three bands 182,154, and 28 bp and for homozygous genotype (AA) two bands 154 and 28bp as shown in fig.1. Genotype and allele frequencies of FTO gene are shown in table 2.

Genotype frequencies of FTO gene (rs9939609) gene polymorphisms were consistent with Hardy–Weinberg equilibrium (HWE) in T2DM without hypertension (P=0.816). The power of this study to detect a significant difference at level of 0.05 was 100%.

The heterozygous genotype (AT) was found to have a protective impact (OR=0.291, CI95%=0.182-0.466, P= 0.001) against the development of hypertension in type 2 diabetic patients, after the adjustment for age, sex and BMI. Also no significant variation was obtained when the analysis was carried out without adjustment. Similarly the homozygous genotype (AA) was exhibited to have a protective role (OR= 0.176, CI 95% 0.68-0.467, P= 0.001) against the occurrence of hypertension in the investigated patients with respect to those with wild type. Further analysis of the genotype distribution with use of the dominant and recessive models pointed out a protective role of the rs9939609 SNP of the FTO gene against the development of hypertension in T2DM. The assessment of the minor allele (T) frequency indicated significant (P=0.0001) elevation in type 2 diabetic patients without hypertension with respect to those without hypertension, strongly suggested the protective impact of the analyzed genotype.

Biochemical characteristics of T2DM with hypertension individuals according to FTO gene polymorphism (rs9939609) genotypes co-dominant and dominant model are shown in table 3 and 4. It demonstrated insignificant association of changes of the investigated parameters with respect to the co-dominant and dominant models.

Table 1: Anthropometric and biochemical characteristics of study individuals

	T2DM with hypertension subjects N=188	T2DM without hypertension subjects	P-value
No (M/F)	188 (98/90)	148 (86/62)	0.275
Age (y)	48.25 ± 6.31	48.58 ± 6.38	0.727
BMI (kg/m$^{2)}$)	30.29 ± 5.53	29.76 ± 4.92	0.352
Cholesterol (mg/dl)	233.65 ± 36.20	232.82 ± 33.80	0.882
Triglycerides(mg/dl)	229.84 ± 41.00	227.32 ± 38.70	0.565
VLDL (mg/dl)	45.96 ± 8.218	45.46 ± 7.74	0.565
LDL(mg/dl)	140.12 ± 37.40	138.84 ± 35.12	0.748
HDL(mg/dl)	47.56 ± 6.71	48.51 ± 6.58	0.195
Resistin (ng/ml)	10.45 ± 2.16	8.20 ± 2.09	0.020
SBP(mmHg)	126.27 ± 17.25	123.54 ± 11.74	0.086
DBP(mmHg)	80.95 ± 9.65	79.12 ± 8.85	0.071

***phenotypic data expressed as mean ± standard deviation**

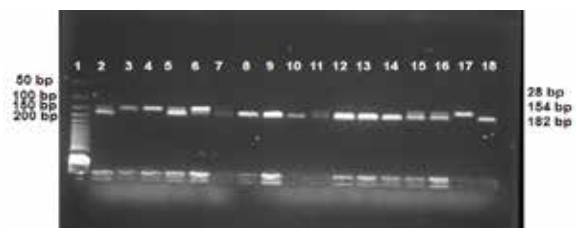

Figure 1: Genotyping Result for FTO Gene (rs9939609**). line 1: Marker Line: For individuals have the Wild Type (TT) of 182bp Fragment (Lines 7-10,12-14, and 18): For Individuals have the Heterozygous (AT) Genotype that Showed Three Fragments with Size of 182 bp, 154 bp, and 28 bp.(Lines 2,5-7,11,15 and 16): For Individuals have the Homozygous (AA) Genotype Exhibited Two Fragments of 154 bp and 28bp Size.(line 3-4,6 and 17)**

Table 2: Genotype and Allele Frequencies of rs9939609 Polymorphism of FTO Gene and Association of this Variant In T2DM With and Without Hypertension in the Study Individuals

rs 9939609 (T/A)	T2DM with HT n=188 (%)	T2DM without HT n=148 (%)	Unadjusted OR (CI 95%)	P-value	adjusted OR (CI 95%)	P-value
Co-dominant						
TT (Ref)	125(66.48)	52(35.13)				
AT	56(29.78)	80(54.05)	0.291 0.182-0.466	0.001	0.291 0.182-0.466	0.001
AA	7(3.72)	16(10.81)	0.182 0.071-0.468	0.001	0.176 0.68-0.467	0.001
Dominant						
AA+AT	63	96	0.273 0.173-0.430	0.001	0.272 0.173-0.429	0.001
Recessive						
TT+AT (Ref)	181	132				
AA	7	16	0.319 0.128-0.797	0.015	0.309 0.123-0.77	0.013
Frequency of A allele	70	112	0.150 0.091-0.248	0.0001		

***HT: hypertension**

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Table 3: biochemical characteristics of T2DM with hypertension individuals according to FTO gene polymorphism (rs9939609) genotype (co-dominant model).

biochemical characteristics	TT (n = 125) Mean ± SD	AT (n = 56) Mean ± SD	AA (n = 7) Mean ± SD	P value
BMI (kg/m^2)	30.34 ± 5.80	30.07 ± 5.13	31.16 ± 2.92	0.875
Cholesterol (mg/dl)	236.67 ± 35.36	225.43 ± 36.95	245.57 ± 33.07	0.106
Triglycerides (mg/dl)	228.51 ± 40.89	229.82 ± 41.09	253.80 ± 37.02	0.288
VLDL (mg/dl)	45.70 ± 8.17	45.96 ± 8.21	50.76 ± 7.40	0.288
LDL(mg/dl)	143.00 ± 36.32	132.81 ± 38.80	147.04 ± 36.48	0.213
HDL(mg/dl)	47.96 ± 6.45	46.65 ± 7.33	47.76 ± 5.05	0.483
Resistin (ng/ml)	8.28 ± 2.02	7.99 ± 2.21	8.44 ± 2.25	0.671

Table 4: biochemical characteristics of T2DM with hypertension individuals according to FTO gene polymorphism (rs9939609) genotype genotype (dominant model).

biochemical characteristics	TT (n =125) Mean ± SD	AT +AA (n = 63) Mean ± SD	P value
BMI (kg/m^2)	30.34 ± 5.80	30.19 ± 4.94	0.860
Cholesterol (mg/dl)	236.67 ± 35.36	227.67 ± 37.09	0.109
Triglycerides(mg/dl)	228.51 ± 40.89	232.49 ± 41.35	0.533
VLDL (mg/dl)	45.70 ± 8.17	46.49 ± 8.27	0.533
LDL(mg/dl)	143.00 ± 36.32	134.39 ± 38.81	0.138
HDL(mg/dl)	47.96 ± 6.45	46.77 ± 7.12	0.256
Resistin (ng/ml)	8.28 ± 2.02	8.04 ± 2.22	0.472

DISCUSSIONS

The associations of common variants in FTO (rs9939609) with BMI were examined in this study and there were insignificance differences were observed among comparison of the three groups of genotypes. However, in the current study, rs9939609 minor AA allele seemed to be associated with high BMI values among the three groups of genotypes in T2DM with hypertension.

SNP of FTO gene (rs9939609) was investigated in the current study, the associations of this variant with BMI were examined and there were insignificant differences observed among comparison of the three groups of genotypes. Furthermore, the alleles of the variant was associated with higher BMI among the three groups of genotypes in T2DM with hypertension. The results of the current study confirmed a link that has been found between FTO variants and BMI.

Results are in agreement with the previous data by Frayling TM *et al.* 2007 who described that carriers of the pathogenic allele of rs9939609 (who represent almost 16% of the population) to be strongly associated with T2DM and weighed 3 kg more than the rest of the population. Also, this association was quickly replicated by Dina C *et al.* 2007 who identified SNPs in FTO that were strongly associated with early-onset obesity among both children and adults. This association was abolished by Schäfer SA *et al.* 2011 and Freathy RM *et al.* 2008 after adjustment for BMI leading to the conclusion that *FTO* is directly linked to BMI and indirectly to T2DM.

The genetic power of the SNP (rs9939609) was calculated. In the current study, the genetic power obtained seemed to be higher than the optimal level (80%).

The Genotype frequencies of FTO (rs9939609) gene were consistent with HWE in T2DM. These findings were also reported by Adeela S *et al.* 2013 and Carmela F *et al.* 2013.

The understanding of common genetic variants influencing T2DM and of the genetic/non-genetic factors with which they interact is a major focus of research to perceive the mechanisms underlying the pathogenesis of the disease as well as related pathological consequences. Combining these genetic variations with new developments in the fields of bioinformatics, genomics, and proteomics will lead to new information on diagnostics, treatment and eventual prevention of the disease of Iraqi society. Advances such as the development of genome-wide association studies (GWAS) have enabled the identification of a number of genes associated with T2DM risk. In this scenario, studies have identified that the variants in FTO (rs9939609) were strongly associated with type-2 diabetes (Frayling T.M. *et al.* 2007) and Dina C *et al.*2007 identified SNPs in FTO (rs17817449, rs1421085) that were strongly associated with early-onset obesity among both children and adults. Thus, the SNP (rs9939609) was investigated in the current study in Iraqi Arab type 2 diabetic patients with and without hypertension. For our knowledge, this study is the first one dealt with this SNP of the FTO gene in respect to the clinical characteristics in Iraq.

The results of genetic frequency of FTO (rs9939609) gene for TT, AT and AA were 125(66.48%), 56(29.78%) and 7(3.72%) respectively in T2DM with hypertension, whereas in T2DM without hypertension were 52(35.13), 80(54.05) and 16(10.81) were observed respectively. The derived allele frequency for T allele of FTO (rs9939609) gene polymorphism was 81.38%, 62.16% in T2DM with and without hypertension respectively whereas, the derived allele frequency for A allele of FTO (rs9939609) gene polymorphism was 18.61%, 37.83% in T2DM with and without hypertension respectively. Results of FTO (rs9939609) gene polymorphism demonstrated a protective role of the investigated polymorphism against the occurrence of hypertension in T2DM with respect to those of the wild type (TT) after adjustment for age, sex and BMI. Also insignificant variation was obtained when the analysis was carried out without adjustment.

The MAF of our study is lower (18.61%) than A allele frequency in South Asian population (35.00%) in diabetic group (Yanik et al 2009) and in Asian study. Reverse results in Asian population were found the T allele frequency is higher in control group (49.8%) than in diabetic group (43.6%) and this suggests a protective role of T allele in South Asian population.

The MAF in our study was higher in T2DM without hypertension than T2DM with hypertension (37.83 vs. 18.61%) respectively. This suggests a protective role of mutant A allele in contrast to study in hazakh children in china population by Li M et al 2010 in which MAF was higher in case group than that in the control (32.6% vs 24.3%) respectively. So this study was not in agreement with our finding that the A allele was protective.

The MAF in our study was higher in T2DM without hyper-

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tension than T2DM with hypertension (37.83 vs. 18.61%) respectively. This suggests a protective role of mutant A allele and this was an agreement with study in Mexican population by Marisela V et al 2008 in which MAF was higher in non-diabetic group than that in the diabetic (19.2% vs 17.9%) respectively.

Also, a study in European population by Harvest F. et al 2010 on T1DM with and without diabetic nephropathy. He found that the MAF exhibited insignificant differences between the two groups and a conclusion was made that the common FTO genetic polymorphism, rs9939609, confers the risk susceptibility to the increasing BMI, but not fundamentally contributes to the development of diabetic nephropathy. This study also was in an agreement with our finding.

The dyslipidaemia that is often present in individuals with type 2 diabetes is characterized by hypertriglyceridaemia, raised LDL-cholesterol and a low HDL cholesterol profile (Krauss RM et al 2004). The overstimulation of lipogenesis at the liver due to hyperinsulinaemic conditions is thought to be a critical component of the overproduction of VLDL particles seen in type 2 diabetes (Adeli K et al 2001). Consequently, the abnormal fat storage and ectopic fat deposition in other insulin target tissues has been suggested to have a role in the progressive nature of insulin resistance. (Lewis GFet al 2002). Adipose tissue can influence glucose homeostasis by release of metabolites (FFA), hormones (leptin, adiponectin, resistin, visfatin) and proinflammatory cytokines (IL-1, TNFα, MCP-1).(Klein S et al 2011, Scherer PE et al 2006). Our findings are consistent with many studies that showed abnormal lipid profile associated with T2DM like, Anne Sofie Andreasen et al. 2010 .

It is reasonable to speculate on the changes of the serum lipid concentrations with the variations of the genotypes in diabetics with hypertension. Unfortunatlly, such changes seemed to be taken place independent on the genotypes. Really, such phenomenon seemed to be surprising since three SNPs were evident to have a protective impact on the occurrence of hypertension in type 2 diabetics. The situation is to complex and further studies are essential for clarification.

The Resistin measurement pointed out significant elevation in the group of type 2 diabetics with hypertension when they were compared with those without hypertension. This finding is consistent with some studies that found increased circulating resistin levels and its mRNA expression in adipose tissue in patients with obesity and T2DM (Degawa-Yamauchi et al., 2003) Again levels of resistin concentration in type 2 diabetics with hypertension seemed to be changed independently on the types of genotypes and further studies are critical to achieve the exact mechanism by which resistin is involved in the pathogenesis of hypertension in type 2 diabetes mellitus

CONCLUSIONS

The SNP of FTO rs9939609 gene have a protective role against the occurrence of hypertension in type 2 diabetic patients in Al-Najaf Governorate,Iraq, and changes of the serum lipid concentration as well as Rseistin levels may be taken place independent on the types of the investigated genotypes. BMI is seemed to be independent on the genotype of the investigated gene (FTO rs9939609).

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