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Original Research Article

Implications of Vitamin D Receptor Gene *Fok*I and *Bsm*I Polymorphisms in Type 2 Diabetes among Saudi Population

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ABSTRACT

Background: The role of vitamin D receptor (VDR) has been involved in different disease states such as cancer, bone disease, tuberculosis and metabolic syndrome. Research on association between VDR polymorphisms and type 2 diabetes mellitus (T2DM) in various ethnic populations and different environmental conditions like atmospheric temperature are so far uncertain. Vitamin D is assumed to function as transcription regulator in controlling the β-cell insulin secretion by its association with its receptor complex.
Aim: This study analyzed the relationship between VDR *Fok*I and *Bsm*I polymorphisms and the susceptibility toT2DM among Saudi subjects in Makkah region that has a warm to hot climate through the whole year.
Materials and Methods: Genomic DNA was extracted from the peripheral blood leucocytes and genotyped for the single nucleotide polymorphisms (SNPs) of *Fok*I (T/C) and *Bsm*I (A/G) using the polymerase chain reaction and restriction fragment length polymorphism analysis (PCR-RFLP).
Results: Our results demonstrated that in Makkah region, which has a hot atmosphere consistently, there is no significant difference in the genotype and allele frequencies of VDR *Fok*I and *Bsm*I polymorphisms between the subjects withT2DM and the control group ($p > 0.05$). Thus our results validate and affirm various research studies already done in different ethnic populations (European, Chinese, and Tunisian subjects) and geographical areas.
Conclusion: The VDR *Fok*I and *Bsm*I polymorphisms may not be related to the vulnerability to T2DM among Saudi population in Makkah area.

Key words: Type 2 diabetes mellitus, Vitamin D Receptor, Gene Polymorphism, restriction endonuclease, polymerase chain reaction.

INTRODUCTION

Diabetes mellitus (DM) is a serious world medical issue including Saudi Arabia. [1,2] Little is known about the reason of T2DM; nevertheless many of its risk factors have been recognized and are investigated. T2DM, as other inflammatory diseases, may be averted if its risk factors are detected during early onset of the disease, and managed. [3-6] Accordingly, learning about

T2DM risk factors and thereby applying preventive measures is the initial phase in prevention, as this will enable T2DM patients to settle on the informed decision that prompts a sound lifestyle. [7,8] In Saudi Arabia, there are moderately few studies directed to decide and assess the T2DM risk factors in the Saudi population and preventive measures. [9]

It is well known that environmental conditions and genetic factors both assume contributory parts in the development of T2DM. In spite of the fact that the hereditary factors play a basic role in different types of diabetes mellitus, how the legacy of these hereditary loci contributing to the disease remains obscure. Besides, such hereditary components may likewise cooperate with environmental factors, for example, diet and atmospheric temperature [10,11] In general, predominantly, T2DM and T1DM are polygenic conditions; however, several monogenic forms of diabetes have been identified. [12] Such identified genes are assembled into various classifications, for example, those involved in control of growth factors, those mediating signal transduction, and those associated with energy metabolism and energy utilization. [13] Various studies have been carried out on the relationship between the genetic variation and diabetes. These studies require affirmation in various racial and ethnic groups and environmental conditions. [4,15]

The gene of the VDR is exceedingly polymorphic and is situated on chromosome 12q12-14. There are six commonly investigated VDR polymorphisms: *Fok*I polymorphism in exon 2; *Bsm*I, *Tru*9I, and *Apa*I polymorphisms situated between exons 8 and 9; the *Taq*I polymorphism present in exon 9; and the poly-A polymorphism downstream of the 3´ un-translated region. [16,17] The contribution of vitamin D in the development of T1DM has been investigated in several studies, and it was demonstrated that children whose diets were supplemented with vitamin D have a lower incidence of T1DM in adulthood. [18] Furthermore, abnormal vitamin D and calcium homeostasis likewise contributes in the development of T2DM. High vitamin D status in subjects has been shown to provide protection against T2DM. [19,20]

Vitamin D Receptor (VDR) is a member of the steroid-thyroid hormone receptor family. [21] Vitamin D is assumed to be an imperative part of the control of the endocrinal functions of pancreas, particularly in the secretion of insulin. [22] The action of vitamin D is mediated through association to its specific nuclear receptor (VDR) which is expressed in beta (β)-cells. [21] Insulin secretion from the beta (β)-cell is directed by Vitamin D and its receptor complex. Moreover, Vitamin-D inadequacy decreases insulin synthesis and secretion in humans and in animal models of diabetes and vitamin D supplement in diet may increase the insulin secretion. [23,24] Polymorphisms depicted in the VDR genomic sequences may be able to modify the activity of VDR protein. [25] Despite the fact that genetic basis of T2DM is still poorly understood, several studies suggested that the VDR gene is a novel candidate gene contributing to the susceptibility to the diabetes and particularlyT2DM. [26-30]

In this study, we planned to investigate the relationship between VDR gene *Fok*I and *Bsm*I polymorphisms and the risk of T2DM among Saudi people in Makkah region and its environs. Few studies about gene polymorphism of VDR gene in T2DM have been conducted in Saudi Arabia. [31] In this manner, it is important to affirm the relationship between VDR polymorphism and the susceptibility of T2DM in Saudi subjects.

MATERIALS AND METHODS

Subjects and sample collection: This research was performed between 2014and 2016 and it included 163 subjects. Fully informed consent was acquired from the control and diseased subjects, and this research was affirmed by the Umm Al Qura University's IRB (Internal Review Board). Seventy eight unrelated type 2 diabetic patients were selected from health centers

and hospitals in Makkah district, Saudi Arabia. The control subjects consisted of eighty five healthy subjects who either attended for a normal wellbeing check at a general practice or at work. Venous blood was collected from all subjects between 9:00 and 11:00 a.m. subsequent to fasting from 10:00-11:00 p.m. the previous day. Each specimen was divided into two halves, one half for the serum preparation and the other half was put in sterile K_3EDTA (tri-potassium ethylene-diamine tetraacetic acid) coated tubes. Low speed centrifugation was used to isolate blood plasma; white cells were aspirated from the buffy coat for the isolation of DNA. Samples were kept at –20˚C till the time of analysis.

Determination of fasting blood glucose and hemoglobin A1c (HbA1c):

We used glucose oxidase technique to determine the fasting glucose level, using a kit from Human Diagnostics, Wiesbaden, Germany. The amount ofHbA1c was determined using enzymatic HbA1c assay kit according to the maker directions (Human Diagnostics, Wiesbaden, Germany).

Genomic DNA extraction:

Genomic DNA was prepared from peripheral blood leukocytes utilizing Qiagen DNA extraction kit (QIAamp DNA Blood Mini Kits, Qiagen, Hilden, Germany).

VDR *Fok*I and *Bsm*I genotyping:

The *Fok*I polymorphic region genotyping of exon 2 of VDR gene was done as described elsewhere with slight modification. [32] PCR was performed using the following oligonucleotide primers: 5' -AGC TGG CCC TGG CAC TGA CTC TGC TCT-3' (forward primer) and: 5' -ATG GAA ACA CCT TGC TTC TTC TCC CTC- 3' (used as the reverse primer). In 25 µl PCR mixture, 100 ng of genomic DNA were utilized for PCR amplification and 2 × PCR master mix was used (Thermo Fisher Scientific, Inc, MA USA). Following conditions were utilized for the PCR amplification: initial DNA denaturation at 96°C for 4 min, then 30 cycles of denaturation for 30 seconds at 94 °C, annealing for 30 seconds at 57 °C, and extension for 30 seconds at 72 °C. The reaction was terminated following 7 min elongation at 72 °C. PCR product was then digested with *Fok*I restriction endonuclease. Restriction fragments were analyzed by electrophoresis through a 2 % agarose gel containing ethidium bromide, the bands were visualized under ultraviolet light and photographed.

For genotyping of VDR *Bsm*I, the primers used were: 5′-AAC CAG CGG GAA GAG GTC AAG GG- 3′(the forward primer) and 5′ -CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA- 3′ (the reverse primer). The PCR reaction was done in 25µl final volume and 2 ×PCR master mix was utilized. The PCR program began by denaturation step at 95 °C for 3 min, then, 35×(95 °C for 30 s, 65°C for 30s, 72°C for 30 s) and lastly, 72 °C for 10 min. The amplified PCR product was digested using *Bsm*I restriction enzyme. DNA fragments were separated on 2 % agarose gel by electrophoresis and genotypes were identified as previously described. [33]

Statistical Analysis: We used SPSS for Windows version 20.0 (SPSS Inc, Chicago, IL, USA) for data analysis. To compare mean values of continuous variable in cases and control, Student's t test was utilized, whereas χ^2 analysis was utilized to evaluate categorical data.

RESULTS

Table1 demonstrates the demographic data in studied groups. Table2 illustrates the genotype and allele frequencies in both T2DM and control groups. The genotype distribution of *Fok*I polymorphism was in Hardy-Weinberg equilibrium in both the T2DM and control subjects. The genotypes FF, Ff and ff were 61.5 %, 24.3 % and 14.1% in subjects with T2DMrespectively and were 55.2 %, 36.4 % and 8.2 % respectively in the control group. We did not observe any significant difference in the genotype and allele

frequencies between patients with T2DM and healthy controls. The *Bsm*I genotype and allele distribution, were also observed to be in Hardy-Weinberg equilibrium in both T2DM and control groups. *Bsm*I genotypes and allele frequencies in T2DM groups and in controls are shown in Table 2. In the T2DM patients, the genotypes BB, Bb and bb were 29.48%, 33.33% and 37.17 % respectively. However, these genotypes were29.62%, 32.1% and38.27 % in the control subjects respectively. There was no significant difference in the distribution of genotypes and allele frequencies of *Bsm*I between patients with T2DM and the matched healthy controls.

Table 1: Demographic data for control and T2DM:

Characteristics	Control group	Patient group	*p* value
Subjects (n)	85	78	
Age (years)	42±5	44±5.8	n.s.
Gender (M/F)	56/29	48/30	
BMI (kg/m^2)	23.83±1.13	24.15±1.12	n.s.
FBS	83±07	160±35	<0.001
HbA1c (%)		7.26±1.61	

**P*-value < 0.05 was considered as significant. Data are shown as mean SD. n.s.= none significant

Table 2. Genotype distribution and allele frequencies of VDR FokI and BsmI polymorphisms in subjects with T2D and control group

VDR polymorphism	Control (n=85)		T2D (n=78)		[a]χ^2	*P value
	No	%	No	%		
FokI Genotypes:						
FF	47	55.2	48	61.5	0.652	0.419
Ff	31	36.4	19	24.3	2.806	0.094
ff	7	8.2	11	14.1	1.425	0.233
Alleles:						
F	125	73.5	115	73.7	3.485	0.972
f	45	26.47	41	26.28		
BsmI Genotypes:						
	Control (n=81)		T2D (n=78)			
BB	24	29.62	23	29.48	0.00	0.984
Bb	26	32.10	26	33.33	0.028	0.868
bb	31	38.27	29	37.17	0.02	0.887
Alleles:						
B	74	45.67	72	46.15	0.031	0.942
b	88	54.32	84	53.84		

[a]Chi-square analysis of genotypes between patients with T2D and healthy controls.
**P*-value < 0.05 was considered as significant.

Table 3: Mecca Weather: Monthly variation in high and low temperatures, humidity, daylight hours and humidity in Mecca region. (Data adapted from, Jeddah Climate Center, Saudi Arabia)

Month	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Year
Mean Daylight hours	11.0	11.0	12.0	13.0	13.0	13.0	13.0	13.0	12.0	12.0	11.0	11.0	12.1
Average high ℃	30.5	31.7	34.9	38.7	42.0	43.8	43.0	42.8	42.8	40.1	35.2	32.0	38.13
Average low ℃	18.8	19.1	21.1	24.5	27.6	28.6	29.1	29.5	28.9	25.9	23.0	20.3	24.7
Average Relative Humidity	58%	54%	48%	43%	36%	33%	34%	39%	45%	50%	58%	59%	46.4%
Average UV index	7	9	11+	11+	11+	11+	11+	11+	11+	10	8	7	9.8

DISCUSSION

Diabetes mellitus is an increasingly global health challenge including Saudi Arabia. It has been reported by the World Health Organization (WHO) that Saudi Arabia has the second alarmingly increasing problem of diabetes in the Middle East and the seventh in the world. [2] It is likely that both hereditary and environmental factors assume important role in the disease pathogenesis. [26] Different research groups have studied a number of candidate genes that are likely to induce the susceptibility to T2DM in various populations. However, until now, very few studies have been conducted in Saudi Arabia to study the relationship between VDR gene polymorphism and the susceptibility to T2DM. VDR gene mediates transcription function, and the interaction with its ligand (vitamin D) is known to alter insulin secretion and insulin function. [34] We have investigated VDR *Fok*I and *Bsm*I gene polymorphisms in a group of Saudi people with T2DM, and matched control subjects

for gender and age in Makkah area in western Saudi Arabia.

No significant difference was seen in the genotype distribution and allele frequencies of both SNPs in *Fok*I and *Bsm*I polymorphisms in VDR gene between the control and the patients with T2DM. A critical factor for consideration in our results on VDR polymorphisms is that, this research has been made in Makkah environs of Saudi Arabia, an area that is known to have two seasonal variations, hot and extremely hot (Table 3). The available sunshine throughout the year is fairly high and thus Makkah environs can be considered a unique reference district for the possible bio-accessibility of vitamin D throughout the year, unlike many European, North American and even areas in Asian countries that are situated in the northern hemisphere.

Several researchers have studied the relationship of VDR polymorphism in various populations. In Polish subjects, Malecki *et al* have examined the polymorphism of four single nucleotide polymorphisms (SNPs) of VDR gene (*Bsm*I, *Taq*I, *Fok*I and *Apa*I) and they found that the genotype and allele distribution is the same in both controls and T2DM. [35] Additionally, in French Caucasian population, Ye*et al* studied the same SNPs of VDR gene (*Bsm*I, *Taq*I, *Fok*I and *Apa*I) and they observed that both the genotype and allele distribution is the same in both controls and T2DM. [36] Furthermore, in Turkish population, Dilmec *et al* found no significant difference in genotype and allele frequencies of the same four SNPs (*Bsm*I, *Taq*I, *Fok*I and *Apa*I) of the VDR gene between both controls and T2DM. [37] Among European Caucasians, Bertoccini *et al* studied the association between VDR FokI polymorphism and T2DM and found no difference of the genotype distributions and allele frequencies between T2DM subjects and controls in Italians. [38] Besides, in Chinese Han subjects, Fei Yu *et al* studied four VDR SNPs and found that VDR *Fok*I and *Bsm*I polymorphisms are not related to T2DM risk in Chinese. [39] In the African continent, for Tunisian subjects, no significant relationship between VDR *Fok*I polymorphism and T2DM was observed, Mahjoubi *et al*. [40] Accordingly, all of the above previously reported observations concur and support our results that the reported polymorphisms of VDR gene have no bearing on the diabetes susceptibility.

Strikingly, contrasting results were obtained by different investigators examining VDR variants and diabetes in different geographical and environmental regions. For instance, in North Indians (Kashmiri population), Malik *et al* reported VDR *Taq*I and *Bsm*I polymorphism and they found that *Bsm*I G allele is associated with T2DM risk. [41] Likewise, in United Arab Emirates, Safar *et al* found that the G allele and GG genotype of *Fok*I and T allele and TT genotype of *Bsm*I are associated with T2DM risk in Emirati population. [42] Among the Chinese Han subjects< 55 years old; Jia *et al* noted that *Fok*I polymorphism is associated with T2DM. [43] In Saudi population of Riyadh region, Aldaghri *et al* examined the polymorphism of four SNPs in VDR gene (*Apa*I, *Fok*I, *Taq*I and *Bsm*I) and an association of *Bsm*I T allele and C/T genotype and *Taq*I A/G genotypes and T2DM was observed. [31] These findings differ from our observations in Makkah district; which may, among other possibilities, be clarified by differences in the genetic background of the participants or because of some enigmatic environmental factors such as the daily exposure to sunlight and temperature variations. The present study has restrictions due to moderately modest number of subjects. Further studies will be needed to assess the serological levels of the VDR and related metabolites and related genetic analysis in a large T2DM cohort with clinical information. These investigations will be important basis to understand the role of VDR in the pathogenesis of T2DM in unique geographical and ethnic region.

CONCLUSION

In conclusion, our investigations on the VDR gene polymorphisms in Makkah district diabetic patients clearly validate similar studies in diverse ethnic populations in Tunisian, and Chinese subjects that the *Fok*I and *Bsm*I polymorphisms in the VDR gene show no significant difference in genotype and allele frequency between controls and patients with T2DM. These data strongly suggest that the *Fok*I and *Bsm*I SNPs may not contribute to the susceptibility to T2DM among Saudi population.

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Conflict Of Interest

The authors declare that no conflict of interest exists.

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Abbreviations: VDR, vitamin D receptor; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism.

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