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ORIGINAL ARTICLE

Vitamin D receptor FokI (rs2228570) polymorphism in diabetic patients

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ABSTRACT

Background: Vitamin D is a steroid hormone. Many biological actions are triggered by vitamin D. FoKI (rs2228570) is VDR single nucleotide polymorphism. The FokI polymorphism is recognized by a start-codon alteration from cytosine to thymine, which results in three amino acids shorter protein. T2DM has been associated with the FokI VDR gene polymorphism. The aim of this study was to determine the relationship between the VDR gene polymorphism FokI and T2DM in Egyptians.

Method: This study was carried out on 111 subjects: 37 healthy individuals, 37 obese non-insulin-dependent diabetic patients with BMI > 30 kg/m2, and 37 non-obese non-insulin-dependent diabetic patients with BMI < 24 kg/m2. VDR FokI genotype was determined by PCR-RFLP, and the 25(OH)D level was measured using the ELISA method.

Results: Diabetic patients had a significantly higher prevalence of the polymorphic genotype of the VDR FokI polymorphism (ff) than the control group (OR = 4.9, 95% CI = 1.94-12.36, p = 0.0007). The FokI (f allele) allele frequency was greater in the T2DM obese patients than in the control group and T2DM non-obese patients (p < 0.0001). Diabetic patients had lower 25-hydroxyvitamin D (25(OH)D) levels than individuals in the control group (P< 0.001).

Conclusions: The VDR polymorphism FokI's f allele and f genotype may increase the risk of diabetes in Egyptians.

Key words: Vitamin D receptor, FokI polymorphism, Vitamin D, Type 2 diabetes mellitus.

INTRODUCTION

Vitamin D is a fat-soluble vitamin found in a few foods or added to others. Ultraviolet rays (UVR) from sunshine strike the skin and start the synthesis of vitamin D [1]. The cytochrome enzyme converts vitamin D in the liver and kidneys to the physiologically active 1,25-dihydroxy vitamin D [1, 25(OH)2 D] [2].

Vitamin D binds to VDRS then enters the nucleus, where it undergoes conformational changes to interact with transcriptional factors [3]. The VDR gene is found on chromosome 12q13.11 and has five promoters, eight coding exons, and six untranslated exons. Single nucleotide polymorphisms (SNPs) in the vitamin D receptor gene include ApaI (rs7975232; intron 8), and FoKI (rs2228570; exon 2) [4].

As shown in figure 1, the FokI polymorphism in the VDR gene results in a thymine (T) to cytosine (C) substitution at the start codon ATG (methionine) that changes the produced protein: the 424 amino acids (F allele) protein and the 427 amino acids (f allele) protein [5].

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia qqq qqqa dysregulation of lipid and protein

metabolism connected with inadequacy in insulin discharge and/or insulin activity with environmental and genetic factors [6]. Egypt is one of the top ten nations in the world for diabetes according to the International Diabetes Federation (IDF). In Egypt, 15.56% of people between the ages of 20 and 79 have diabetes [7]. Macrovascular and microvascular complications are two categories of long-term diabetes complications [8].

Vitamin D plays different roles in the genesis of type 2 diabetes. Calcium homeostasis and the control of insulin production from β-cells are both regulated by vitamin D [9]. It has been established that calcitriol improves islet function and maintains β -cell mass [10].

Vitamin D increases insulin sensitivity through the binding of 1,25(OH)2D3 to VDR in insulin-responsive cells. 1,25(OH)2D interacts with VDR and then with the retinoid X receptor (RXR). 1,25(OH)2D3, VDR, and RXR bind to VDRE in the human insulin receptor gene promoter. As a result, both the quantity of insulin receptor substrates (IRs) and the transcriptional activity of insulin receptor genes rises [11].

Not only does the FokI polymorphism influence the function of vitamin D3, but it also interferes with the effectiveness of vitamin D and VDR's binding, minimizing insulin action and causing T2DM [3]. The aim of the study was to determine the relationship between the VDR gene polymorphism FokI and T2DM in Egyptians.

METHODS

Study Design:

At the Medical Biochemistry Department of Zagazig University, Faculty of Medicine, case-control research was carried out. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University.

111 participants in this study were divided into three groups. The control group consisted of 37 healthy individuals who had not been diagnosed with type 2 diabetes mellitus and had no family history of the disease or any other illness that might interfere with our study. The diseased groups included 37 obese non-insulin-dependent diabetic patients with a BMI > 30 kg/m2 and 37 non-obese non-insulin-dependent diabetic patients with a BMI< 24 kg/m2.

Specimens' collection:

After 8 hours of overnight fasting, 5 ml of venous blood was withdrawn from every subject under complete aseptic conditions by sterile vein puncture and divided into three samples. One ml was collected in sodium fluoride for the estimation of fasting blood glucose levels. Two ml were collected in plain tubes, left for 20 minutes until clotting, separated from serum, and stored at -20 °C for the assay of 25(OH)D level by enzyme-linked immunosorbent assay (ELISA) kits. Two ml were collected in sterile EDTA tubes for the extraction of DNA for PCR.

Biochemical Measurements:

The determination of fasting blood glucose level was performed by the enzymatic colorimetric method using SPINREACT (Girona, Spain) [12]. Estimation of 25-hydroxy vitamin D (25(OH)D) level was calculated by a commercially available ELISA kit (catalog no: In-Hu4145, NOVA, China).

DNA extraction and RFLP analysis:

Genomic DNA extraction from blood leukocytes was analyzed for the VDR FokI gene polymorphism using the PCR-RFLP using the gSYNCTM DNA Extraction Kit, ver. 02.10.17 as directed by the manufacturer (Geneaid Biotech Ltd.).

The purity of DNA was assessed by a spectrometer to detect absorbance at 260 and 280 nm wavelengths and calculate the A260/A280 ratio.

PCR-RFLP test was performed using a specific forward primer 5′ AGCTGGCCCTGGC ACTGACTCTGCTCT3′ and reverse primer: 5′ ATGGAAACACCTTGCTTCTTCTCCCTC 3′ . The PCR was performed in a final volume of 20µl, including 10 µl of 2x i-TaqTM PCR Master Mix (Geneaid Biotech Ltd), 1 ul of each primer (Biolegio, Nijmegen, Netherland), 5 µl of genomic DNA, and 3 ul of deionized water.

The amplification was performed using the DNA thermal cycler 480, Perkin Elmer (Norwalk,

CT 06856, USA), serial No. P16462, and was programmed for the following conditions: An initial cycle of 95°C for 10 minutes for initial denaturation and then 35 denaturation cycles at 94°C for 30 s, annealing at 61°C for 60 s, and extension at 72°C for 60 s, followed by a final extension of 10 minutes at 72°C.

Detection of PCR amplification products using 1.5% agarose gel electrophoresis stained by ethidium bromide and ultraviolet transilluminator visualization. Digestion products with a restrictive enzyme (FoKI) for gene VDR rs2228570 involved 267 bp bands for the wild type (FF), 267, 197, and 70 bp bands for heterozygous (Ff), and 197 and 70 bp bands for homozygous (ff).

Statistical Analysis:

All statistical analysis was performed using the statistical package for social science (SPSS) version 22 (Chicago, IL, USA). Data were compared between cases and controls using Chi-squared tests and two-sided unpaired t-tests, and Fisher's exact (F) test was used in the small sample-sized groups. Odd's Ratio (ORs) and Confidence interval (95% CIs) were estimated to measure the association between genotype frequency in studied groups of T2DM. The P-value is considered significant when the P-value<0.05.

RESULTS

Demographic and clinical characteristics of the studied group

Regarding the demographic data, no statistically significant differences were found in age and sex, (P=0.06), (P=0.27) respectively, whereas there was a significant increase in BMI, FBS, 2HPPBG, HbA1C, total cholesterol, LDL-C, and TG in obese T2DM than in each of the control and non-obese T2DM (P<0.001) (Table 1).

In this study, table 2 illustrates the genotype distribution of the selected SNPs and their associations with T2DM risk. In both cases and controls, the genotype frequencies of SNPs were consistent with the Hardy-Weinberg equilibrium (HWE). There was a statistically significant increase in the ff genotype in the diabetic patient group when comparing them with the control group (OR = 4.9, CI 95% = 1.94–12.36, p = 0.0007). Concerning allele frequency, there was a significantly increased frequency of the f allele (polymorphic allele) in the diabetic patient group compared with the control group (OR = 3.62, CI 95% = 1.94–6.79, p = >0.0001) (Table 2).

Comparison of the frequency of the FokI genotype in obese and non-obese type 2 diabetic patients showed that the frequency of the ff genotype and f allele of the FoKI gene was higher in obese type 2 diabetic patients when compared with non-obese type 2 diabetic patients, indicating that carriers of the f allele may be considerably correlated with a higher risk of obesity and type 2 diabetes (Table 3).

Demographic and biochemical parameters of Type 2 diabetic patients categorized according to FoKI gene polymorphism

Comparing FoKI genotypes (FF, Ff, and ff) in clinical data showed that all type 2 diabetic patients' carriers of the f allele showed a significantly longer duration compared with the carriers of the F allele (FF and Ff) (P=0.03). Also, they had significantly lower vitamin D levels than those with the F allele (P=0.001). There was no significant difference regarding other demographic and biochemical markers (Table 4).

Regarding demographic and biochemical parameters of obese type 2 diabetic patients classified based on FoKI gene polymorphism patients, carriers of the ff genotype had significantly lower levels of Vitamin D compared to FF and Ff. There was no significant difference in other demographic and biochemical data (Table 5).

Non-obese type 2 diabetic patients with the ff genotype, on the other hand, had significantly higher BMI, longer duration, and lower Vitamin D levels when compared to other genotypes (Table 6).

Analyzing these findings revealed that the f allele may alter vitamin D protein expression, resulting in a decrease in plasma levels in all diabetic patients. However, the largest drop was in obese diabetic individuals.

Table 1: Demographic data of the studied groups

	Control subjects (n=37)	Obese T2DM (n=37)	Non-obese T2DM (n=37)	F	*P*
Age	56.1 ± 3.9	58.4 ± 3.4	57.1 ± 4.9	2.9	0.06
Sex Female	18 (49%)	24 (65%)	18 (49%)	X^2= 2.6	0.27

Male	19 (51%)	13 (35%)	19 (51%)		
BMI (kg/m2)"	26.6 ± 1.57	36.8 ± 2.03[a]	22.01 ±1.45[ab]	724.7	<0.001*
duration of DM (years)	-	9.1 ± 2.8	8.65 ± 3.09	T=0.66	0.5
FBS (mg/dl)	101.9 ± 45	179.9 ± 39 [a]	178.4 ± 42.5 [a]	65.8	<0.001*
2h-PPBG	122.7 ± 7.2	290.2 ± 36.6 [a]	281.7 ± 43.3 [a]	301.2	<0.001*
HbA1C (%)	4.8 ± 0.3	8.1 ± 0.95 [a]	7.9 ± 1.04 [a]	180.8	<0.001*
Total cholesterol	154.4 ± 15.2	185.2 ± 20.2[a]	176.9 ± 3.7[ab]	42.9	<0.001*
HDL-C	52.7 ± 7.9	45.3 ± 3.5[a]	48.4 ± 9.7[ab]	9.1	<0.001*
LDL-C	71.2 ± 17.7	103.8 ± 22.8[a]	97.2 ± 4.6[ab]	38.2	<0.001*
TG	152.02 ± 13.06	171.4 ± 7.4[a]	165 ± 12.9 [b]	27.4	<0.001*
Vitamin D level	28.4 ± 10.8	10.5 ± 4.2[a]	28.5 ± 6.6 [b]	20.1	<0.001*

Table 2: Genotype and allele frequency distribution of FoKI in type 2 diabetic patients and control subjects

FoKI gene polymorphism	**Controls (n=37)**	**T2DM (n=74)**	**OR**	**95%CI**	**P**
FF	19 (51%)	14 (19%)	1 (reference)		
Ff	5 (14%)	13 (18%)	3.5	1.02-12.2	0.04*
ff	13 (35%)	47 (63%)	4.9	1.94-12.36	0.0007*
Alleles					
F	43 (58%)	41 (28%)	1 (reference)		
f	31 (42%)	107 (72%)	3.62	1.94-6.79	<0.0001*

Table 3: Genotype and allele frequency distribution of FoKI in obese and non-obese type 2 diabetic patients

FoKI gene polymorphism	**Obese T2DM (n=37)**	**Non-obese T2DM (n=37)**	**OR**	**95%CI**	**P**
FF	**5 (14%)**	**9 (24%)**	**1 (reference)**		
Ff	**6 (16%)**	**7 (19%)**	**1.54**	**0.32-7.2**	**0.58**
ff	**26 (70%)**	**21 (57%)**	**2.2**	**0.64-7.6**	**0.2**
Alleles					
F	**16 (43%)**	**25 (34%)**	**1 (reference)**		
f	**58 (78%)**	**49 (66%)**	**1.84**	**0.88-3.8**	**0.1**

Table 4: Demographic and biochemical parameters of type 2 diabetic patients categorized according to FoKI gene polymorphism

	FF (n=14)	**Ff (n=13)**	**ff (n=47)**	**F**	**P**
Age	56.07 ± 5.6	56.6 ± 8.3	57.8 ± 7.1	0.41	0.66
Sex **Female** **Male**	 7 (50%) 7 (50%)	 7 (54%) 6 (46%)	 28 (60%) 19 (40%)	X^2= 0.45	0.79
BMI (kg/m2)"	26.4 ± 7.6	28.1 ± 8.5	30.6 ± 7.2	1.8	0.16
duration of DM (years)	9.7 ± 2.8	7.5 ± 3.07[a]	10.03 ± 2.9[b]	3.6	0.03*
FBG (mg/dl)	173.7 ± 29.03	168.2 ± 32.6	183.8 ± 45.03	0.9	0.4
2h-PPBG	287.3 ± 28.7	282.6 ± 38.8	286.5 ± 43.8	0.05	0.94
HbA1C (%)	8.07 ± 0.84	7.83 ± 0.87	8.1 ± 1.08	0.5	0.6
T. cholestrol (mg/dl)	162.3 ± 23.4	170 ± 20.4	171.9 ± 24.5	0.89	0.41

HDL-C	51.2 ± 8.5	52.07 ± 7.8	49.9 ± 9.6	0.31	0.73
LDL-C	80 ± 27.9	85.7 ± 21.3	90.2 ± 26.8	0.85	0.42
TG	155.3 ± 15.8	161.1 ± 13.9	158.7 ± 14.3	0.53	0.58
vitamin D level	28 ± 6.3	24.3 ± 5.8[a]	12.7 ± 4.3[ab]	0.64	0.001*

Table 5: Demographic and biochemical parameters of obese type 2 diabetic patients categorized according to FoKI gene polymorphism

	FF (n=5)	**Ff (n=6)**	**ff (n=26)**	**F**	**P**
Age	56.8 ± 5.8	58.1 ± 5.06	57.2 ± 6.7	0.06	0.93
Sex **Female** **Male**	 3 (60%) 2 (40%)	 4 (67%) 2 (33%)	 17 (65%) 9 (35%)	X2=0.07	0.95
BMI (kg/m2)"	36.1 ± 2.7	36.8 ± 0.96	36.8 ± 2.1	0.28	0.75
duration of DM (years)	10.8 ± 2.9	9.3 ± 1.5	10.8 ± 2.2	0.53	0.59
FBG (mg/dl)	195 ± 18.7	157.8 ± 33.9	182.1 ± 41.6	1.4	0.25
2h-PPBG	305.2 ± 21.6	286 ± 40.7	288.3 ± 38.4	0.47	0.61
HbA1C (%)	7.6 ± 0.56	8.3 ± 0.81	8.2 ± 1.03	0.95	0.39
T. cholesterol (mg/dl)	177.8 ± 27.2	185 ± 17.6	186.7 ± 19.9	0.39	0.67
HDL-C	44.6 ± 5.08	50.5 ± 7.06	48.6 ± 10.8	0.51	0.6
LDL-C	100.1 ± 31	101.7 ± 16.1	105 ± 23.4	0.12	0.88
TG	165.4 ± 12.4	164 ± 13.9	165.1 ± 13.3	0.02	0.97
vitamin D level	20.6 ± 4.6	14.8 ± 4.3[a]	10.5 ± 4.2[ab]	12.7	0.001*

Table 6: Demographic and biochemical parameters of non-obese type 2 diabetic patients categorized according to FoKI gene polymorphism

	FF (n=9)	**Ff (n=7)**	**ff (n=21)**	**F**	**P**
Age	53.4 ± 3.7	51.1 ±5.5	53.7 ± 5.2	0.74	0.48
Sex **Female** **Male**	 4 (45%) 5 (55%)	 3 (43%) 4 (33%)	 11 (52%) 10 (48%)	X2= 0.27	0.87
BMI (kg/m2)"	21.1 ± 1.07	20.8 ± 1.16	22.8 ± 1.06 [ab]	15.4	<0.001*
duration of DM (years)	9.11 ± 2.7	6 ± 3.1	9.3± 2.8 b	3.6	0.03*
FBG (mg/dl)	162 ± 27.5	177.1 ± 31.1	185.9 ± 49.8	1.002	0.37
2h-PPBG	277.4 ± 28.3	279.7 ± 40.1	284.2 ± 50.6	0.08	0.92
HbA1C (%)	8.3 ± 0.9	7.4 ± 0.74	8 ± 1.15	1.45	0.24
T.cholestrol (mg/dl)	153.7 ± 17.05	157.2 ± 12.9	153.7 ± 15.7	0.14	0.86
HDL-C	55 ± 7.6	53.4 ± 8.7	51.6 ± 7.8	0.59	0.56
LDL-C	68.8 ± 19.9	72.1 ± 14.9	71.9 ± 18.3	0.1	0.9
TG	149.7 ± 15.2	158.5 ± 14.5	150.8 ± 11.4	1.11	0.34
Vitamin D level	30.4 ± 3.4	28.8 ± 4.9	18.5 ± 6.13[ab]	19.7	<0.001*

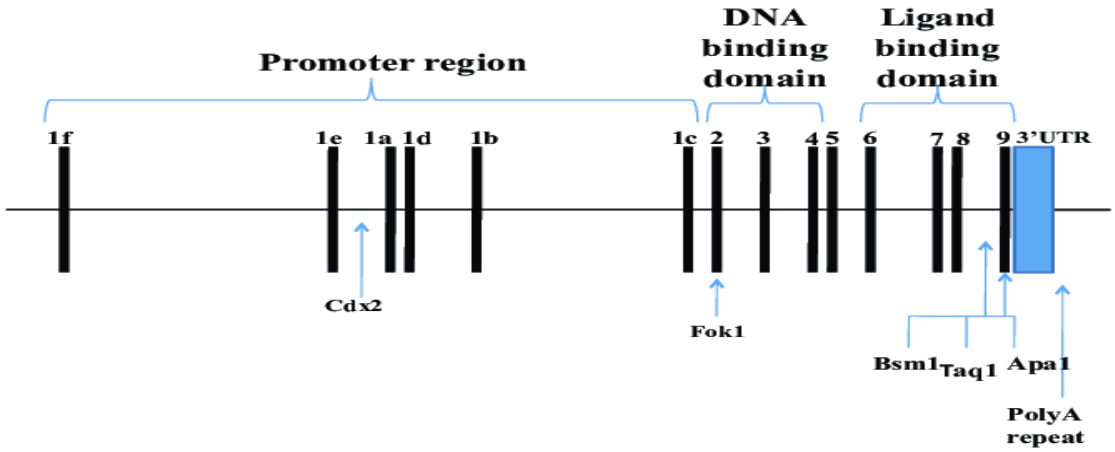

Figure 1. Structure of Vitamin D Receptor (VDR) Gene [1]

DISCUSSION

Diabetes Mellitus (DM) is a chronic medical illness caused by both environmental and inherited causes [6]. Active vitamin D binds to vitamin D receptors (VDRs) that affect gene expression. VDR is expressed in numerous organs, including those responsible for controlling glucose metabolism, including pancreatic β-cells [2].

The pathogenesis of T2DM is thought to be significantly influenced by genetic variants in the VDR [13]. Currently, FokI reflects the SNP's most significant related to type 2 diabetes. It has been established that VDR gene polymorphisms affect the VDR protein's activity. FokI can suppress the initial translation initiation site, resulting in a peptide lacking three amino acids [14].

Our findings revealed that there were no significant differences in age and sex between the examined groups (P=0.06) (P=0.27) respectively. However, there was a significant rise in BMI, FBS, 2h-PPBG, HbA1C, LDL-C, and TG in obese T2DM compared to control and non-obesity T2DM (P0.001). Also, HDL-C was significantly lower in obese T2DM than in control and non-obese T2DM.

In agreement with our results, Zaki et al. [15] revealed that there was a significant increase in BMI, FBG, LDL-C, and triglycerides in obese women when compared with age-matched healthy women. HDL-C is significantly decreased in obese women. Mackawy and Badawi [16] reported that lipid profile parameters showed a significant rise in T2DM patients.

Our findings go hand in hand with Mohamed et al. [2] who revealed that there was a statistically significant increase in BMI in diabetic groups compared to the control group (P<0.001). Also, a comparison of HbA1c, FBG, 2-HPPBG, TC, HDL, and LDL between the studied groups showed a highly significant increase in the diabetic groups compared to the control group (P<0.001).

In contrast to our study, Bertoccini et al. [17] found no significant differences in plasma concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, and circulating triglycerides because all patients and controls in this study were Caucasian, and this study did not include obese T2DM patients.

Our results also showed a significant decrease in vitamin D levels in obese T2DM patients when compared to non-obese T2DM and control groups (P<0.001), while no significant difference in vitamin D levels was detected when control and non-obese T2DM were compared.

In keeping with our findings, Zaki et al. [15] proposed that serum vitamin D concentrations were inversely associated with metabolic characteristics such as BMI, FBG, LDLC, and TG and positively correlated with HDL-C.

Three FokI genotypes (dominant homozygous FF, heterozygous Ff, and recessive homozygous ff) were analyzed using the RFLP method. Our results revealed that genetic analysis of FoKI gene polymorphism revealed that the ff genotype was significantly higher in T2DM patients compared with the control group. Carriers of the ff genotype had 5 times the risk of having T2DM than other genotypes (OR = 4.9, P = 0.0007). f allele was high in type 2 diabetic patients when compared with control, as carriers of the f allele were significantly more likely to develop T2DM about 4 times than those with the F allele (OR = 3.62, P < 0.0001). These findings proved that the f allele may be a risk factor for T2DM.

Another similar study [13] reported that the frequency of both ff and Ff genotypes was high in patients with T2DM in comparison with controls with statistically significant differences P< 0.016, 0.005 respectively. Also, there was an increased frequency of the f allele in the patient group, with a significant difference in the control group ($p < 0.001$).

Unlike our results, Bertoccini et al. [17] were unable to find an association between the FokI SNP and metabolic traits, including diabetes. This contrast can be explained by the fact that all subjects included in Bertoccini's study were Caucasians, and all of those patients were not obese.

Moreover, the frequency of the ff genotype was higher in obese type 2 diabetic patients when compared with non-obese type 2 diabetic patients (P = 0.02). Regarding FoKI alleles, the frequency of the f allele was high in obese type 2 diabetic patients when compared with non-obese type 2 diabetic patients.

In studying the association between demographic and clinical data, carriers of ff genotype significantly have low vitamin D levels and a longer duration of diabetes when compared with FF genotype carriers. In the obese diabetic group, the only significance was that carriers of the ff genotype in the obese group had lower levels of vitamin D compared with FF. The ff genotype has been associated with higher total cholesterol, higher LDL, lower HDL-C, and lower vitamin D levels compared to FF genotypes, but the association was not statistically significant.

The main finding of the study of Zaki et al. [15] women with mutant alleles for the VDR FokI (Ff + ff) had considerably lower serum 25(OH) D levels than those with the wild genotype for the VDR (FF).

This was in harmony with Mackawy & Badawi [16], who found that lipid profile parameters showed a significant association with the VDR (FokI) polymorphism in diabetic patients. They reported higher TC, TG, LDL, and lower HDL levels in Ff and ff genotype carriers.

In a study of diabetic patients, researchers discovered a relationship between VDR polymorphisms, especially FokI. When compared to FF genotypes, the ff genotype has been linked to a larger waist circumference, lower HDL-C levels, and lower vitamin D levels. The FokI VDR gene has been linked to lipid profiles in people with diabetes [15].

In contrast to our findings, Hatmal et al. [9] found no link between the FokI polymorphism genotypes and lipid profile parameters in T2DM patients and controls ($p > 0.05$). Furthermore, no significant relationship was found between the VDR 2228570 (FokI) polymorphism and the risk of obesity in persons with good and poor DM [18].

CONCLUSION

Our study suggests that the FokI polymorphism in the VDR gene may represent a significant genetic molecular marker to predict the risk of diabetes in its polymorphic form (ff genotype). The frequency of the f allele was higher in obese type 2 diabetic patients than in non-obese type 2 diabetic patients, and the presence of the f allele may be accompanied by a marked decrease in vitamin D protein expression level, so further studies of other polymorphisms in the VDR gene and their relationships with diabetes should be carried out. Also, further research is required in different ethnic populations and on large numbers of patients to indicate its usefulness as a potential new genomic indicator and biomarker to screen populations for diabetes.

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