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Vitamin D receptor gene polymorphisms among Emirati patients with type 2 diabetes mellitus

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ABSTRACT

At a prevalence rate close to 19.5%, the UAE has one of the highest rates of Type 2 Diabetes Mellitus (T2DM) in the world. Genome wide association studies (GWAS) have led to the identification of several genetic variants that are associated with T2DM. Recently, genes involved in vitamin D metabolism have gained interest because of the association between vitamin D deficiency (VDD) and increased risk for T2DM. Among these, the Vitamin D receptor (VDR) gene is a good candidate for T2DM susceptibility. The aim of this study was to investigate the association between VDR polymorphisms and T2DM among a representative sample of the Emirati population. In this cross sectional study, two hundred and sixty four patients with T2DM and ninety-one healthy controls were enrolled. The study population was genotyped for the three *VDR* gene mutations, TaqI (rs731236), FokI (rs2228570) and BsmI (rs1544410). VDR alleles and haplotypes were compared between patients and their healthy controls. The mean age of the T2DM cohort was 60 ± 11.59 years and 48.21 ± 12.17 years for the healthy controls. The G-allele and GG genotype of rs2228570 and T-allele and TT genotype of rs1544410 SNPs were associated with T2DM. In regards to T2DM-related metabolic complications, the AG and GG genotypes of rs731236 were significantly associated with higher total cholesterol ($p = 0.011$) and LDL-cholesterol ($p = 0.009$) levels in the patients with T2DM. In contrast, the CT genotype of rs1544410 was significantly associated with lower BMI ($p = 0.031$) and the TT genotype was associated with lower LDL-cholesterol level ($p = 0.007$). The frequency of AAT and GGC haplotypes was also different between groups ($p = 0.014$; $p = 0.032$, respectively), implying that these haplotypes of the *VDR* gene are associated with the susceptibility to T2DM in the Emirati population. To conclude, an association between SNPs in the *VDR* gene (except for rs731236) and T2DM *per se* was demonstrated. The rs731236 variant was shown to be associated with high cholesterol and LDL-cholesterol levels in T2DM patients, while rs1544410 was associated with lower BMI and lower LDL cholesterol levels. Our results imply that alleles and haploypes of the *VDR* gene are associated with the susceptibility to T2DM in the Emirati population.

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic diseases worldwide and often characterized by serious complications such as kidney failure, neuropathy, blindness and cardiovascular disease. In 2015, statistics showed that 415 million people suffered from diabetes world-wide and this rate is expected to increase by 54.5% and reach 642 million by 2040 [1]. The Middle Eastern population accounts for approximately 20% of these cases [2]. According to the International Diabetes Federation, the United Arab Emirates (UAE) has 745,940 diabetics, 304,000 undiagnosed diabetics and 934,300 pre-diabetics. These are very foreboding figures that require urgent attention to improve identification

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method of people at risk of T2DM and implement prevention strategies. Therefore, the UAE is in a desperate need for extensive research studies to unravel the genetic architecture of T2DM, especially as consanguineous marriages are common among the UAE culture [1].

Environmental, behavioral and genetic factors have an important role in the development of T2DM, which is a multifactorial disease that results from defects in insulin function [3]. Clinical and epidemiological studies have indicated that obesity, family history of diabetes, lack of physical activity and unhealthy dietary practices are more prevalent in T2DM patients [4]. Studies on genetic susceptibility to T2DM among different ethnic populations reported links between T2DM and certain genes such as *TCF7L2*, *PPARG*, *KCNJ11* [5,6]. A recent study in the UAE has shown that several genes including *ACE* and *AGT* were significantly associated with the prevalence of T2DM among the UAE Bedouins [7]. Genome wide association studies (GWAS) have led to the identification of many novel susceptibility genes (*FAM60A*, *DMRTA1*, *ASB3*, *ATP8B2*, *SLC30A8*) for T2DM and may provide further insight into the UAE population [8,9].

Genes involved in vitamin D metabolism have also gained an interest because of their observed association between vitamin D deficiency (VDD) and glucose intolerance, insulin resistance and increased risk for T2DM [10,11]. Autier et al., [12] reported that vitamin D supplementation could significantly reduce mortality among patients with T2DM. Moreover, high vitamin D levels have been associated with a lowered risk for T2DM in Australian adults [13].

We have previously documented the prevalence of VDD among adult Emiratis [14]. It is known that vitamin D is involved in regulating the transcriptional activity of the insulin receptor gene [15]. Vitamin D improves glucose tolerance and β-cells function, particularly insulin secretion in humans and animal models of diabetes [16]. Because vitamin D exerts its action via the vitamin D receptor (*VDR*) which is a genetic determinant for vitamin D status, the *VDR* gene is a candidate gene for T2DM. *VDR* is a member of the nuclear receptor superfamily which is located on chromosome 12q13.11 [17]. *VDR* is expressed in most tissues of the body including the pancreatic β-cells, which are involved in the regulation of glucose metabolism [18]. Several polymorphisms of the *VDR* gene have been reported. Amongst these TaqI (rs731236), FokI (rs2228570), and BsmI (rs1544410) have been suspected to alter the activity of the VDR protein [19]. All variants are located in intron 8 of 12q13.11 except for FokI, which is in exon 2 of the DNA gene segment. FokI is a variant code for a potentially shortened receptor protein, which is more active than the long form in transcriptional activation [20,21].

The association between VDR polymorphisms and T2DM is controversial with some studies showing an association [17], while others have failed to demonstrate this finding [22]. Despite the emergence of genetic studies on T2DM among the Emirati population, there is still no data available to date about the association between *VDR* gene polymorphisms and T2DM in this part of the world. Therefore, this study aimed to examine the association of *VDR* polymorphisms and T2DM in the Emirati population.

2. Materials and methods

2.1. Subjects and sample collection

Participants included two hundred sixty four unrelated diabetic patients (130 females and 134 males) and ninety one healthy controls (68 females and 23 males) who were recruited during their routine visit to an endocrinology clinic in Abu Dhabi, United Arab Emirates (UAE). Each participant agreed to take part in this study after a briefing session, with each signing an informed consent form that had been approved by the Institutional Ethics Committee of the Sheikh Khalifa Medical City (SKMC). There were several inclusion and exclusion criteria used in this study. Inclusion criteria were UAE National, healthy individuals, diabetic patients with or without complications, able to give consent and above 18 years of age. Exclusion Criteria: pregnant female, not be able to consent and less than 18 years old.

The mean age ± standard deviation (SD) of the T2DM cohort was 60 ± 11.59 and 48.21 ± 12.17 for the control group. One milliliter of saliva was collected from each participant using the Oragene OGR-500 kit (DNA Genotek, Ottwa, Canada) for DNA extraction. Blood was collected using anti-coagulant tubes (BD Vacutainer®, Franklin Lakes, New Jersey, USA) for measuring biochemical markers. Participants filled out a validated questionnaire that provided information on anthropometric data, lifestyle and environmental factors, which could play a role in the predisposition to T2DM. Diabetic patients were diagnosed based on World Health Organization (WHO) criteria [23].

The individuals with a body mass index (BMI) score of greater than 30 were considered to be 'obese' and those with a BMI less than 30 were grouped into the 'non-obese' population. According to the JNC 8 classification, all the individuals with blood pressure of greater than 140/90 mmHg were considered to be hypertensive [24].

2.2. Genotyping

Genomic DNA was extracted from the saliva samples using the prepIT®L2P system (DNA Genotek, Ottwa, Canada) according to manufacturer's instructions. The genotyping for the three *VDR* SNPs TaqI (rs731236), FokI (rs2228570) and BsmI (rs1544410) (Applied Biosystems, Foster City, CA) was performed using TaqMan® real-Time PCR assays (Applied Biosystems, Foster City, CA). All TaqMan® real-Time PCR reaction were performed in 96 well plates (Applied Biosystems, Foster City, CA) with a final reaction volume of 10 μl that contained 10 ng of genomic DNA, 5 μl of TaqMan GTXpress Master Mix (Applied Biosystems, Foster City, CA) and 0.5 μl primers and probes (20×). Negative controls for all of SNPs were included in each plate. The real-Time PCR thermal conditions were as follows: Initial denaturing at 95 °C for 20s; 40 cycles of 95 °C for 3 s (denaturing) and 60 °C for 20 s (annealing/extension). Amplification was performed in ViiA™ 7 Real-time PCR system (Applied Biosystems, Foster City, CA) and results were assessed using the ViiA™ 7 software (Applied Biosystems, Foster City, CA).

Total cholesterol was measured using enzymatic, colorimetric method on the Roche C 702 analyzer. Hemoglobin A1c was measured using turbidimetric inhibition immunoassay on the Cobas Integra 400 plus.

2.3. Statistical analysis

All statistical analyses were performed using the statistical program Stata version 13 (Stata Corp., TX, USA). The results for continuous variables were expressed as means ± SD and as percentages for categorical variables. Data quality control was performed using the Hardy-Weinberg equilibrium (HWE) test. Epidemiology case-control studies were implemented by using DeFinetti program for testing the deviation from HWE. A Chi square test was used to compare the genotype and allele frequencies for each SNP between cases and controls. For continuous variables, differences between the groups were tested by Student's *t*-test. The relationships between the *VDR* SNPs polymorphisms and the demographic data and biochemical tests

Table 1
Clinical characteristic of patients with T2DM and the healthy control enrolled in this study.

		T2DM patients	Healthy controls	*p*-value
Demographic data	Subjects, n.	264	91	
	Age (years)	60.50 ± 11.59	48.21 ± 12.17	0.00001*
	BMI (kg/m2)	32.12 ± 5.93	30.57 ± 6.18	0.018*
	Systolic blood pressure (mmHg)	131.30 ± 17.01	122.25 ± 15.64	0.00001*
	Diastolic blood pressure (mmHg)	73.92 ± 11.49	71.57 ± 10.13	0.042*
Biochemical tests	HbA1c (%)	7.48 ± 1.36	5.55 ± 0.52	0.00001*
	Triglyceride (mmol/l)	1.81 ± 2.11	1.09 ± 0.51	0.004*
	Total cholestrol (mmol/l)	4.13 ± 1.59	4.57 ± 0.97	0.982
	HDL cholestrol (mmol/l)	1.24 ± 0.61	1.32 ± 0.39	0.820
	LDL cholestrol (mmol/l)	2.18 ± 1.14	2.76 ± 0.97	0.999

Mean plus standard deviation are presented for all variables, except male and female. *significant p-value <0.05. T2DM: Type 2 diabetes mellitus, BMI: Body mass index, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein, LDL: low density lipoprotein, n: number of individuals.

of the patients were analyzed by analysis of variance (ANOVA) statistics. All statistical tests performed in this study were two tailed. Results were considered statistically significant when p value was <0.05.

3. Results

The clinical characteristics of participants are summarized in Table 1. Compared to healthy controls, T2DM patients had significantly higher systolic and diastolic blood pressure, BMI and percentage of HbA1c as well as higher serum triglyceride concentration.

Table 2 presents the allele and genotype frequencies of the *VDR* SNPs rs731236, rs2228570 and rs1544410. The genotype distributions for all SNPs follow HWE proportions. Results revealed that some *VDR* polymorphic sites were significantly more frequent in diabetic subjects.

The mutant alleles G of rs2228570 and T of rs1544410 were associated with increased odds ratio (OR) for T2DM (OR = 1.843, 95% CI = 1.288–2.637, $p = 0.0007$; OR = 1.45, 95% CI = 1.032–2.036, $p = 0.031$ respectively). The rs2228570-AG, -GG genotypes and the rs1544410-TT genotype showed a significant association with increased risk of T2DM (OR = 2.488, 95% CI = 1.178–5.256, $p = 0.015$; OR = 3.482, 95% CI = 1.678–7.224, $p = 0.0005$; OR = 1.921, 95% CI = 1.009–3.658, $p = 0.045$, respectively). The dominant model AG + GG of rs2228570 and CT + TT of rs1544410 were associated with an increased risk of T2DM (OR = 3.013, 95% CI = 1.512–6.000, $p = 0.001$; OR = 1.664, 95% CI = 1.000-2.770, $p = 0.048$, respectively). No significant differences were observed for the *VDR* SNP rs731236.

Table 3 describes the anthropometric and metabolic parameters in accordance to *VDR* SNPs in T2DM patients. The results revealed that AG and GG genotypes of rs731236 were associated with higher total cholesterol ($p = 0.011$) and LDL-cholesterol (p = 0.009) levels. On the contrary, the CT genotype of rs1544410 was associated with lower BMI ($p = 0.031$) and the TT genotype was associated with lower LDL-cholesterol level ($p = 0.007$).

Table 4 shows the haplotype frequency of the three *VDR* SNPs observed in the Emirati T2DM and control cohorts. In comparison to the control group, the frequency of AAC and GAC haplotypes was significantly decreased in T2DM ($\chi^2 = 23.587$, $p = < 0.00001$; $\chi^2 = 11.296$, $p = 0.0007$, respectively). However, a significant increase in the frequency of AAT and GGC haplotypes was observed in T2DM patients ($\chi^2 = 6.018$, $p = 0.014$; $\chi^2 = 4.575$, $p = 0.032$, respectively). The frequency of other haplotypes did not show any significant difference between groups. These results suggest that the haplotypes AAT and GGC of the *VDR* gene are associated with the susceptibility to T2DM in the Emirati population.

Table 2
Genotype and allele frequency of the polymorphisms of the *VDR* gene in T2DM patients and healthy controls.

SNPs Allele/Genotype	T2DM patients n = 264[a] (%)	Healthy controls n = 91[a] (%)	OR [25]	*p*-value
rs731236				
AA	108 (41.22)	37 (40.66)	1 (Reference)	
AG	111 (42.37)	38 (41.76)	1.001 [0.592–1.691]	0.997
GG	43 (16.41)	16 (17.58)	0.921 [0.464–1.826]	0.813
AA:AG+GG	108 (41.22):154 (58.78)	37 (40.66):54 (59.34)	0.977 [0.601–1.587]	0.925
AA+AG:GG	219 (83.59):43 (16.41)	75 (82.42):16 (17.58)	1.087 [0.578–2.042]	0.796
A	327 (62.40)	112 (61.54)	1.037 [0.733–1.468]	
G	197 (37.60)	70 (38.46)	0.964 [0.681–1.364]	0.835
rs2228570				
AA	20 (7.66)	18 (20.00)	1 (Reference)	
AG	94 (36.01)	34 (37.78)	2.488 [1.178–5.256]	0.015*
GG	147 (56.33)	38 (42.22)	3.482 [1.678–7.224]	0.0005*
AA:AG+GG	20 (7.66):241 (92.34)	18 (20.00):72 (80.00)	3.013 [1.512–6.000]	0.001*
AA+AG:GG	114 (43.67):147 (56.33)	52 (57.78):38 (42.22)	0.567 [0.349–0.920]	0.020*
A	134 (25.67)	70 (38.89)	0.543 [0.379–0.777]	
G	388 (74.32)	110 (61.11)	1.843 [1.288–2.637]	0.0007*
rs1544410				
CC	67 (25.47)	33 (36.26)	1 (Reference)	
CT	118 (44.87)	38 (41.76)	1.529 [0.879–2.663]	0.131
TT	78 (29.66)	20 (21.98)	1.921 [1.009–3.658]	0.045*
CC:CT+TT	67 (25.47):196 (74.53)	33 (36.26):58 (63.74)	1.664 [1.000–2.770]	0.048*
CC+CT:TT	185 (70.34):78 (29.66)	71 (78.02):20 (21.98)	0.668 [0.381–1.172]	0.158
C	252 (47.91)	104 (57.14)	0.69 [0.491–0.969]	
T	274 (52.09)	78 (42.86)	1.45 [1.032–2.036]	0.031*

[a]Numbers may not add up to total due to missing genotyped data. SNP: Single nucleotide polymorphism, T2DM: Type 2 diabetes mellitus, n: number of individuals, OR: Odds ratio, CI: confidence intervals. OR [95% CI] was calculated by chi-squared-test. *significant p-value <0.05.

Table 3
Anthropometric and metabolic parameters according to genotypes of *VDR* polymorphism in T2DM patients.

Parameters	rs731236			p-value	rs2228570			p-value	rs1544410			p-value
	AA n = 108	AG n = 111	GG n = 43		AA n = 20	AG n = 94	GG n = 147		CC n = 67	CT n = 118	TT n = 78	
BMI (kg/m^2)	32.67 ± 6.07	31.21 ± 5.62	33.27 ± 6.16	0.078	31.88 ± 4.71	32.65 ± 6.49	31.84 ± 5.77	0.582	33.31 ± 6.78	31.09 ± 5.41*	32.66 ± 5.76	0.031
Systolic blood pressure (mmHg)	132.57 ± 17.55	129.46 ± 16.92	133.47 ± 15.83	0.279	131.15 ± 14.36	131.24 ± 15.40	131.33 ± 17.96	0.998	132.74 ± 17.38	130.29 ± 17.28	131.33 ± 16.34	0.645
Diastolic blood pressure (mmHg)	74.98 ± 11.20	73.40 ± 11.49	73.16 ± 12.35	0.524	72.00 ± 11.02	72.89 ± 11.56	75.03 ± 11.54	0.269	74.84 ± 12.36	73.92 ± 11.55	73.28 ± 10.73	0.720
HbA1c (%)	7.52 ± 1.31	7.44 ± 1.33	7.57 ± 1.57	0.842	7.10 ± 1.02	7.46 ± 1.36	7.54 ± 1.40	0.426	7.79 ± 1.52	7.28 ± 1.23	7.52 ± 1.37	0.055
Triglyceride (mmol/l)	1.56 ± 1.32	1.97 ± 2.54	2.03 ± 2.50	0.297	1.43 ± 0.80	1.70 ± 1.73	1.90 ± 2.41	0.597	2.06 ± 2.33	1.75 ± 2.28	1.66 ± 1.58	0.511
Total cholestrol (mmol/l)	3.78 ± 1.19	4.40 ± 1.69*	4.36 ± 2.02 ‡	0.011	3.59 ± 0.55	4.08 ± 1.28	4.24 ± 1.84	0.252	4.34 ± 1.97	4.25 ± 1.51	3.76 ± 1.27	0.054
HDL cholestrol (mmol/l)	1.24 ± 0.69	1.24 ± 0.59	1.27 ± 0.43	0.972	1.10 ± 0.30	1.28 ± 0.60	1.28 ± 0.60	0.515	1.32 ± 0.82	1.17 ± 0.35	1.28 ± 0.70	0.249
LDL cholestrol (mmol/l)	1.93 ± 0.87	2.38 ± 1.19*	2.37 ± 1.46 ‡	0.009	1.71 ± 0.55	2.11 ± 0.84	2.30 ± 1.33	0.091	2.33 ± 1.43	2.33 ± 1.07	1.83 ± 0.86 ‡	0.007
Fasting blood glucose (mmol/l)	8.10 ± 3.33	8.58 ± 2.95	9.32± 3.53	0.413	6.775 ± 1.55	8.69 ± 3.45	8.56 ± 3.10	0.523	9.66 ± 3.93	8.13 ± 2.82	8.30 ± 2.99	0.148

Data are presented as mean ± standard deviation. * Indicates that the second genotype is significantly different from the first group and ‡ indicates that the third genotype is significantly different from the first genotype. BMI: Body mass index, HbA1c: glycosylated hemoglobin, HDL: high density lipoprotein, LDL: low density lipoprotein, n: number of individuals.

4. Discussion

The UAE is a subtropical country, which is sunny almost all year. Nevertheless, a vitamin D deficiency is widespread and severs among the population due to numerous factors like avoidance of sun exposure and genetics. [26]. Although social and cultural factors are important determinants of VDD status through their influence on sun exposure and diet, genetic factors can contribute to the effect on VDD [27]. Results on the role of common genetic variants of vitamin D status and their link to T2DM have recently started to emerge [28]. Recent studies have shown links not only with moderate or severe VDD and diabetes but also with very minor vitamin D decreases and metabolic dysfunction [29]. Metabolic abnormalities may be associated with the ubiquitous presence of the *VDR* and its role in the regulation of up to 1250 genes with either direct or indirect pleiotropic effects on glucose metabolism [30,31].

The UAE has one of the highest frequencies of diabetes in the world, particularly T2DM (International Diabetes Federation, 2006). In addition to genetic risk factors, epigenetic mechanisms (DNA methylation, histone modification and non-coding RNA-mediated pathways) triggered by the rapid environmental and behavioral changes of the UAE population are involved in the pathogenesis of this complex disease. Findings from a recent study in Saudi Arabia indicated that *VDR* genetic variants including rs731236, rs1544410 were significantly associated with T2DM. Moreover, the metabolic parameters, which characterize T2DM including dyslipidemia, hypertriglyceridemia, and low HDL levels, were correlated with the reported *VDR* variants [32]. These results were in concordance with another research conducted among Caucasians of European descent [33]. However other researchers failed to demonstrate a similar link among Indian and Turkish population-based studies [34]. This difference in findings could be attributed to differences in population genetics.

Additionally, recent studies in this region have shown that the Gulf region has the highest rate of vitamin D insufficiency and deficiency around the globe, despite their sunny climate [35].

The *VDR* is the mediator that regulates vitamin D functions in the body; it regulates the immunomodulation, calcium and bone homeostasis and cellular replications in different target tissues [36]. In addition, A positive correlation between circulating Vitamin D levels and insulin sensitivity and that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and T2DM [25], via a mechanism that can be related to direct action via VDR activation.

The *VDR* gene polymorphisms have been associated with multiple traits and disease phenotypes and more specifically some researchers previously linked the *VDR* gene polymorphisms to T2DM [37–40]. Our results now demonstrate a link between specific *VDR* SNPs and T2DM in the Emirati population. There was an association between polymorphisms in rs2228570 SNP and T2DM patients. Genetic ethnicity variations could be the key to understand the spread of diseases among a particular race compared to another. These results link rs2228570 polymorphism directly to T2DM among the Emirati population. Obesity, hypertension and cholesterol levels have been shown to be linked T2DM risk. The rs731236 SNP was not significantly associated with T2DM but was significantly different between genotypes and significantly influenced levels of total cholesterol and low-density lipoprotein, suggesting that rs731236 may have interactive effects with rs2228570 in progression of diabetes and its complications.

FokI is located in the exon 2 and it is not in linkage disequilibrium with the other two polymorphisms. VDR gene has three blocks of linkage disequilibrium: one involving the Cdx2 polymorphisms in the promoter; a second one including FokI and other polymorphisms in the gene, and the third including both TaqI

Table 4
Haplotype frequency of the three SNPs rs731236, rs2228570 and rs1544410 in T2DM patients and their healthy controls.

Haplotypes[a]			Frequency		χ^2	*p*-value	OR (CI 95%)
			T2DM patients	Healthy controls			
A	A	C	0.067	0.195	23.587	<0.00001*	0.301 (0.182–0.499)
A	A	T	0.111	0.050	6.018	0.014*	2.422 (1.171–5.012)
A	G	C	0.134	0.088	2.818	0.093	1.631 (0.917–2.901)
A	G	T	0.311	0.279	0.787	0.375	1.186 (0.814–1.728)
G	A	C	0.053	0.129	11.296	0.0007*	0.379 (0.212–0.679)
G	A	T	0.026	0.016	–	–	–
G	G	C	0.229	0.156	4.575	0.032*	1.634 (1.039–2.571)
G	G	T	0.069	0.089	0.673	0.412	0.773 (0.418–1.432)

[a] The order of SNPs in haplotypes: rs731236, rs2228570 and rs1544410. *p*-value are calculated by chi square test using the SHEsis online haplotype analysis software. T2DM: Type 2 diabetes mellitus. OR: Odds ratio, CI: confidence intervals.

and BsmI together with ApaI polymorphisms. Our results suggested that the haplotypes AAT and GGC of the *VDR* gene are associated with the susceptibility to T2DM in the Emirati population, while AAC and GAC haplotypes confer protection from T2DM. Apart from one study investigating the role of *VDR* gene polymorphisms in polycystic ovary disease (associated with insulin resistance), no studies on T2DM/VDR gene polymorphism investigated the haplotype frequencies of *VDR* gene and T2DM. The G allele of Fok-1 polymorphism encodes a 424 amino acid protein [17,18]. The shorter protein has a higher transcriptional activity which further increases its capacity of binding to 1,25-dihydroxyvitamin D [18]. This can reduce the risk of T2DM by enhancing pancreatic β-cell secretion function and improving insulin resistance [11]. Our study revealed that the G allele of Fok-1 polymorphism is more frequent in T2DM patients possibly as a body reaction against insulin resistance.

Taken together, an association between SNPs in the *VDR* gene and T2DM *per se*, except for rs731236 was found. The rs731236 mutation was shown to be associated with high cholesterol and LDL-cholesterol levels in T2DM patients, while rs1544410 mutation was associated with lower BMI and lower LDL cholesterol level. These results suggest a possible association between alleles and haplotypes of *VDR* gene and susceptibility to T2DM in the Emirati population.

Type 2 diabetes is an urgent public health problem that kills or maims tens of thousands people each day due to its severe vascular complications. Epidemiological studies have persuasively shown that this disease is mainly due to vitamin D deficiency [25,41,42]. This deficiency could be addressed by vitamin D3 supplementation of the whole adult population. Furthermore there is a need for further studies to investigate the association of genetic variation in other genes involved in *VTD* metabolism and T2DM. Additionally, serum 1,25 $(OH)_2$D as well as the functional binding of it to the VDR ligand binding domain could be measured in patients with the mutant alleles to properly elucidate the metabolic pathway of vitamin D and back genetic data.

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