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Vitamin D receptor gene polymorphisms in pathogenesis and susceptibility of diabetes mellitus

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Abstract

Background: Numerous researches have demonstrated that DM susceptibility is associated with polymorphisms in the VDR gene. But the findings have been conflicting, varying depending on the location. **The purpose of this study** was to assess the relationship ofvitamin D level and VDR gene polymorphisms with DM in Egyptian patients.

Methods: Enrollment consisted of 50 T1DM cases, 50 T2DM cases, and 50 healthy volunteers. By ELISA, 25hydroxyVDlevel was determined. PCR-RFLP was used to detect VDR gene polymorphisms.

Results: Compared to healthy individuals, the mean serum VD level was lower in diabetic cases. Regarding the VDR BsmI genotype, there was no statistically significant variation seen between the case and healthy individuals. Regarding the FokI genotype, there was a significant variation between the T2DM and healthy individuals. The FF genotype had a greater risk of T2DM than the Ff genotype (odds ratio: 12.80). The distribution of the Fok-I genotype showed a significant variation between the T1DM and T2DM cohorts; 8% of TIDM had the ff genotype, compared to 0% in T2DM (P=0.039).

Conclusion: The relationship between T2DM in the Egyptian population and the VDR gene FokI polymorphism is supported by this study. And there's no connection between DM and BsmI polymorphism.

Key words: VD receptor, DM mellitus, VDR polymorphism, BsmI, FokI.

INTRODUCTION:

The most prevalent endocrine condition, DM, is typically brought on by an insufficient or absent amount of insulin or by a reduction in insulin action (insulin resistance)**(1).**According to IDF estimations, fifteen percent of Egyptians are expected to have DM; however, this figure may be understated **(2).**T1DM, T2DM, which is the most prevalent type, and gestational DM are the three main varieties. Long-term untreated DM can lead to micro and macrovascular problems that increase morbidity and death in those with the disease **(3).**

IDDM, also referred to as T1DM, primarily affects children and young adults. Its onset is typically abrupt and can be fatal **(4).** Immunologic, environmental, and genetic factors all influence T1DM. According to genetic research, this is a polygenic disorder with one major locus (IDDM1=HLA) and an unknown number of smaller loci**(5).** Adult-onset DM is another name forT2DM which is characterized by insulin resistance leading to increasing insulin secretary malfunction. **(6).** The reasons are multifaceted, and risk factors for middle-aged and older adults include obesity, a sedentary lifestyle, ageing, and genetics. These individuals are more likely to experience macro and microvascular problems **(7).**

There are two types of VD, which is considered as a precursor of hormone. VD2, also known as ergocalciferol,is found in certain fish and plants. Sunlight is the source of cholecalciferol, or VD3, which the skin produces **(8).**Together with parathyroid hormone, VD maintains blood calcium homeostasis, mediates skeletal mineralization, and controls calcium absorption in the small intestine. Furthermore, low VD have been associated to a number of disease states in recent epidemiologic research, most likely as a result of its immune-modulating, anti-inflammatory, and potential cytokine-related actions**(9).**

The pathophysiology and prevention of DM have garnered a lot of attention lately, thanks in large part to VD role. VD, as the primary modulator of calcium homeostasis, increases insulin secretion either directly or indirectly by means of calcium-dependent endopeptidase activation. Additionally, VD enhances glucose tolerance **(10)**. The prevalence of VD deficiency is sharply rising worldwide, and epidemiological data points to the relation for VDdecrease in the etiology of T1DM. It has also been demonstrated that variations in genes essential for VD metabolism affect the likelihood of T1DM**(11).**Damage to beta cells caused by cytokines and other inflammatory substances have important role in the development of T1DM. Clearly, a VD deficit affects insulin secretion and causes glucose intolerance **(12).**

Insulin resistance and changed insulin exocytosis are hallmarks ofT2DM. The variation according to seasons in glycemic control observed in people withT2DM being bad in the winter may be attributed to the decrease in VDas a result of diminished sunlight. This suggests a role for VD in T2DM. Studies have shown a connection between VD levels and the prevalence ofT2DM**(13).**

In a range of tissues, the VDR, a ligand-activated transcription factor, effectively mediates the effects of 1, twenty-five-dihydroxyVD. There are multiple polymorphisms known. Hereditary mutations in the VD-responsive gene cause polymorphisms **(14).**

Given that VD regulates insulin release, genetic variations in the VDR gene could participate in the onset of DM. According to some theories, genetic modifications or changes in the VDR may influence at least four distinct pathways that lead to the pathophysiology ofT2DM mellitus: altered calcium metabolism, altered adipocyte function, altered insulin secretion, and altered cytokine expression **(15).**The VDR gene has four frequent allelic variants, or polymorphisms, that have been found and thoroughly explained: FokI, TaqI, BsmI, and ApaI**(16).**

The translation start site's FokI single-nucleotide polymorphism is the only one of the VDR SNPs that produces a VDR protein with a distinct structure. It plays a special role because it is the sole polymorphism that is unrelated to any of the other VDR polymorphisms. The distribution of the various FokI genotypes in Caucasians is roughly 45% Ff, 40% FF, and 15% ff **(17).**

Postprandial serum C-peptide levels were shown to be greater in cases with DM and obesity who carried the BB (GG) genotype of the BsmI allele in the VDR gene. This finding suggests a

potential involvement for the BsmI allele in the pathophysiology ofT2DM**(18).**Despite substantial evidence linking VDR polymorphism to DM, there is significant variation in the outcomes across populations**(19).**

This study's primary goals were to determine the role ofVDand VDR gene polymorphisms in Egyptian patients in susceptibility to and pathogenesis of DM.

SUBJECTS AND METHODS:

- ***Study design and population:***
  - This was a study with 150 participants; 100 DM cases attended the Mansoura University Specialized Medical Hospital's incase and outcase diabetic clinics (involving 50 T1DM cases, 15 males and 35 females, and 50T2DMcases, 18 males and 32 females), and 50 healthy subjects, matched in age and sex, were selected as the healthy individualcohort. Individuals undergoing VD supplementation or those with immune-mediated illnesses, including pancreatitis, were not included. The Medical Research Ethics Committee accepted the study protocol.
- ***Clinical data and laboratory investigation:***
  - The complete history, clinical examination, BMI evaluation, and laboratory investigations, such as CBC, liver function, kidney function, albumin to creatinine ratio, RBS, HbA1c, and lipid profile, were performed on the study's cases and healthy individuals.
  - Enzyme Linked Immunosorbent Assay (ELISA) technique for measuring serum VD levels using the competitive binding principle in accordance with the kit's instructions: 25-hydroxy VD ELISA (BD-200BA) bioactivadiagnostica (Bad Homburg, Germany).
- ***Molecular studies:***
  - PCR-RFLP of VDR gene polymorphisms (bsm1&fokI), following DNA extraction:

The Gene JET Genomic DNA Purification Kit from ThermoFisher Scientific Company was used to extract DNA from the peripheral venous blood of all cases and healthy individualcohorts (Waltham, MA, America). To calculate the amounts of genomic DNA, nanodrop spectrophotometric analysis wasused to quantify absorbance at 260 and 280 nm wavelengths. The forward primer **for bsm1** (rs1544410) is 5'-CAA CCA AGA CTA CAA GTA CCG CGT CAG TGA-3' and 5'-AAC CAG CGG GAA GAG GTC AAG GG-3'is the reverse primer.Whereas 5-AGC TGG CCC TGG CAC TGA CTC TGC TCT-3 is the **FokI**(rs2228570) forward primer and the reverse primer is 5-ATG GAA ACA CCT TGC TTC TTC TCC CTC-3 ***(20, 21).*** The COSMO PCR RED Master Mix (CAT: ND-1289-50, Willowfort, UK) was used for the PCR amplification. 15 µl of Red Master Mix, 20 µl nuclease-free water, 1 µl of each forward and reverse primer, and 1 µl DNA template made up the PCR mixture. The PCR reactions **for bsm1** were conducted for five minutes at 95 degrees Celsius, then for thirty-five cycles at 95 degrees Celsius, 53 degrees Celsius, and 72 degrees Celsius, as well as an extension step at 72 degrees Celsius for ten minutes. The PCR products were then cleaved with one microliter of the restriction enzyme bsm1 (New England Biolabs Inc., Ipswich, MA, USA) at 65 degrees Celsius for two hours. **FokI PCR** reactions were run for five minutes at 94 degrees Celsius, then at 94, 60, and 72 degrees Celsius for thirty seconds each, with an extension step of 72 degrees Celsius for ten minutes. The PCR amplification products were then cleaved with one microliter of the restriction enzyme FokI (Thermo Fisher Scientific, Waltham, MA, USA Fast Digest) at 37 degrees Celsius for ten minutes **(22).** Figures 1 and 2 show how the cleavage products were examined using agarose gel electrophoresis (3%) and stained with ethidium bromide to see them under a UV lamp.

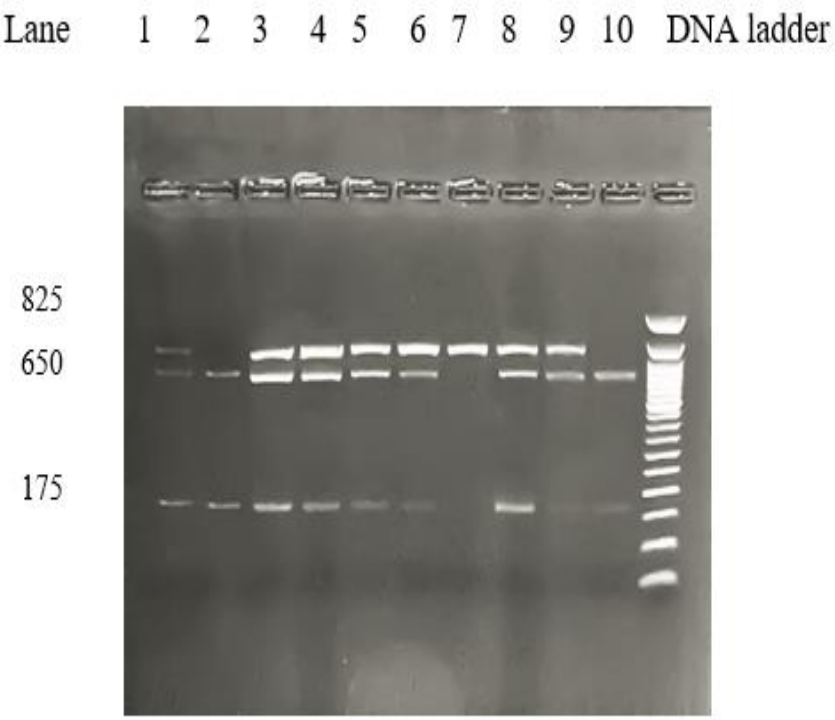

Figure (1): PCR- RFLP with Bsm1 restriction enzyme.

The figure shows Agarose gel electrophoresis (3%) of PCR–RFLP technique of the amplified bsm1 genotypes where DNA ladder (50 bp) is used (Thermoscientific, cat no 10416014, Lithuania, EU) showing that lanes (1,3,4,5,6,8,9) represent AG genotype (825,650 and 175 bp), lanes (2,10) represent GG genotype (650,175bp) and lane (7) represent AA genotype (825 bp).

lane 1 2 3 4 5 6 DNA ladder

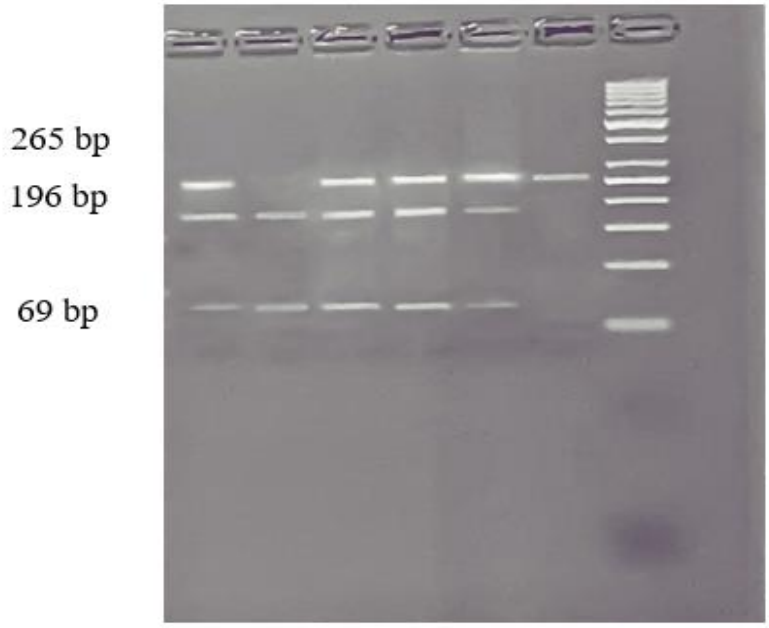

Figure (2): PCR- RFLP with FokI restriction enzyme.

The figure shows Agarose gel electrophoresis (3%) of PCR–RFLP technique of the amplified FokI genotypes where DNA ladder (50 bp) is used (Thermoscientific, cat no 10416014, Lithuania, EU) showing that lane (1,3,4,5) represents Ff genotype (265,196 and 69 bp), lane (2) represent ff genotype (196,69bp) and lane (6) represent FF genotype (265 bp).

STATISTICAL ANALYSIS:

The SPSS software, version 25 (PASW statistics for Windows, Chicago: SPSS Inc.), was used for data analysis using numbers and percentages for qualitative data. And mean± SD for quantitative normally distributed data following the Kolmogorov-Smirnov test to confirm normality. The acquired results were deemed
significant at the (0.05) level.

RESULTS:

There were 150 participants in this study: 50 healthy individuals with similar age and sex were selected as the healthy individualcohort, and 100 DM cases (15 men and 35 females for T1DM and 18 males and 32 females forT2DM). Table (1) and Figure (3) demonstrate that the VD level in the T1DM cohort was lower than that of the healthy individualcohort. The area under the ROC curve for VD in differentiating between T1DM &healthy individual is good (Area Under Curve (AUC)=0.706), with the best cut off point being 15.23, yielding 80% sensitivity and 52% specificity.

When T2DM cases' VD levels were compared to those of the healthy individualcohort, the cases had lower VD levels than the cohort with Table (1) and Figure (3) demonstrate that the VDAUC for discriminating between T2DM and healthy individual is excellent (AUC=0.824), with the optimal cut off point being 9.38, achieving 74% sensitivity and 64% specificity.

When VD levels were compared between T1DM and T2DM cohorts, it was found that T1DM had higher serum VD values than T2DM. The area under the ROC curve for VD in separating T1DM and T2DM is good (AUC=0.715), and the best cut off point is 10.13, yielding 80% sensitivity and 58% specificity, as indicated in table (1) and figure (3).

Table (1): validity of VD in differentiation between studied cohorts.

	AUC (95%CI)	**P value**	**Cut off point**	**Sensitivity %**	**Specificity %**
DM I &healthy individual	0.706 (0.582-0.829)	0.004*	15.23	80.0	52.0
DM II &healthy individual	0.824 (0.733-0.916)	0.001*	9.38	74.0	64.0
DM type I & type II	0.715 (0.611-0.818)	0.001*	10.13	80.0	58.0

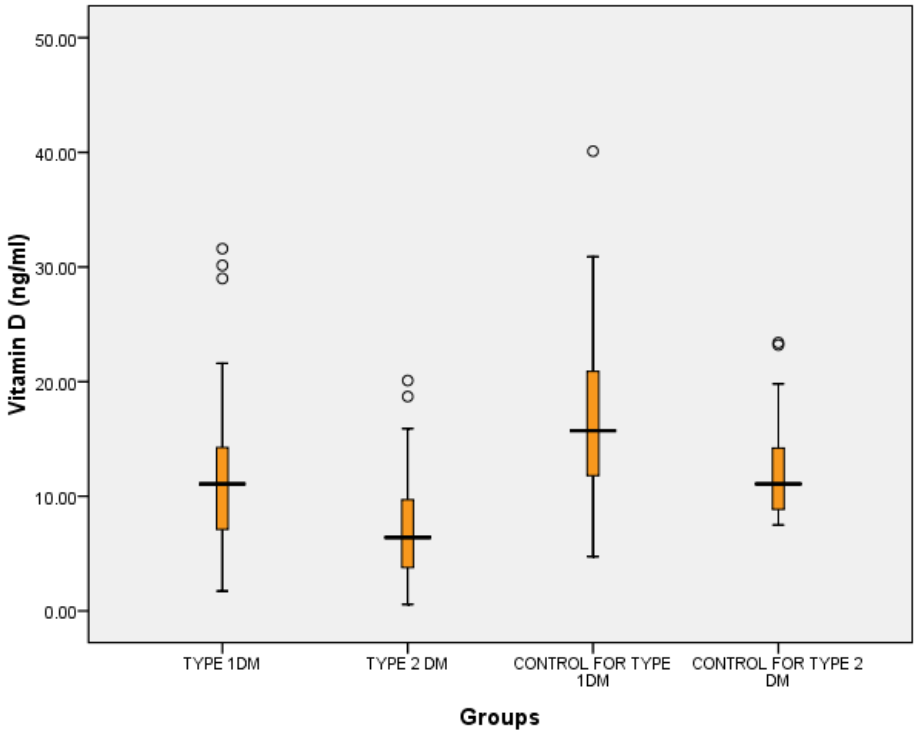

Figure (3): box and whisker plot for comparison of VD level between different cohorts.

There was no statistically significant variation found in the genotype and allele distribution of VDR BsmI between the T1DM and healthy individualcohorts. Furthermore, as indicated by table (2) and figure (4), there was no statistically significant variation in the VDR BsmI genotype between the type 1 andT2DMcohorts or between T2DM and the healthy individualcohort.

There was no statistically significant variation found in the genotype and allele distribution of VDR FokI between the T1DM and healthy individualcohorts. While there is a statistically significant variation in the FokI genotype between T2DM and the healthy individualcohort, the FF genotype is more expressed in T2DM cases, and having this genotype raises the risk of T2DM by 12.8 (Odds ratio 12.80(1.58-103.52)). Additionally, a statistically significant variation in the prevalence of FokI genotypes between T1DM and T2DM was found; 8% of T1DM individuals had the ff genotype, compared to 0% of T2DM cases (P=0.039). Table (2) and Figure (4), however, indicate that there was no statistically significant variation in the Allele distribution for the FokI genotype between the T2DM and healthy individualcohorts, nor between the T1DM and T2DM cohorts.

Table (2) comparison of genotype and allele distribution between studied cohorts.

	T1DM n=50	**control 1 n=25**	**test of significance**	**Odds ratio (95%CI)**
BsmI				
GG	2(4.0)	0	p=0.317	undefined
AG	41(82.0)	22(88.0)	p=0.760	0.798(0.188-3.39)
AA (r)	7(14.0)	3(12.0)	reference cohort	reference cohort
Hardy Weinberg equilibrium	χ^2=13.25 P=0.001*	χ^2=13.98 P=0.001*		
Allele				
G	45(45)	22(44)	P=0.907	1.04(0.525-2.06)
A(r)	55(55)	28(56)		1
FokI				
FF	16(32.0)	4(16.0)	p=0.13	2.0(0.265-15.08)
Ff	30(60.0)	19(76.0)	p=0.796	0.789(0.132-4.74)
ff (r)	4(8.0)	2(8.0)	reference cohort	1
Hardy Weinberg equilibrium	χ^2=13.225 P=0.001*	χ^2=5.59 P=0.02*		
FokI				
F (r)	62(62)	24(48)	P=0.102	1
F	38(38)	26(52)		0.566(0.285-1.12)
	T2DM n=50	**control 2 n=25**	**test of significance**	**Odds ratio (95%CI)**
BsmI				
GG	4(8.0)	1(4.0)	p=0.122	8.0(0.500-127.91)
AG	44(88.0)	20(80.0)	p=0.08	4.40(0.744-26.03)
AA (r)	2(4.0)	4(16.0)		1
Hardy Weinberg equilibrium	χ^2=29.09 P=0.001*	χ^2=12.67 P=0.0003*		
Allele				
G	52(52)	22(44)	P=0.355	1.38(0.696-2.73)
A(r)	48(48)	28(56)		1
FokI				
FF	16(32.0)	1(4.0)	p=0.003*	12.80(1.58-103.52)

Ff(r)	34(68.0)	24(96.0)		1
Hardy Weinberg equilibrium	χ^2=2.04 P=0.153	χ^2=0.008 P=0.927		
FokI **F (r)** **F**	 66(66) 34(34)	 26(52) 24(48)	 P=0.09	 1 1.79(0.896-3.58)
	T1DM **N (%)**	**T2DM** **N (%)**	**test of significance**	**Odds ratio (95%CI)**
BsmI **GG** **AG** **AA (r)**	 2(4.0) 41(82.0) 7(14.0)	 4(8.0) 44(88.0) 2(4.0)	 p=0.085 p=0.09	 0.142(0.014-1.44) 0.266(0.052-1.36) 1
Allele **G** **A(r)**	N=100 45(45) 55(55)	N=100 52(52) 48(48)	 P=0.321	 0.755(0.433-1.32) 1
FokI **FF** **Ff (r)** **Ff**	 16(32.0) 30(60.0) 4(8.0)	 16(32.0) 34(68.0) 0	 p=0.77 reference p=0.039*	 1.13(0.485-2.65) 1 Undefined
FokI **F (r)** **F**	 62(62) 38(38)	 66(66) 34(34)	 P=0.555	 1 1.189(0.667-2.12)

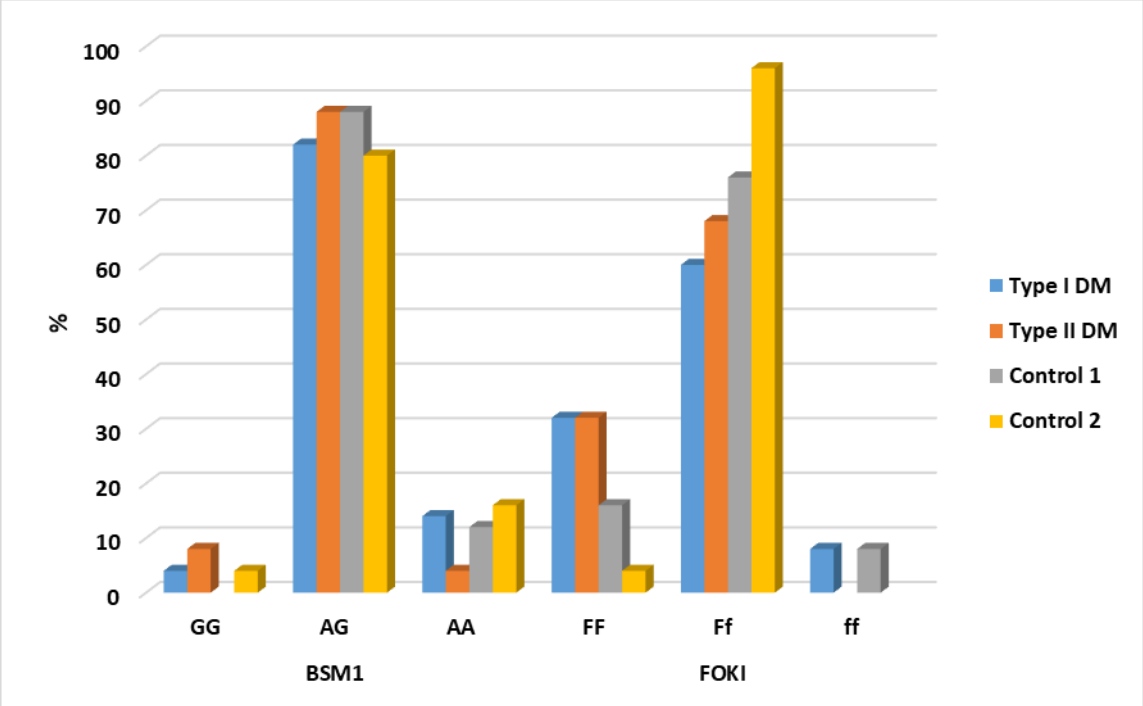

Figure (4) comparison of genotype and allele distribution between studied cohorts.

With the exception of two statistically significant relationships between BsmI and TGS (P=0.01) and WBCs (P=0.003) among T1DM subjects, there was no statistically significant link between

BsmI and any of the examined laboratory measures. Additionally, evaluating the relationship between the FokI genotype and laboratory results in individuals with T1DM shows that the FF FokI genotype has a statistically significant older age than the Ff and ff genotypes. The Fok1 genotype also showed a statistically significant correlation with platelets (p=0.017), cholesterol (p=0.018), TGS (p=0.04), and AST (p=0.013). Indicating that there are greater mean AST, cholesterol, and TGS among Ff as cleared in table (3).

With the exception of bilirubin, which was statistically substantially higher in T2DM cases with AA genotype than AG BsmI genotype, there is no statistically significant correlation between BsmI genotype and any of the laboratory data examined in T2DM cases. Further analysis of the relationship between the FokI genotype and laboratory parameters in T2DM cases showed that the Ff FokI genotype had a statistically significant lower VD level than the FF FokI genotype (6.16±3.85 versus 8.68±4.66, P=0.049) in T2DM casesas illustrated in table (3).

Table (3):relation between (BsmI&FokI) and laboratory findings among diabetic cases.

T1DM	**Bsm1**			**Test of significance**	**FokI**			**Test of significance**
	GG	AG	AA		FF	Ff	Ff	
Albumin (gm/dl)	3.50(3.33-3.68)	3.80(3.33-4.2)	3.0(2.6-3.4)	Kw=1.18 P=0.552	3.9(3.25-4.4)	3.9(3.7-4.2)	3.55(3.0-4.1)	kw=0.628 P=0.732
AST (U/L)	21.0±1.41	17.88±4.35	18.86±5.89	F=0.552 P=0.579	17.13±4.06	19.37±4.46	13.0±0.0	F=4.77 P=0.013*
ALT (U/L)	19.0±1.41	18.41±3.91	18.92±3.47	F=0.071 P=0.930	18.28±4.09	19.0±3.70	15.75±0.50	F=1.39 P=0.258
Bilirubin (mg/dl)	1.50±0.42	13.1±0.22	1.51±0.27	F=2.71 P=0.08	1.42±0.29	1.32±0.22	1.22±0.09	F=1.36 P=0.266
RBG (mg/dl)	248.0±67.9	242.92±27.71	227.14±19.55	F=0.996 P=0.377	244.19±31.62	237.57±24.42	253.0±44.07	F=0.673 P=0.515
Creatinine (mg/dl)	0.90(0.625-1.18)	0.950(0.800-1.38)	0.80(0.70-0.90)	Kw=1.56 P=0.458	0.85(0.625-1.08)	0.7(0.6-0.8)	1.9(0.9-2.9)	kw=11.94 P=0.003*
Cholesterol (mg/dl)	183.50±6.4	167.78±21.2	167.0±30.4	F=0.483 P=0.620	168.0±22.57	172.30±20.59	139.50±10.97	F=4.39 P=0.018*
TGS (mg/dl)	163.5±4.95	107.63±28.3	96.29±15.5	F=4.99 P=0.01*	105.94±21.39	104.97±24.68	142.50±60.62	F=3.37 P=0.04*
HDL (mg/dl)	38±1.41	50.87±9.82	49.86±11.4	F=1.60 P=0.212	52.0±11.41	49.88±9.79	45.50±5.19	F=0.699 P=0.502
HBA1C %	11.50±1.69	10.95±2.44	10.07±1.79	F=0.495 P=0.613	10.52±2.19	11.07±2.55	10.49±0.589	KW=0.331 P=0.720
HB g/L	14.20±2.12	12.43±1.67	12.11±1.95	F=1.17 P=0.319	11.76±	12.89±1.58	11.95±0.87	KW=2.58 P=0.086

					1.94			
WBC x 10^9/L	10.50±0.71	7.96±1.58	6.33±1.19	F=6.61 P=0.003*	7.98± 1.51	7.87± 1.88	6.98± 0.29	F=0.573 P=0.567
Platelet x 10^9/L	155.5±9.2	163.29±18 .81	177.57±33 .5	F=1.58 P=0.217	159.8 1±21. 38	170.80± 20.29	142.0± 2.31	F=4.44 P=0.017*
Albumin/ creatinine (mg/gm)	51.1(25.05-290.75)	41(17.58-158.50)	19.8(17.6-22.0)	Kw=3.28 P=0.194	26.1 (10.0 5-78.28)	12.0(7.6 -53.28)	179.5 (9.0-350.0)	kw=1.84 P=0.397
VD (ng/ml)	10.05±0.81	11.95±6.9 9	10.09±9.4 2	KW=0.243 P=0.785	13.09 ± 8.67	10.69± 6.44	12.61± 6.34	KW=0.616 P=0.545
T2DM	Bsm1			Test of significanc e	FokI			Test of significance
	GG	AG	AA		FF		Ff	
Albumin (gm/dl)	4.15(3.9-4.4)	3.8(3.5-4.1)	4.2(2.9-4.4)	kw=3.16 P=0.206	3.4(2.85-4.15)		3.70(3.4-4.2)	z=1.22 p=0.269
AST (U/L)	17.5±2.08	19.68±3.8 6	16.0±5.66	F=1.40 P=0.256	18.06±4.29		19.97±3. 52	z=2.76 p=0.103
ALT (U/L)	17.25±3.86	20.86±4.8 5	17.0±2.83	F=1.59 P=0.214	19.19±4.29		21.0±5.0	z=1.56 p=0.218
Bilirubin (mg/dl)	1.43±0.26	1.27±0.19 a	2.05±0.21 a	F=16.38 P=0.001*	1.33±0.30		1.31±0.2 2	z=0.114 p=0.737
RBG (mg/dl)	248±16.81	227.45±52 .7	240±14.14	F=0.346 P=0.709	240.44±29.35		224.50±5 6.79	z=1.11 p=0.297
Creatinine (mg/dl)	0.65(0.60-0.70)	0.70(0.60-0.90)	1.0(0.6-1.4)	kw=1.55 P=0.461	0.9(0.72-1.18)		1.0(0.77-1.33)	z=0.448 p=0.503
Cholesterol (mg/dl)	184.75±11.2 9	165.3±21. 99	145±46.7	F=2.33 P=0.109	158.88±26.52		169.35±2 0.54	z=2.34 p=0.132
TGS (mg/dl)	114±30.73	113.98±26 .3	89.50±0.7 1	F=0.832 P=0.441	113.44±24.37		112.79±2 7.37	z=0.006 p=0.936
HDL (mg/dl)	43.50±9.26	47.83±8.3 2	45.50±7.7 8	F=0.544 P=0.584	47.72±7.17		47.24±8. 87	z=0.037 p=0.848
HBA1C %	11.88±1.28	9.85±3.11	9.65±1.06	Kw=0.849 P=0.434	9.89±2.49		10.06±3. 23	z=0.057 p=0.816
HB g/L	11.93±2.67	11.38±1.8 7	13.80±1.8 4	Kw=1.59 P=0.214	11.43±2.06		11.57±1. 93	z=0.066 p=0.798
WBC x 10^9/L	7.08±1.49	7.45±1.46	6.70±0.14	F=0.355 P=0.703	7.30±1.58		7.42±1.3 8	z=0.087 p=0.848
Platelet x 10^9/L	163.75±22.5 2	173.41±20 .9	143.50±4. 95	F=2.27 P=0.12	170.06±22.88		172.09±2 0.93	z=0.096 p=0.758
Albumin/cr	8.25(5.0-	15(9.0-	24.0(15.8-	kw=1.12	21.5(15.55-		46.1(20-	z=1.80

eatinine (mg/gm)	11.5)	56.85)	169)	P=0.572	110.75)	307.85)	p=0.180
VD (ng/ml)	7.56±2.05	6.65±3.99	12.56±10.66	Kw=1.97 P=0.151	8.68±4.66	6.16±3.85	z=4.08 p=0.049*

A Spearman correlation analysis was used to examine the relationship between VD and the demographic, clinical, and laboratory findings of the T1DM and T2DM cohorts. The results showed that among T1DM, VD exhibited a statistically significant positive correlation with HDL and a statistically significant negative correlation with bilirubin and sex (with lower VD levels in males) as shown in table (4). Table (4) also demonstrates a statistically significant negative connection between VD and ALT (r=-0.321) in the T2DM cohort.

Table (4) correlation between VD and demographic, clinical and laboratory findings among T1DMand T2DMcohorts.

	T1DM		**T2DM**	
	VD (ng/ml)		VD (ng/ml)	
	r	P	R	P
Age / years	0.167	0.246	-0.056	0.698
Sex	-0.331	0.019*	-0.240	0.094
Marital status	-0.023	0.873	-0.009	0.951
Occupation	-0.012	0.936	-0.194	0.177
Smoking	0.246	0.085	-0.09	0.534
Physical activity	0.057	0.695	0.051	0.725
Mental Stress	-0.249	0.081	0.100	0.490
BMI (kg/m2)	0.118	0.416	-0.193	0.180
Hypertension	0.068	0.639	-0.164	0.255
RBG (mg/dl)	-0.203	0.158	-0.072	0.621
Albumin (gm/dl)	0.106	0.463	-0.087	0.546
AST (U/L)	0.032	0.827	-0.138	0.340
ALT (U/L)	-0.274	0.06	-0.321	0.023*
Bilirubin (mg/dl)	-0.328	0.02*	-0.178	0.216
Cholesterol (mg/dl)	-0.045	0.754	-0.046	0.752
TGS (mg/dl)	-0.267	0.061	-0.048	0.741
HDL (mg/dl)	0.283	0.046*	-0.235	0.100
HBA1C %	-0.227	0.113	-0.004	0.975
HB(g/L)	0.113	0.435	0.229	0.100
WBCs x 10^9/L	0.04	0.784	-0.227	0.110
Platelet x 10^9/L	0.074	0.609	-0.018	0.900
Albumin/creatinine (mg/gm)	-0.157	0.278	-0.114	0.433

DISCUSSION:

A widespread medical ailment that has become more prevalent over the past few decades and is a significant public health concern of the twenty-first century is DM mellitus ***(23).***Type 1 andT2DM are the two main types of the disease. The hallmark of T1DM, also known as insulin-dependent DM mellitus, is autoimmune beta cell death, which prevents the pancreas from producing insulin, which is necessary for survival ***(3)***.

Although it usually manifests in children and teens, T1DM is becoming more and more noticeable as people age. It is linked to a genetic predisposition as well as chemical and viral causes ***(24).***It is a complex autoimmune illness, meaning that immunologic, environmental, and genetic variables all influence a person's vulnerability. According to genetic research, this is a polygenic disorder with one major locus (IDDM1=HLA) and an unknown number of smaller loci ***(5).***

Insulin resistance, or the body's incapacity to react appropriately to the pancreatic hormone insulin, is the cause of T2DM, also known as noninsulin-dependent DM. T2DM is substantially more common and makes up about 90% of all DM cases globally ***(25).***Although it is more common in adults, teenagers are also starting to experience it on a regular basis. Most of these individuals are fat, though some may also have abdominal obesity. This kind typically manifests beyond the age of 40, and autosomal HLA association is absent in T2DM***(26).***

Insulin resistance is linked to ageing, obesity, sedentary lifestyles, and genetics. The eating of high-calorie foods and inactivity are important risk factors for obesity and type 2 diabetes. Additionally, inflammation, oxidative and endoplasmic reticulum stress, high lipid levels, and amyloid accumulation cause β-cell failure in T2DM***(7).***

A growing body of evidence from extensive observational studies has linked the onset ofT2DM to low 25-hydroxyVD levels ***(27).***A review compiled data demonstrating a negative relationship between VDdecrease and glycemic healthy individual, a positive correlation between VDdecrease andT2DM, and a significant positive relationship between serum 1,twenty-five-hydroxy-VD and insulin sensitivity and secretion ***(28).***Moreover, the polymorphisms of the VDR gene emerge as a potential gene that affects the development of T2DM. The most significant polymorphisms are ApaI, TaqI, FokI, and BsmI, which have been the subject of several investigations in various fields and ethical contexts ***(29).***

Crucially, there is a sharp rise in the prevalence of VD deficiency worldwide, and epidemiological data points to a role for VDdecrease in the aetiology of T1DM. It has also been demonstrated that variations in genes essential for VD metabolism affect the likelihood of T1DM***(11).***It has been demonstrated that VD may stop human pancreatic islets from dying due to cytokines. A study involving 1,316 kids with T1DM diagnosis revealed an unexpected negative correlation between VD consumption and fasting C-peptide, a measure of pancreatic beta cell residual insulin secretion ***(30).***

According to reports, VD interacts with immune cells to activate human macrophages, promote the maturation of antigen-presenting cells, inhibit dendritic cell differentiation, and regulate the production of cytokines. As a result, it may be regarded as an immune system modifier ***(31)***. Since VD acts through the nuclear VDR, the VDR gene may be a candidate or susceptibility gene for T1DM***(22)***.

The current study set out to determine the relationship between VD levels and Egyptian cases' susceptibility to DM mellitus, as well as the relationship between VDR gene polymorphisms and DM mellitus (susceptibility and pathogenesis) in Egyptian cases.

150 participants were involved in this study: 50 healthy individuals with matched age and sex were selected as the healthy individualcohort, and 100 DM cases who attended the incaseDM and endocrinology unit and outcase diabetic clinics of the Specialized Medical Hospital at Mansoura University (15 males and 35 females for T1DM and 18 males and 32 females for T2DM).

In addition to its known function in healthy individualin calcium homeostasis and bone mineralization, VD has been shown during the past several decades to have anti-inflammatory and immunomodulatory properties. The current study's T1DM cases had lower mean serum VD levels than the healthy individualcohort, supporting the vitamin's function in the etiology and susceptibility of T1DM. The evaluation of VD's validity in differentiating between the cohorts under study shows that the vitamin's area under the ROC curve for distinguishing between T1DM and healthy individual is good (AUC = 0.706), with the optimal cut off point being 15.23, which results in 80% sensitivity and 52% specificity.

In Olu and Lapland, northern Finland, a study by ***Rak and Bronkowska, 2018*** discovered that 83.3% of T1DM participants had reduced VD concentrations at the time of disease identification. This finding is consistent with our research ***(31)***.According to ***Infante et al. (2019),***VD insufficiency may also influence a child's predisposition to acquire T1DM throughout the early years of life, especially in those with a high hereditary risk. Furthermore, a high rate of VD insufficiency is seen in T1DM cases. Numerous pre-clinical investigations demonstrated the role of VDdecrease in islet autoimmunity and the development of autoimmune DM***(11)***. In a different ***Ahmed et al. 2019 study***, 16% and 68% of diabetic cases, respectively, had inadequate or deficient VD. Notably elevated glycemic control and VD levels in children with T1DM who were given VD supplements ***(32)***.

Compared to the healthy individualcohort, T2DM cases in this study had considerably lower mean serum VD levels. With a best cut off point of 9.38, VD had an outstanding (AUC=0.824) for differentiating between T2DM and healthy individual, producing 74% sensitivity and 64% specificity. Additionally, the T2DM cohort exhibits lower serum VD than the T1DM cohort when comparing their two cohorts. The current investigation, along with a meta-analysis of epidemiologic research carried out by ***Mohammadi et al., 2022***, revealed that serum VD level was dose-responsibly and inversely linked with the risk of T2DM and combined T2DM and pre-DM in adults. For pre-DM, the connection was not very noteworthy, though***(33)***.Additionally, **Sacerdote et al., 2019** verified that serum 25OHD and glucose metabolism indices, such as HOMA-IR, had an inverse connection***(28)***.

Because of the potential implications that VD may play in decreased pancreatic β-cell activity and insulin sensitivity, many studies have suggested that VD status may increase the risk ofT2DM. This theory is biologically feasible. However, it appears from published systematic reviews and meta-analyses that VD treatment does not reduce the risk ofT2DM in those with preDM***(34)***. Low VD status has also been linked to increased insulin resistance and impaired insulin sensitivity in human investigations. Furthermore, as obesity is a known risk factor forT2DM, and low serum 25OHD concentration is an indicator of obesity ***(35)***.

When comparing the VD levels of type 1 andT2DM, the type 1 cohort's serum VD is higher than the type 2 cohort's. The VD area under the ROC curve (AUC=0.715) shows good discrimination between DM 1 and 2, with a cutoff value of 10.13 that yields 80% sensitivity and 58% specificity. According to data gathered by ***Parva et al. (2018),*** 14.13% of study participants who were VD deficient had DM, compared to 11.67% of participants who were VD sufficient (p-value 0.0107). This shows that type 1 andT2DM may be influenced by VD deficiency. The

presence of VD receptors on the pancreatic beta islet cells that secrete insulin and the enhanced insulin secretion in DM individuals treated with VD have been identified as the mechanisms behind this association. The relationship between VD insufficiency and DM may also be explained by higher rates of obesity, renal failure, and injury to the kidneys in diabetics, which can affect the hydroxylation of 25-hydroxyVD and, ultimately, secondary hyperparathyroidism***(36)***.

Amrein et al., 2020 also found that compared to healthy people, cases with T1DM had a greater frequency of VD insufficiency. And acknowledged that life stage appears to have an impact on the effect of VD supplementation on the start of T1DM. When supplements were given between the ages of 7 and 12 months, the chance of acquiring T1DM was nearly twice as low as when supplements were given earlier. There has also been evidence of an increased risk ofT2DM mellitus in people with low twenty-five hydroxyl VD levels. But generally, taking VD supplements did not reduce the chance of gettingT2DM***(37)***.

It is thought that VD has a role in immune regulation, and in individuals with T1DM, a lack of it leads to the attack of beta cells that produce insulin by auto-antibodies. Given that VD acts through the nuclear VDR, the VDR gene may be associated to increased risk of developing T1DM***(22).***

The VDR gene has four frequent SNPs: rs2228570 for FokI, rs731236 for TaqI, rs1544410 for BsmI, and rs7975232 for ApaI. These include the ApaI, BsmI, and TaqI polymorphisms, which are found at the 3′-end of the VDR gene and cause silent mutations linked to higher VDR mRNA stability. FokI SNP, on the other hand, is found at the start codon that generates a shorter (424 amino acid) protein that has higher activity than the longer (427 amino acid) variant ***(38).***There is conflicting evidence from multiple research linking polymorphisms in the VDR gene to type 1 andT2DM***(39)(40)***.

The genotype distribution variation in T1DM cases from the general population was evaluated in this study using the Hardy-Weinberg equilibrium, which shows statistically significant variations from the reference population for each of the genotypes (Bsm1 and Fok-I). Nonetheless, our analysis reveals no statistically significant variation in the Bsm1 and Fok-I genotypes between the T1DM and healthy individualcohorts. No statistically significant variation was seen between the T1DM and healthy individualcohort when examining the allele distribution for the Bsm1 and Fok-I genotypes. Furthermore, there is no statistically significant variation in the Bsm1 genotype between the T1DM and T2DM cohorts when comparing genotypes. The distribution of Fok-I genotypes in type 1 andT2DM, however, showed a statistically significant variation: 8% of T1DM cases had the ff genotype compared to 0% of T2DM cases (P=0.039).

These findings were consistent with an Egyptian study published in 2013 by **Hamed et al**., which found that there was no statistically significant variation in the distribution of genotypes or alleles pertaining to FokI VDR polymorphism between T1DM cases and healthy individuals. 1.08 (P=0.76) was the odds ratio, while the 95% confidence interval covered 0.64 to 1.85 ***(21)***.

In Kuwait, **Rasoul et al., 2019** study demonstrated that there was no correlation between T1DM and the polymorphisms of the VDR gene BsmI (A > G, rs1544410). Furthermore, when comparing the homozygous ff genotype of VDR gene polymorphism (FokI, C > T, rs10735810) between T1DM cases and healthy individuals, statistically significant variations were found ($P < 0.0001$), and the frequency of variant 'f' allele was found to be significantly higher in T1DM cases while the 'F' allele was more prevalent in the healthy individuals ***(22)***.

However, **Ali et al., 2018** Saudi study discovered that T1DM cases had a significantly higher frequency of the heterozygous genotype (Ff) than healthy individuals did for the Fok-I.

Meanwhile, the homozygous (ff) genotype frequency was considerably lower. The (f) allele was also shown to be substantially less common in cases than in healthy individuals. However, the prevalence of the Bsm-I homozygous AA (bb) and heterozygous AG (Bb) genotypes was substantially greater in the cases. Cases also showed significantly higher frequency of A (b) allele compared to healthy individual***(41)***.

Additionally, an Egyptian study by **Ahmed et al., 2019** confirmed that, in comparison to healthy individuals, T1DM children presented more frequently with the BsmI A (b) allele ***(32)***. **Thirunavukkarasu et al., 2024** found that whilst the FokI-Ff genotype frequency was substantially lower in T1DM cases than FDRs, the FokI-FF genotype frequency was significantly more common in T1DM cases than FDRs in north India. However, there were no appreciable variations in BsmI genotype or allele frequencies amongst the research cohorts ***(42)***.

These variations may be the result of limited statistical power, diverse ethnic cohortings, short sample sizes, and clinical heterogeneity. Thus, the most effective approach to resolving these issues may be to do a thorough meta-analysis.

Zhai et al. (2020) did a meta-analysis encompassing 39 case-healthy individual studies, which concluded that there was no significant correlation between VDR gene polymorphisms and T1DM risk in the general population. Subcohort analysis aggregated data, however, showed substantial positive and negative correlations, respectively, between T1DM in Americans and Africans and the FokI and BsmI polymorphisms. Regarding FokI polymorphisms, for all genotype models, the subcohort analysis by ethnicity revealed that the European population had a lower risk of T1DM susceptibility while the African population had a higher risk.Furthermore, FokI polymorphism had no effect on Asian susceptibility to T1DM relative to that of Africans and Europeans. Across all genotype models, there was no discernible correlation between the risk of T1DM and the BsmI polymorphism in the general population. Nevertheless, across all genotype models, the combined results of the subcohort analysis showed notably significant negative relationships between the BsmI SNP and the risk of T1DM susceptibility in American populations. Regarding the populations of Europe, Asia, and Africa, no discernible correlation was found ***(38)***.

Nine case-healthy individual studies focusing on a specific population in the EMRO countries were included in the **Shahmoradi et al., 2021** meta-analysis. The results showed that the BsmI polymorphism, a predisposing genotype, was positively related to an increased risk of T1DM in a recessive genetic model. Other VDR gene polymorphisms, such as the FokI polymorphism, did not, however, seem to be significantly correlated with the total risk of T1DM***(43)***.

Regarding the BsmI genotype, there is no statistically significant variation between the T2DM and healthy individualcohorts in the current investigation. Nonetheless, a statistically significant variation in the FokI genotype between the T2DM and healthy individualcohorts was found, with FF genotypecarrying a greater risk of T2DM than Ff genotypes.

The genotype distribution variation from the whole population was evaluated using the Hardy-Weinberg equilibrium, which also shows the statistically significant variation from the reference population for each BsmI for both the cases and the healthy individualcohort.

Nonetheless, for the FokI genotype in the cases and healthy individualcohort, there is no statistically significant variation in the genotype distribution from the overall population. When T1DM and T2DM cohorts' genotypes are compared, there is no statistically significant variation between T1DM and T2DM in terms of BsmI genotype. For type 1 and T2DM, there was a statistically significant variation in the distribution of the FokI genotype; 8% of T1DM had the ff genotype, compared to 0% in type 2 DM.

By examining the allele distribution for the BsmI and FokI genotypes, it was possible to determine that there was no statistically significant variation between the T2DM cohort and the healthy individualcohort. Furthermore, no statistically significant variation between type 1 andT2DM was found, according to the allele distributions for the BsmI and FokI genotypes.
There is debate regarding the relationship between VDR polymorphisms and T2DM; some researches have shown a relationship, while others have not. In a study, **El Gendy et al., 2019** assessed the VD status and VDR gene polymorphisms (Fok1, Bsm1, and Taq1) in Egyptian cases withT2DM. The polymorphisms in the VDR gene were identified using the polymerase chain reaction technique known as PCR-RFLP. Only the distribution of Fok I genotypes showed statistically significant variations between T2DM cases and healthy individuals in this investigation. Cases with T2DM had higher frequencies of the ff and Ff genotypes than healthy individuals, with a statistically significant variation. Additionally, there was a statistically significant variation in the frequency of allele f genotype in the sick cohort compared to the healthy individualcohort. The Bsm1 genotype and T2DM did not correlate***(44)***.

In contrast to our findings, **Tawfeek et al.'s 2018** study in Menoufia, Egypt, assessed the relationship between genetic susceptibility toT2DM and the polymorphism of the VD receptor (BsmI) gene in an Egyptian population. The study found that, although not statistically significant, the AG (Bb) genotype was higher in the T2DM cohort (42.5%) compared to the healthy individualcohort (12.5%), and the AA (bb) genotype was higher in the T2DM cohort (7.5%) than in the healthy individualcohort (5%). The T2DM cohort had a greater frequency of the A (b) allele (28.8%) compared to the healthy individualcohort (11.3%). It was determined that there was a 5.610 variation in risk between the AG (Bb) and GG (BB) alleles, and a 2.475 variation between the AA (bb) and GG (BB) alleles. It was discovered that the A (b) allele carried a 3.18 higher risk than the G (B) allele***(45)***.
Al-hazmi, 2019 study on Saudi cases, which corroborated our findings, concluded that there was no connection between T2DM cases' BsmI genotype with their condition. Using PCR-RFLP, genomic DNA was amplified and examined for the VDR genotype for the Apa1 Taq1 and BsmI genotypes. This study did not include the FokI genotype. TaqI genotypes and T2DM have been shown to be associated, although there is no correlation between BsmI, ApaI, and T2DM ***(29)***.
Contrary to our findings According to a study by **Malik et al., 2018** conducted in the Kashmir Valley, Bsm-1 was highly correlated withT2DM among northern Indians. The findings showed that in the Kashmiri community, the single nucleotide polymorphism B (G allele) in Bsm-1 may be a susceptibility allele for DM. The PCR-RFLP method was applied. This divergence from our findings could be the result of various ethnic cohorts ***(46)***.
Another Indian study that looked at the SNPs of BsmI, TaqI, and FokI was carried out in Northeast India by **Sarma et al., 2018**. They used polymerase chain reaction and gene sequencing techniques. There was no discernible variation in the frequency of the wild type and mutant genotypes, but the distribution of the BsmI polymorphism revealed that the frequency of the heterozygous GA (Bb) genotype was significantly higher in cases of T2DM compared to healthy individuals. The mutant allele A (b) did not significantly differ between the cases and healthy individuals. The wild type ff (TT) variant was the most prevalent genotype in both cases (80%) and healthy individuals (75%), according to an analysis of the FokI polymorphism genotypes. However, this variation was not statistically significant. The instances under analysis did not contain the heterozygous genotype Ff (TC). Although cases (20%) had a higher frequency of the mutant FF (CC) genotype than healthy individuals (10%), the variation was not

statistically significant. The mutant F (C)allele did not significantly differ between cases and healthy individuals. ***(47)***.

Aravindhan et al., 2021 conducted a meta-analysis on 47 case-healthy individual studies and found that the total population data indicated a substantial correlation between T2DM and the polymorphisms of the heterozygote model, FokI and BsmI. A meta-analysis of the FokI polymorphism revealed that, across all five genotyping models, the pooled results of the overall analysis showed a substantial positive correlation between the FokI gene polymorphism and T2DM. Furthermore, a subcohort analysis based on ethnicity revealed that Asian people were more susceptible to T2DM in all five genotype models. African Americans, Europeans, and persons of mixed ethnicity—the majority of whom were Caucasians, Latinos, and American-Africans—showed no discernible correlation. The BsmI (rs1544410) polymorphism was subject to a meta-analysis, which revealed no significant correlation for either the overall analysis or the ethnic-specific subcohort analysis. The only exceptions were Asians and the (AG vs.GG) Bb vs. BB model in the overall study ***(39)***.

In the current study, there was no statistically significant correlation found between BsmI and any of the other laboratory findings studied among T1DM cases, with the exception of two statistically significant correlations found between BsmI and WBCS and TGS. The BsmI variation of the VDR gene was linked to hypertriglyceridemia and may be susceptible to metabolic syndrome, according to research by **Kowalowka et al., 2020**. It was said, in contrast to our results, that the BsmI BB + Bb genotypes were associated with the lower twenty-five hydroxyl VD levels in the metabolic syndrome cohort***(48)***.

In the current study, there was no statistically significant correlation found between BsmI and any of the other laboratory findings examined among T2DM cases, with the exception of bilirubin, which was statistically significantly higher among AA genotype than AG BsmI genotype. These findings are consistent with a study by **Fatma and Abdul, 2019** on T2DM cases in Pakistan, which discovered no meaningful correlation between metabolic markers and the BsmI restriction site ***(49)***.According to **Al-Kashwan et al., 2021,** there were no appreciable variations in fasting plasma sugar, TC, BMI, VD, and insulin levels between the BB, Bb, and bb genotypes. In contrast to Bb and bb carriers of T2DM participants, homozygote carrier GG (BB) has substantially higher TG and VLDL concentrations and the lowest HDL level***(50)***.

Our study's analysis of the relationship between FokI and laboratory results in T1DM cases shows that the FF FokI genotype has a statistically significant older age than the Ff and ff genotypes. The FokI genotype also showed a statistically significant correlation with platelets, cholesterol, TGS, and AST. **Eissa et al., 2021**, corroborated our findings and found a substantial correlation between FokI polymorphisms and triglycerides and total cholesterol***(51)***. As opposed to our research, **Mostafa et al., 2024** found that when they examined the relationship between metabolic phenotypes and FokI genotype polymorphism in the parameters they examined in children with T1DM, there was a statistically significant variation between the two parameters (lipid profile and HbA1c) and between the two genotypes and VD***(52)***.

Our analysis of the relationship between FokI and laboratory results in T2DM reveals a statistically significant reduction in VD levels in those with the (Ff) FokI genotype compared to those with the (FF) genotype. FF FokI cohort had a statistically significant higher mean VD than Ff genotype. **Mohamed et al., 2020** case healthy individual study on T2DM cases found that a statistically significant rise in TGS levels was seen in the ff genotype when compared to the FF and Ff genotypes when FokI genotypes and clinical data were examined. There was no statistically significant variation between *FokI* genotypes, and the clinical data studied such as

age, BMI, PPBS, HbA1c, TC, TGS, HDL, LDL, urea, and creatinine. Comparison between *FokI* genotypes and 25OHD levels in the cohorts studied showed no statistically significant variation***(53)***.

Gomaa et al. (2022) found that the ff genotype had significantly higher levels of both TC and LDL-C than the FF genotype. However, they could not discover any meaningful association between the various VDR genotypes and VD levels ***(54)***.

When VD levels are compared to demographic, clinical, and laboratory results (RBG, HbA1c, Albumin, ALT, AST, bilirubin, TGS, cholesterol, HDL, and CBC) in individuals with T1DM in the current study, statistically significant negative correlations are found. Males have lower VD levels than females do. Among T1DM cases, a statistically significant positive connection between VD and HDL was found. An inverse linear connection between VD and HbA1C, FBS, BMI, and disease duration was found in contrast to these results by **Ghavam et al., 2018** study. Furthermore, there was a direct linear relationship between HbA1C and illness duration and FBS, and an inverse linear relationship between HbA1C and BMI. Considering the function of this vitamin in secretion and the impact of insulin, it would appear beneficial to track the serum level of VD in DMcases and, if needed, recommend supplements ***(55)***.

According to **Farhat et al. 2019,**VD deficiency is prevalent in Saudi Arabia, especially in younger men and those with DM and high cholesterol***(56)***.In **Ahmed et al., 2019** assessment of the relationships between serum twenty-five hydroxyl VD levels and a number of case-related variables, the researchers found nonsignificant relationships between serum VD levels and BMI, age at onset or duration of DM, and both HbA1c% and daily insulin requirement ***(32)***.

There is a statistically significant negative connection betweenVD and ALT and demographic, clinical, and laboratory data (RBG, HbA1c, Albumin, ALT, AST, bilirubin, TGS, Cholesterol, HDL, and CBC) among T2DM cases. An inverse linear connection was found in a study by **Ghavam et al., 2018** between VD and HbA1C, BMI, and disease duration. Additionally, there was an inverse linear link between HbA1C and BMI and a direct linear relationship between HbA1C and FBS and disease duration***(55)***. Pearson's correlations between VD levels in the blood and biochemical markers in cases withT2DM in **Alharbi et al., 2021** conducted a correlation analysis which revealed a significant negative correlation between VD levels and HbA1c. However, no significant correlation was observed between VD and any other biochemical marker, including FBG, PPBG, HDL, LDL, VLDL, and TG***(57)***.

CONCLUSION:

- The mean serum VD levels in T1DM and T2DM cases were both considerably lower than in the healthy individualcohort, indicating that VDdeficiency plays a role in the susceptibility and pathophysiology of DM.
- There was no statistically significant variation seen in the genotype and allele distribution of VDR BsmI between the T1DM and healthy individualcohorts, T2DM and healthy individualcohorts, nor T1DM and T2DM cohorts.
- There was no statistically significant variation found in the genotype and allele distribution of VDR Fok-I between the T1DM and healthy individualcohorts. Nonetheless, there was a statistically significant variation in the incidence of T2DM with FF genotype compared to Ff genotype (odds ratio 12.80) between the T2DM and healthy individualcohorts with reference to the FokI genotype. However, in terms of the allele distribution of the Fok-I genotype, there was no statistically significant variation between the T2DM cohort and the healthy individualcohort.

- For the Fok-I genotype distribution, there was a statistically significant variation between T1DM and T2DM; in T1DM, 8% of individuals had the ff genotype, but in T2DM, there were zero cases (P=0.039).

List of abbreviations:

DM	Diabetes mellitus
IDF	International Diabetes Federation
T1DM	Type 1 DM
T2DM	Type 2 DM
IDDM	insulin- dependent diabetes mellitus
HLA	Human leukocyte antigen
VD	Vitamin D
VDR	Vitamin D Receptor
SNPs	single nucleotide polymorphisms
ELISA	Enzyme Linked Immunosorbent Assay
PCR-RFLP	polymerase chain reaction –Restriction Fragments Length Polymorphism
UV	Ultraviolet
SPSS	Statistical Package for the Social Sciences
ROC	Receiver operating characteristics
AUC	Area Under Curve
TGS	Triglycerides
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
FDRs	First-degree relatives
TC	Total cholesterol
BMI	Body Mass Index

VLDL	Very low-density lipoprotein
HDL	High Density Lipoprotein
HbA1c	Hemoglobin A1C
PPBS	Post prandial blood sugar
LDL	Low Density Lipoprotein
FBS	Fasting Blood Sugar
RBG	Random Blood Glucose

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