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Associations between Vitamin D and Type 2 Diabetes Mellitus: The Role of Vitamin D Receptor and Binding Protein

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a chronic disease that is characterized by β-cell dysfunction and resistance for insulin. Vitamin D is necessary for insulin secretion so it is a crucial factor in the development of T2DM. This study was done to investigate the association between serum 25-hydroxy Vitamin D [25(OH)3D], VDR (Vitamin D receptor) and VDBP (Vitamin D binding protein) with type 2 diabetic patients compared to control subjects. **Subjects and Methods:** This study carried out 110 female patients who were previously diagnosed with type 2 diabetes and 110 age, sex and weight matched as controls. All participants were subjected to full history taking, clinical examination and assessment of fasting blood glucose, HbA1c , lipid profile, 25-hydroxy Vitamin D [25(OH)3D], VDR and VDBP. **Results:** Results showed that the level of 25(OH)3D was significantly lower in diabetic group compared to controls and was significantly negatively correlated with glycated hemoglobin, serum total cholesterol and low density lipoprotein cholesterol in type 2 DM. Decreasing Vitamin D level was significantly associated with decreasing VDR. No significant association was found between Vit D and VDBP levels. **Conclusions:** Vitamin D deficiency is frequent in diabetic patients and associated with poor control and outcome. This suggests a role of Vitamin D in the pathogenesis and control of T2DM. Serum VDBP in diabetes may be independent to the level of 25(OH)3D and needs further studies.

Keywords

Diabetes Mellitus, Type 2, 25-Hydroxy Vitamin D, Vitamin D Receptor, Vitamin D Binding Protein

1. Introduction

T2DM (Type-2 diabetes mellitus) is a chronic disease characterized by both β-cell dysfunction and increased insulin resistance [1]. The prevalence of T2DM continues to rise not only in developing countries, but also in developed countries now [2]. Several genetic and environmental factors can result in the progressive loss of β-cell function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, patients are at risk of developing chronic complications [3]. Vitamin D is one of fat-soluble vitamin with steroid nucleus; it is described as a hormone and acts through intracellular receptors, which belong to the thyroid-steroid receptor superfamily [4].

Total serum levels of 25(OH)3D are a sensitive indicator for Vit D deficiency [5]. Vitamin D deficiency occurs worldwide due to insufficient sunlight and/or dietary intake common in adults. Vitamin D insufficiency is often detected in diabetic patients and it is believed to be linked to the disease development and severity [6].

The main carrier of Vitamin D in the serum is Vitamin D-binding protein (VDBP). It is a low-molecular weight glycoprotein (58 kDa) which significantly predicts the bioavailability of active levels of (25(OH)3D) in the bloodstream [7].

The VDBP/25(OH)D complex formation, its filtration and reabsorption through receptor-mediated uptake in proximal renal tubular cells are vital for activation of Vitamin D [8].

Vitamin D is involved in skeletal development, thyroidal metabolism, immune response regulation, cardiovascular health and glucose-mediated insulin secretion via regulation of insulin receptor expression [9]. There is emerging evidence that low 25(OH)3D levels may be associated with increased risk of the MetS (metabolic syndrome), which represents a cluster of risk factors for type 2 diabetes [10]. Vitamin D supplementation may increase insulin production and secretion by acting via the regulation of the Vitamin D receptors dependent calcium and phosphorus metabolism cascade in pancreatic beta cells [11] [12]. There are several mechanisms proposed to relate the role of Vitamin D with the development of diabetes mellitus. Some of these include expression of Vitamin D receptors in the beta cells of pancreas, role of Vitamin D in maintenance of normal calcium homeostasis which plays a major role in insulin secretion, presence of Vitamin D receptor in skeletal muscle, improvement of insulin mediated glucose utilization following Vitamin D therapy, role of cytokines like Interleukin 6 and TNF alpha (Tumour Necrosis factor alpha) in causing insulin resistance and down regulation of cytokine production by Vitamin D [10]. Vitamin

D may act on pancreatic beta cells in two possible pathways; Vitamin D may act directly to induce beta-cell insulin secretion by increasing the intracellular calcium concentration or it may mediate activation of beta-cell calcium-dependent endopeptidases to produce the cleavage that facilitates the conversion of pro-insulin to insulin [13].

In peripheral insulin-target tissues, Vitamin D might directly enhance insulin action through stimulation of the expression of insulin receptors [14].

2. Subjects and Methods

2.1. Subjects

This study was carried out by cooperation between Medical Biochemistry and medicine Departments, Faculty of Medicine, Taiba University & Medical Biochemistry and Molecular biology Department, Faculty of Medicine, Menoufia University, in the period from December 2017 to February 2018. It included 220 females classified into two groups, Group 1: included 110 female patients with type II diabetes mellitus. Group 2: included 110 females of matched ages apparently healthy volunteers as controls.

Before sample collection, an informed written consent (approved by Human Rights & Ethics Committee in Research at Taibah University, Madinah, KSA) was taken from all patients and controls. All subjects were subjected to detailed history taking (smoking, work, hypertension, family history of diabetes and duration of DM) physical and clinical examination, anthropometric measurements including waist circumference measurement and estimation of body mass index [BMI] was done by dividing body weight in kilograms by (height in meter^2) and laboratory investigations including: fasting blood glucose (FBS), glycated hemoglobin (HbA1c), lipid profile {serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglycerides (TG) and low density lipoprotein cholesterol (LDL-c)}, 25-hydroxyvitamin D(25(OH)3D), Vitamin D receptor (VDR) and Vitamin D binding protein (VDBP)were done.

2.2. Exclusion Criteria

Included patients currently on oral steroid, endocrine disorders or patients on drugs that could have effect on bone (antiepileptic, corticosteroids, antidepressants, Vitamin D and calcium).

2.3. Methods

8 ml of venous blood were withdrawn from every subject after a 12 h fasting and dividing into three tubes: One ml of blood was transferred into sodium fluoride containing tube for enzymatic colorimetric determination of blood glucose. Blood glucose was determined by enzymatic colorimetric test, using Spinreact kit, SPAIN [15].

6 ml was transferred into a plain tube, left to clot, centrifuged for 10 min at 3000 R.P.M. The serum obtained was stored at −80˚C until colorimetric deter-

mination of serum (TC) [16], LDL-c [17], HDL-c [18], TG [19], total serum levels of Vitamin D 25(OH)D, VDR and VDBP in samples were carried out by ELISA technique, using available commercial kit (CUSABIO and R&D SYSTEMS) using horseradish peroxidase detection in accordance with the manufacturer's instructions (50, 100 and 50 μL of sample respectively were used). Samples were assayed as duplicates with a minimal detection level of 5 μg/L for 25(OH)D, 1.65 pg/ml for VDR, and 0.65 ng/ml for VDBP. Deficiency of vitamin was defined as if 25(OH)D level of less than 50 nmol/L (20 ng per milliliter), insufficient Vitamin D if 25(OH)D levels were between 50 and 75 nmol/L (20 - 30 ng per milliliter); and normal if levels of 25(OH)D levels were 75 nmol/L (30 ng per milliliter) to 100 nmol/L. Serum levels of 25(OH)D greater than 150 nmol/L. was defined as Vitamin D intoxication [20].

The remaining 1 ml from the blood sample was placed in EDTA tube for quantitative colorimetric determination of glycated hemoglobin as percent of total hemoglobin using kits supplied by Teco diagnostics, USA [21].

2.4. Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. For qualitative data we used number and percent. The Kolmogorov-Smirnov test used to verify the normality of distribution. For quantitative data we used mean, standard deviation and median. Significance of the obtained results was at the 5% level.

3. Results

Diabetic cases were significantly associated with higher frequency of smoking, hypertension, higher BMI, wider WC, higher HA1C, TC, LDL, FBG and metabolic syndrome. Lower Vitamin D level was significantly associated with DM cases when compared to control group. VDR and VDBP did not differ significantly between both groups (**Table 1**).

Decreasing Vitamin D level was significantly associated with increasing BMI, WC, HA1C, TC, LDL, as well as with decreeing VDR. No significant association was found between Vit D and VDBP levels when DM cases were classified according to Vitamin D level (**Table 2**).

There were no significant differences found in Vitamin D level, VDR and VDBP according to studied data (nationality, work, smoking and hypertension) in DM cases (**Table 3**).

There was significant negative correlation between Vit D level and BMI, WC, HA1C, TC and LDL. There was significant negative correlation between VDR andHA1C, TC and LDL on the other hand; there was significant positive correlation between VDR and Vit D level (**Table 4**).

There was significant negative correlation VDBP level and VDR. Otherwise, no significant correlations were found between Vitamin D levels, VDR, VDBP with other studied parameters in DM cases (**Table 4**).

Table 1. Demographic and laboratory parameters between the studied groups.

			Control N = 110		Cases N = 110		*P*
Age (years)		**Mean ± SD**	53.9	8.8	54.8	11.2	0.508
nationality	**NS**	**N, %**	19	17.3%	21	19.1%	0.727
	S	**N, %**	91	82.7%	89	80.9%	
work	**NW**	**N, %**	77	70.0%	80	72.7%	0.655
	W	**N, %**	33	30.0%	30	27.3%	
smoking		**N, %**	4	3.6%	12	10.9%	**0.038**
HTN		**N, %**	63	57.3%	81	73.6%	**0.011**
BMI (kg/m^2)		**Mean ± SD**	31.7	8.9	35.5	9.0	**0.002**
WC (cm)		**Mean ± SD**	90.0	23.2	97.3	20.8	**0.014**
Duration		**Median, min, max**	-	-	13	1-35	-
HA1C (%)		**Mean ± SD**	4.9	0.6	9.2	1.7	**<0.001**
TG (mg/dL)		**Mean ± SD**	141.7	28.8	150.8	33.6	**0.031**
TC (mg/dL)		**Mean ± SD**	182.6	37.5	193.5	38.1	**0.034**
LDL-c (mg/dL)		**Mean ± SD**	112.0	34.7	160.0	36.8	**<0.001**
HDL-c (mg/dL)		**Mean ± SD**	49.5	9.4	44.1	10.1	**0.012**
FBG (mg/dL)		**Mean ± SD**	86.5	13.7	323.3	88.5	**<0.001**
25(OH)D (nmol/L)		**Median, min, max**	43.0	22.92 - 85.38	24.4	2.20 - 85.38	**<0.001**
Deficient		**N, %**	0	0%	35	31.8%	
Insufficient		**N, %**	12	10.9%	37	33.6%	**<0.001**
Adequate		**N, %**	98	89.1%	38	34.5%	
VDR (pg/ml)		**Median, min, max**	150	40.0 - 336.0	126.6	40.0 - 350.0	0.796
VDBP (ng/ml)		**Median, min, max**	120.5	44.0 - 258.3	117.1	44.0 - 258.3	0.857

Table 2. Comparison of studied data between DM cases classified according to Vitamin D level.

			Deficient N = 35		Insufficient N = 37		Adequate N = 38		*P*1	*P*2
Age (years)		**Mean ± SD**	54.7	9.6	53.7	9.8	56.2	13.7	0.625	0.371
nationality	**NS**	**N, %**	7	20.0%	6	16.2%	8	21.1%	0.856	0.704
	S	**N, %**	28	80.0%	31	83.8%	30	78.9%		
work	**NW**	**N, %**	31	88.6%	22	59.5%	27	71.1%	0.021	0.774
	W	**N, %**	4	11.4%	15	40.5%	11	28.9%		
smoking		**N, %**	5	14.3%	3	8.1%	4	10.5%	0.691	0.925
HTN		**N, %**	29	82.9%	26	70.3%	26	68.4%	0.320	0.367
BMI(kg/m2)		**Mean ± SD**	38.4	8.5	35.5	8.9	32.8	9.0	**0.026**	**0.022**
WC (cm)		**Mean ± SD**	101.9	19.8	98.5	20.3	91.9	21.5	**0.042**	**0.049**
Duration		**Median, min, max**	13.0	1.0 30.0	10.0	2.0 35.0	14.0	2.0 32.0	0.732	0.514
HA1C (%)		**Mean ± SD**	11.1	1.0	9.2	0.5	7.5	0.6	**<0.001**	**<0.001**
TC (mg/dL)		**Mean ± SD**	232.3	21.3	200.3	9.9	151.1	21.2	**<0.001**	**<0.001**
LDL (mg/dL)		**Mean ± SD**	199.0	19.4	165.1	7.6	119.2	20.5	**<0.001**	**<0.001**
FBG (mg/dL)		**Mean ± SD**	332.0	100.0	321.6	92.3	316.8	74.0	0.761	0.582
VDR(pg/ml)		**Median, min, max**	93.5	40.0 330.0	126.6	74.0 350.0	206.0 70.5	336.0	**<0.001**	**<0.001**
VDBP (ng/ml)		**Median, min, max**	120.6	44.0 171.2	166.9	100.6 172.7	105.2 63.4	258.3	0.062	0.080

Table 3. Comparison of Vitamin D level, VDR, VDBP according to studied data in DM cases.

		Vit D				VDR				VDBP			
		Median	Range		*P*	median	range		*P*	Median	Range		*P*
Nationality	**NS**	27.43	2.20	68.79	0.855	93.5	40.0	350.0	0.967	100.6	44.0	258.3	0.214
	S	24.44	2.20	85.38		126.6	40.0	336.0		120.6	44.0	258.3	
Work	**NW**	23.9	2.20	85.38	0.120	117	40.0	336.0	0.255	120.6	44.0	258.3	0.670
	W	27.4	2.20	85.38		161.5	40.0	350.0		100.6	44.0	258.3	
Smoking	**No**	24.88	2.20	85.38	0.628	126.6	40.0	350.0	0.950	111.7	44.0	258.3	0.106
	Yes	23.68	2.20	85.38		104.0	65.5	336.0		161.2	63.4	258.3	
HTN	**No**	27.4	2.20	60.53	0.259	93.5	40.0	336.0	0.601	105.5	44.0	258.3	0.709
	Yes	24.4	2.20	85.38		126.6	40.0	350.0		120.6	44.0	258.3	
	Yes	25.3	2.20	68.79		105.3	65.5	336.0		124.9	44.0	258.3	
	Yes	23.4	2.2	85.4		115.8	40	350		113.5	44	258.3	

Table 4. Correlation of Vitamin D level, VDR, VDBP with other studied parameters in DM cases.

	Vit D		VDR		VDBP	
	p	r	p	r	p	r
Age (years)	0.039	0.687	0.095	0.325	−0.113	0.238
BMI (kg/m²)	−0.270	**0.004**	−0.066	0.494	0.02	0.84
WC (cm)	−0.250	**0.009**	0.017	0.860	0.022	0.818
HA1C (%)	−0.930	**<0.001**	−0.452	**<0.001**	0.001	0.999
TC (mg/dL)	−0.911	**<0.001**	−0.473	**<0.001**	0.002	0.984
LDL (mg/dL)	−0.943	**<0.001**	−0.499	**<0.001**	−0.017	0.863
FBG (mg/dL)	−0.073	0.450	−0.098	0.307	−0.039	0.685
Duration	0.065	0.501	0.002	0.997	−0.025	0.797
Vit D (nmol/L)	-	-	0.515	**<0.001**	−0.038	0.696
VDR (pg/ml)	-	-	-	-	−0.244	**0.010**

At the cutoff point of 29.7 (RQ) Vit D can discriminate DM cases and control groups with a sensitivity of 65.5%, a specificity of 89.1%, positive predictive value (85.7%), negative predictive value (72.1%) and accuracy (77.3%). While at a cutoff point of 115.75 (RQ), VDR can discriminate DM from control with a sensitivity of 44.5%, a specificity of 63.6%, positive predictive value (55.1%), negative predictive value (53.4%) and accuracy (54.1%). At the cutoff point of 107.65 (RQ) VDBP can discriminate DM cases and control groups with a sensitivity of 43.6%, a specificity of 61.8%, positive predictive value (53.3%), negative predictive value (52.3%) and accuracy (52.7%) (Table 5).

Smoking, HTN, higher BMI, WC, TC, LDL and lower Vit D were associated with risk of DM in univariable analysis. However, taking significant covariates into multivariable analysis revealed that higher TC, LDL and lower Vit D were considered as independent predictors of T2DM (Table 6).

Table 5. Area under ROC curve and performance criteria of Vitamin D, VDR, VDBP levels for discrimination between DM cases and control groups.

	Vit D	VDR	VDBP
AUC (95% CI)	0.757 (0.690 - 0.823)	0.528 (0.452 - 0.605)	0.507 (0.430 - 584)
Cut off	29.7	115.75	107.65
Sensitivity (%)	65.5	44.5	43.6
Specificity (%)	89.1	63.6	61.8
PPV (%)	85.7	55.1	53.3
NPV (%)	72.1	53.4	52.3
Accuracy (%)	77.3	54.1	52.7

Table 6. Regression analysis for prediction of T2DM.

	Univariable				Multivariable			
	p	OR	95% CI		p	OR	95% CI	
Age (year)	0.544	1.005	0.989	1.022				
smoking	**0.038**	2.075	1.041	4.136	0.060	0.247	0.058	1.060
Vit D (nmol/L)	**<0.001**	0.969	0.959	0.979	**<0.001**	0.954	0.936	0.972
VDR (pg/ml)	0.773	1.000	0.998	1.002	**<0.001**	4.534	2.408	8.534
VDBP (ng/ml)	0.839	1.000	0.996	1.003				

4. Discussion

Type 2 diabetes mellitus (T2DM) is a heterogeneous group of disorders resulting from the combination of genetic, behavioral, nutritional, and environmental risk factors. The pathogenesis of T2DM involves deficiency in insulin secretion and insulin resistance [22].

The nutritional risk factors play an important role in pancreatic β-cell physiology and their effects on insulin secretion [23]. Vitamin D is a critical and essential micronutrient for human health; it has a potential effect on pancreatic insulin secretion and insulin action [22].

Our study's aim is to study the association between serum 25-hydroxy Vitamin D [25(OH)3D], VDR &VDBP and type 2 diabetic patients.

In the present study, analysis of the demographic and clinical data of two groups revealed that, smoking, hypertension and obesity were significantly high in diabetic patients group. These results agree with that reported by Mohammad *et al.* [24]. Several studies reported that elevations of both BMI and waist circumference are associated with increased incidence of diabetes [24] [25]. This is explained by the fact that obesity links to insulin resistance by increasing production of adipokines/cytokines, including tumor necrosis factor-α, resistin and retinol-binding protein that contribute to insulin resistance [26].

In the present study, diabetic cases were significantly associated with higher TG, TC and LDL and significantly lower HDL. Several studies agree with our result [1] [22] [25] [26]. Dyslipidemia is a common feature of diabetes mellitus leads to cardiovascular complications [27].

This result can be explained by the fact that dyslipidemia association with atherosclerosis and the progression of atherosclerosis in diabetes is mainly due to the associated hyperglycemia, obesity and insulin resistance. Excess free fatty acids (FFA) liberation from adipose tissue occurs in T2DM due to insulin resistance. To a large extent lipoproteins hepatic metabolism is controlled by insulin [28].

The co-occurrence of metabolic risk factors in patient group (abdominal obesity, hyperglycemia, dyslipidemia and hypertension) suggested the existence of a metabolic syndrome.

In our study, the level of Vitamin D is significantly lower in type 2 diabetic patients than controls as shown in **Figure 1(a)**. Many studies observed that Vit D level is significantly lower in type 2 diabetes [1] [29] [30]. This result can be explained by the fact that Vitamin D deficiency plays a role in the pathogenesis of T2DM. T2DM manifests as a result of insulin resistance, increased hepatic glucose production and β-cell failure. Vitamin D deficiency increases insulin resistance and decreases insulin secretion [31].

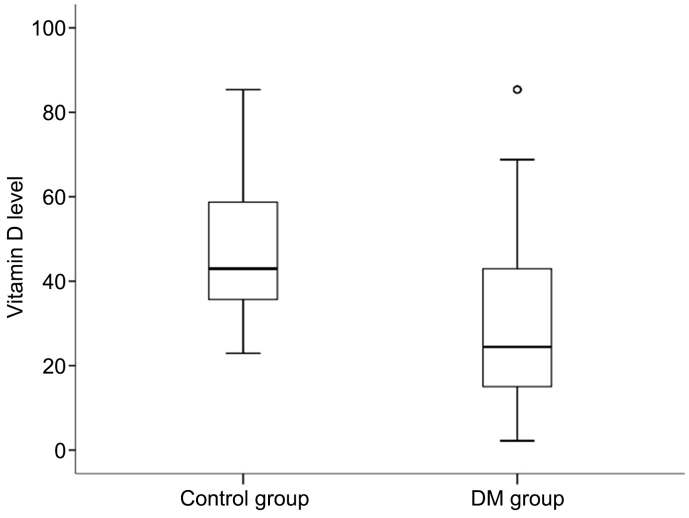
In our study, VDR and VDBP did not differ significantly between both groups as shown in **Figure 1(b)** & **Figure 1(c)**. This result in contrast that reported by Manal *et al.*, who found both serum and urine VDBP levels were significantly elevated in patient than controls and this result explained by increased production of serum VDBP as a compensatory mechanism of increase losing of it in urine as a part of albuminuria that indicates tubular dysfunction in diabetes [32].

In our study, as shown in **Figure 2** Vit D level showed significant negative correlation with BMI, WC, Wortsman *et al.* [33] have shown that both obese and normal weight persons' skin produces the same amount of Vitamin D under the same conditions, but that 57% less Vitamin D is absorbed into the circulation of obese persons, because of the higher amount of subcutaneous fat that traps the cholecalciferol. Also Vit D showed negative correlation with HA1C which was in agreement with many studies [1] [34] [35] and in contrary to other studies [36] [37].

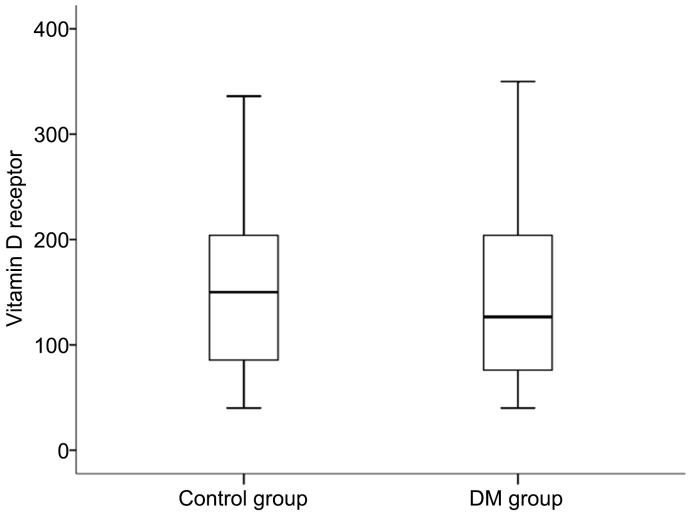
Nwosu *et al.* showed that after three months of Vitamin D supplementation, there was a significant increase in 25(OH)3D in Type II diabetes mellitus patients and there was significant decrease in HbA1c from 8.5% ± 2.9% at baseline to 7.7% ± 2.5% in Type II diabetic patients [38].

In our study, Vit D level showed significant negative correlation with TC and LDL and metabolic syndrome. VDR and VDBP did not differ significantly according to presence or absence of metabolic syndrome. This result agrees with that reported by Shan *et al.*, who found that 25(OH)D levels were significantly lower in subjects with obesity, high TG, type 2 diabetes, or metabolic syndrome compared to their control [39].

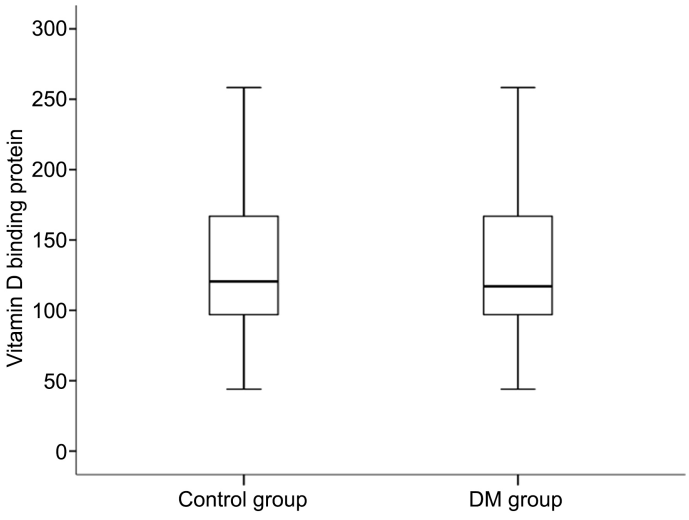
In our study, at cutoff 29.7 with AUC (0.757) Vit D can discriminate DM cases and control groups while for VDR, it was at cutoff point of 115.75 with AUC (0.528), also VDBP, at cutoff 107.65 with AUC (0.507) as shown in **Figure 3**.



(a)

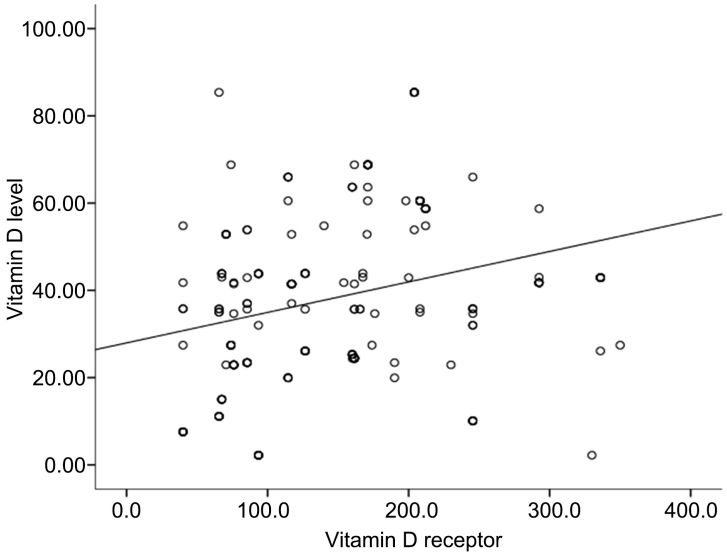


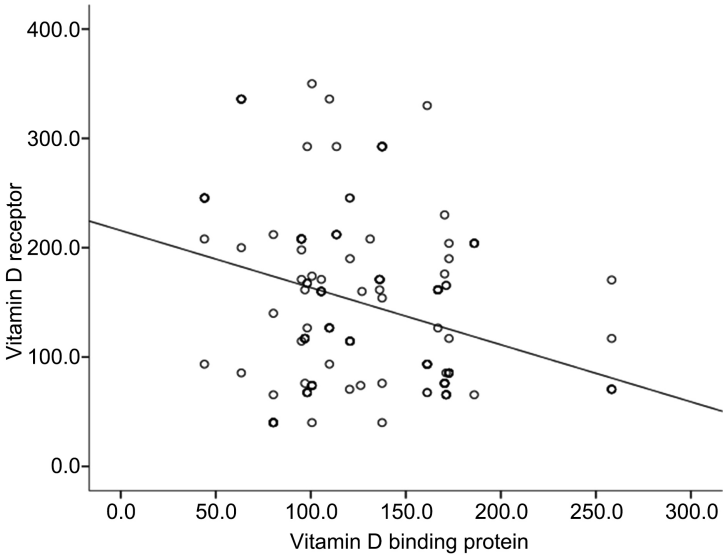
(b)



(c)

Figure 1. Levels of (a) Vitamin D, (b) Vitamin D receptor, (c) Vitamin D BP in DM cases and control groups.





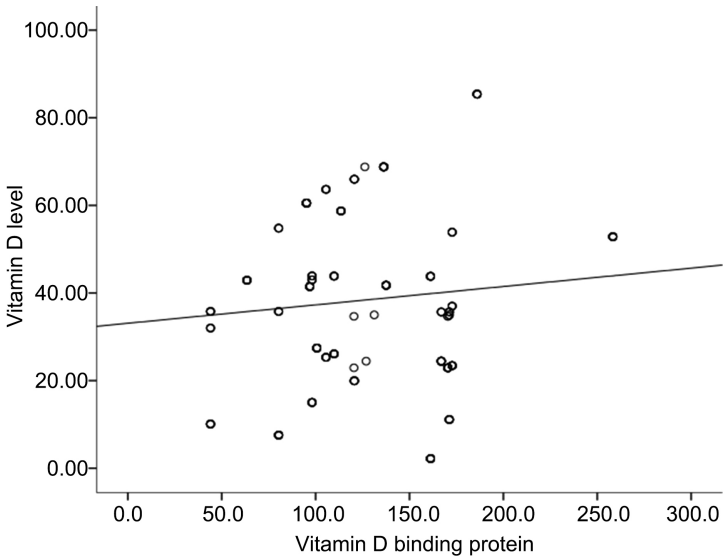


Figure 2. Correlations between Vitamin D, VDR, VDBP levels in DM cases.

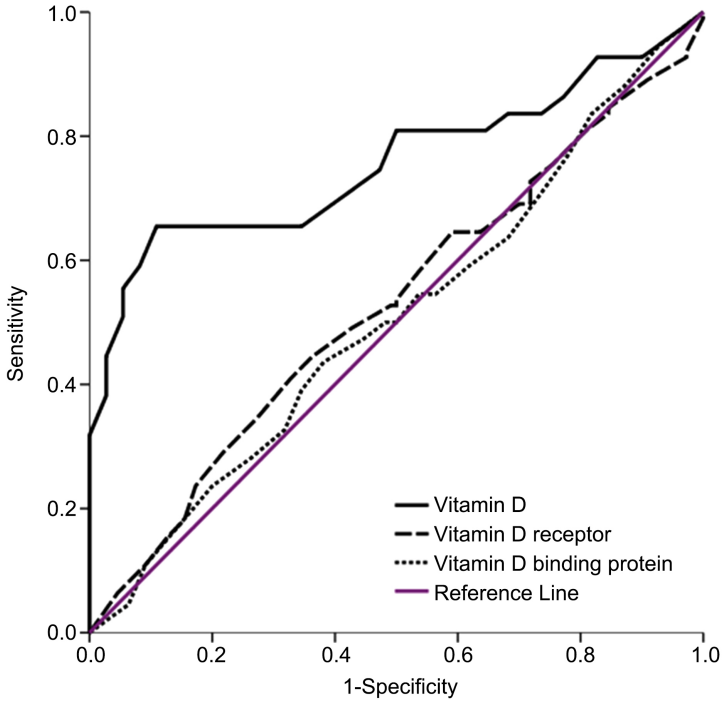


Figure 3. ROC curve of Vitamin D, VDR, VDBP levels for discrimination between DM cases and control groups.

Rui *et al.* demonstrated that ROC analysis of Vitamin D yielded AUC of 0.614 in the differentiation of diabetic patients from control with cutoff (16.01 ng/mL); Sensitivity: 66.73%; Specificity: 55.72% [40].

Manal *et al.* demonstrated that ROC analysis of uVDBP to detect patients with DN showed AUC of 0.807 in the differentiation of diabetic patients from control with cutoff (214 ng/mL); Sensitivity: 82.5%; Specificity: 65% [32].

In our study, both low Vit D and MetS were associated with risk of DM in univariable and multivariable analysis. Yun *et al.* showed that, logistic regression models revealed that low 25(OH)3D levels were independently predictive of the development of hyperglycemia, including prediabetes and T2DM. So 25(OH)3D concentration was a strong biomarker of diabetes risk [22].

The levels of Vitamin D, Vitamin D binding protein and Vitamin D receptors (VDR) have effect on the role of Vitamin D in stimulating insulin release [41].

Our study confirms the association between Vitamin D deficiency and type 2 diabetes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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