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Original Article

Serum Vitamin D Level in Type 2 Diabetic Subjects: Relation to Glycemic Control, Insulin Resistance and Proinflammatory Markers

Talaat A. Abdel Aaty[1], **Magdy H.Z. Magallaa**[1], **Hend Abdel Moneim**[1 ¥], **Hanaa M. Ismail** [2], **Doaa M. Genena**[3], **Riham Frugina**[1]

[1] Department of Internal Medicine, Faculty of Medicine, Alexandria University, Egypt.

[2] Department of Nutrition, High Institute of Public Health, Alexandria University, Egypt.

[3]Medical Research Institute, Alexandria University, Egypt.

Abstract

Background: Type 2 diabetes mellitus (DM) is one of the most common diseases worldwide. Early diagnosis and management has a significant role in reducing complications. Vitamin D is a fat-soluble vitamin that showed important functions regarding calcium and phosphate homeostasis, immunity and insulin resistance. There is a well-established link between vitamin D level and type 2 DM.

Objective(s): The aim of this study was to assess serum 25(OH) vitamin D_3 level in type 2 diabetic subjects and to investigate its relation to glycemic control, proinflammatory markers and insulin resistance.

Methods: The study included 60 type 2 diabetic subjects in the age group 40-70 years and 30 controls matched for age and gender. Pregnant females, renal, hepatic and cancer patients were excluded from the study. All participants were subjected to detailed history taking, anthropometric measurements including weight, height and waist circumference, full clinical examination and laboratory investigations including serum 25(OH)vitamin D_3, FSG, HbA_1c, serum insulin, and CRP.HOMA-IR was calculated using FSG and serum insulin values.

Results: The mean serum concentration of 25(OH) vitamin D3 was significantly lower in type 2 diabetics compared to controls (2.91±4.20 ng/ml, 12.04 ±7.74 respectively) (p<0.001). There was a significant increase in BMI, WC, FSG, HbA1c, serum insulin, and HOMA-IR in type 2 diabetics compared to controls (p<0.05). A statistical significant negative correlation was found between 25(OH) vitamin D3 level and the following parameters: BMI (r=-0.584, p<0.001), WC (r=-0.233, p=0.027), FSG (r=-0.735, p<0.001), HbA1C (r=-0.387, p<0.001), HOMA-IR (r=-0.729, p<0.001), serum insulin (r=-0.272, p=0.010). Meanwhile, 25(OH) vitamin D3 did not significantly correlate with the proinflammatory marker CRP (r=-0.126, p=0.238).

Conclusion Subjects with type 2 DM have low 25(OH) vitamin D_3 level compared to healthy normal individuals. The negative association of 25(OH) vitamin D3 with glycemic control and its irrelevance to the proinflammatory markers suggest that vitamin D may be an important determinant in the pathogenesis of type 2 DM. Hence, cautious Vitamin D supplementation may have a therapeutic potential in prevention and management of Type 2 DM.

***Key word*:** Type 2 DM, glycemic control, vitamin D, proinflammatory markers, CRP, insulin resistance.

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¥***Correspondence*:**
Email:
hendhasan2012@hotmail.com

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INTRODUCTION

Diabetes mellitus (DM) is a chronic multi-systemic multi-etiological illness characterized by chronic hyperglycaemia with abnormal carbohydrate, fat, and protein metabolism.(1) Rates of type 2 DM are increasing worldwide.(2) The etiology of type 2 DM appears to involve complex interactions between environmental and genetic factors.(3) The American Diabetes Association (ADA) criteria for the diagnosis of diabetes are any of the following: Glycated hemoglobin (HbA1c) level of 6.5% or higher, A fasting serum glucose (FSG) level of 126 mg/dL or higher, a 2-hour serum glucose level of 200 mg/dL or higher, a random serum glucose of 200 mg/dL or higher.(4) Vitamin D is a fat-soluble vitamin that is important for calcium homeostasis and for optimal skeletal health. The major function of vitamin D is to increase the efficiency of calcium absorption from the small intestine.(5) Vitamin D, as either D2 or D3, does not have significant biological activity. Rather, it must be metabolized within the body to the hormonally-active form known as 1,25-dihydroxycholecalciferol which is done by the liver and the kidney.(6) Vitamin D was also found to play an important

role in immune system[7,8], inhibits the growth of cancer cells[9,10], and plays a significant role in insulin resistance.[11-14] More recently, there is accumulating evidence to suggest that altered vitamin D and calcium homeostasis may also play a role in the development of type 2 DM.[15] Therefore , the aim of this study was to assess serum 25 (OH) vitamin D3 level in type 2 diabetic subjects and to study its relation to glycemic control, proinflammatory markers and insulin resistance.

METHODS

Study setting, Design and Participants: This case control study was performed in Alexandria university students' hospital in the period from September 2014 to August 2015.The study included 90 participants of both sexes aged 40-60 years; i) group I comprised 60 type 2 diabetic subjects (21 males and 39 females) diagnosed since at least 6 months, and ii) group II that included 30 healthy subjects (8 males and 22 females) matched for age and gender and served as a control group. Pregnant females renal, hepatic, parathyroid, and cancer patients, as well as subjects on vitamin D supplementation and those with abnormal serum calcium level were excluded from the study. All participants were subjected to detailed history taking with a special focus on the duration of diabetes, smoking and its duration, medical history and history of diabetic complications. Full clinical examination was done, including neurological examination and detection of diabetic complications.

Anthropometric assessment: Measurements of weight, height, waist circumference was done according to criteria described by Gibson (2005).[16] An increased waist circumference (≥35 in [88 cm] for women, ≥40 in [103 cm] for men) defines excess abdominal adiposity according to the Adult treatment program III criteria.[17] Body mass index (BMI) was calculated according to the formula (weight) in Kg/ (height)^2 in meters.

laboratory investigations: Following 12 hours of fasting, 5ml of whole blood was drawn from each participant. One ml of blood was added to Ethylene Diamine Tetra Acetic Acid (EDTA) to perform HbA1C assay.[18] The remaining 4 ml of the sample was left to clot and was centrifuged. Sera were separated and were used to measure the concentration of fasting serum glucose (FSG) using colorimetric analysis.[19] Serum 25(OH) vitamin D3 levels were measured using high performance liquid chromatography (HPLC).[20,21] Serum insulin levels were determined using enzyme linked immunosorbent assay (ELISA).[22] Insulin resistance was evaluated by homeostasis model assessment of insulin resistance (HOMA-IR) using the following equation: HOMA-IR= Fasting serum glucose (mmol/L)×Serum insulin (µU/mL).[23] C-reactive protein (CRP) was measured by the immunoturbidimetry method.[24,25]

Statistical Analysis

Data were analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean and standard deviation. Student's t test and Mann Whitney test were used to evaluate the significance of the difference between means. Spearman coefficient was used to correlate between two abnormally quantitative variables. Significance of the obtained results was judged at the 5% level.[26]

Ethical Considerations

This study was conducted according to the guidelines laid down for medical research involving human subjects and was approved by the ethics committee of the faculty of medicine, Alexandria University, Egypt. All measurements were taken in full privacy and the collected data were kept confidential. All participants were informed about the objective of the study and that they had the right to accept or refuse to participate in the study, then their written consent was obtained.

RESULTS

Ninety Egyptian adults of both sexes were included in this study. In group I (diabetic subjects) 21 males and 39 females which did not differ significantly from that of group II (controls; 8 males and 22 females) (p= 0.425). The mean ± SD ages (Subjects: 55.97 ± 8.63 years; controls: 54.27 ± 10.13 years) were not significantly different between the two groups (p= 0.408) (Table 1). Concerning the anthropometric measures of the participants, table (2) shows that BMI and WC was significantly higher in diabetics (32.33 ± 4.92kg/m2, 104.70 ± 8.94cm respectively) as compared to controls (27.21 ± 4.42kg/m2, 98.13 ± 9.99 cm respectively).

Table (1): Comparison between the two studied groups according to their demographic data

	Subjects (n=60)		Control (n=30)		Test of sig.	*p*
	No.	%	No.	%		
Sex						
Male	21	35.0	8	26.7	χ2=0.636	0.425
Female	39	65.0	22	73.3		
Age (years)						
Min. – Max.	40.0 – 70.0		40.0 – 70.0		T=0.831	0.408
Mean ± SD.	55.97 ± 8.63		54.27 ± 10.13			

Table (2): Anthropometric measures of the participants

	Subjects (n=60)	Control (n=30)	t	*p*
BMI (kg/m^2)				
Min. – Max.	23.88 – 44.08	21.0 – 36.0	4.810*	<0.001*
Mean ± SD.	32.33 ± 4.92	27.21 ± 4.42		
Waist circumference (cm)				
Min. – Max.	85.0 – 120.0	90.0 – 116.0	3.159*	0.002*
Mean ± SD.	104.70 ± 8.94	98.13 ± 9.99		

Table (3) shows the glycemic profile and CRP levels for the two studied groups. Significant mean levels of FSG, HbA1c, serum insulin and HOMA-IR were found in diabetics (164.07 ± 56.08 mg/dL, 7.94 ± 1.89 %, 20.51 ± 16.4 µ/ml, 7.70 ± 6.0 respectively) comparing to controls (93.89 ± 9.16 mg/dL, 5.39 ± 0.44%, 8.94 ± 4.04 µ/ml, 2.03 ± 0.91) were found, with levels being higher in diabetic subjects comparing to the controls. No statistical significance was found regarding the CRP levels in each group. The serum level of 25(OH) vitamin D3 was significantly lower in diabetics [ranged from 0.01 to 22.30 ng/ml with mean of (2.91± 4.20) ng/ml] comparing to controls [ranged from 2.10 to 26.9 ng/ml with mean of (12.04 ± 7.74) ng/ml] (p<0.001) (Figure 1). Additionally, a significant higher level of 25(OH) vitamin D3 was found in males comparing to female subjects (Figure 2).

Table (3): Glycemic profile and CRP levels of the participants

	Subjects (n=60)	Control (n=30)	Test of sig.	*p*
FSG (mg/dL)				
Min. – Max.	92.0 – 378.0	80.0 – 110.0	Z= 7.603*	<0.001*
Mean ± SD.	164.07 ±56.08	93.89 ± 9.16		
HbA$_1$C (%)				
Min. – Max.	5.20 – 13.50	4.40 – 6.20	t= 9.930*	<0.001*
Mean ± SD.	7.94 ± 1.89	5.39 ± 0.44		
Serum Insulin (u/ml)				
Min. – Max.	1.40 – 69.60	1.50 – 16.0	Z= 4.007*	<0.001*
Mean ± SD.	20.51 ± 16.40	8.94 ± 4.04		
HOMA-IR				
Min. – Max.	0.77 – 24.0	0.30 – 3.80	Z= 5.864*	<0.001*
Mean ± SD.	7.70 – 6.0	2.03 – 0.91		
CRP				
Min. – Max.	1.0 – 118.0	0.95 ± 88.0	Z= 1.268	0.205
Mean ± SD	8.87 ± 16.53	14.82 ± 23.80		

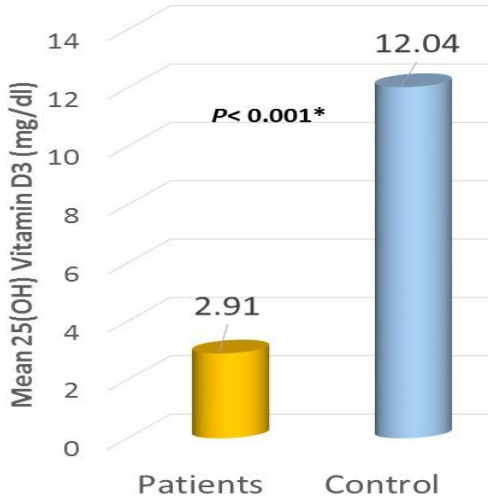

Figure (1): 25(OH) Vitamin D3 level of the participants

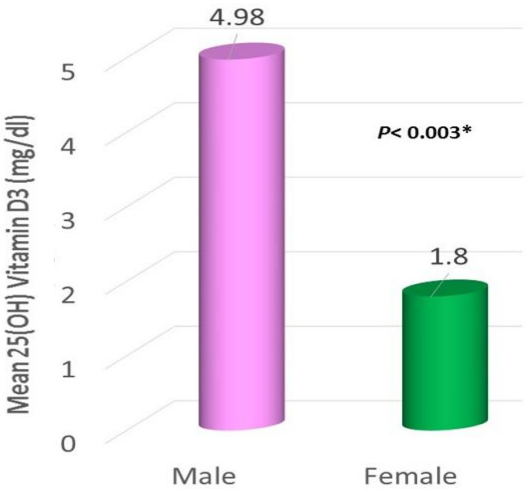

Figure (2): Relation between gender and 25(OH) Vitamin D3 in Subjects (n = 60)

A statistical significant negative correlation was found between 25(OH) vitamin D3 level and the following parameters: BMI (r=-0.584, $p<0.001$), WC (r=-0.233, $p=0.027$), FSG (r=-0.735, $p<0.001$), HbA1C (r=-0.387, $p<0.001$), HOMA-IR (r=-0.729, $p<0.001$), and serum insulin (r=-0.272, $p=0.010$). No statistical significant correlation was found between 25(OH) vitamin D3 and CRP (r=-0.126, $p=0.238$) (Table 4).

Table (4): Correlation between 25(OH) vitamin D3 and different parameters

	25(OH) Vitamin D_3	
	Total sample	
	r_s	*P*
Age (years)	-0.124	0.244
BMI (Kg /m^2)	-0.584*	<0.001*
WC (cm)	-0.233*	0.027*
Smoking index	0.212	0.384
Systolic BP (mmHg)	-0.077	0.473
Diastolic BP (mmHg)	-0.199	0.060
Duration of DM (years)	0.062	0.639
FSG (mg/dL)	-0.735*	<0.001*
Hb A_1C (%)	-0.387*	<0.001*
CRP	-0.126	0.238
Serum Insulin (μ/mL)	-0.272*	0.010*
HOMA-IR	-0.729*	<0.001*

rs: Spearman coefficient

*: Statistically significant, $p \leq 0.05$

DISCUSSION

The objective of this study was to assess serum 25(OH) vitamin D3 level in type 2 diabetic subjects and to examine its relation to glycemic control, proinflammatory markers and insulin resistance. The principal finding was that 25 (OH) vitamin D3 level is significantly lower in type 2 diabetics than controls and the values in both groups were lower than the ideal level of 32 ng/ml. In diabetic subjects 25(OH) vitamin D3 level ranged from 0.01 to 22.3 ng/ml, while in controls it ranged from 2.1 to 26.9 ng/ml. Our findings are comparable to those found in previous studies.[27-30] Need et al.,[31] reported that the Subjects who had higher levels of Vitamin D concentration had lower FBS in comparison with the other groups. In contrast, other studies, did not trace any difference in 25(OH)D between subjects with diabetes comparing to normal population.[32-34] Since the current study was conducted in Egypt, an area that receives adequate sunlight throughout the year, The high occurrence of vitamin D deficiency among participants encountered herein could be considered unexpected, and may be attributed to inadequate vitamin D intake which is prevalent around the world, regardless of the age or health status.

Significantly lower levels of 25(OH) vitamin D3 in females than in males in diabetic subjects was found in this study. A study done by, Verdoia, et al., (2015)[35] supported this finding and concluded that gender significantly affects vitamin D status. Additionally, Takiishi et al., and van der Meer et al.,[36, 37] suggested that female gender is an independent predictor of vitamin D deficiency. In the present study, vitamin D3 levels were found to be negatively correlated with FBG, HbA1c, serum insulin and HOMA-IR, indicating that vitamin D may be related to glycemic control in type 2 DM. This was consistent with a study done by Kostoglou-Athanassious et al., (2013)[38] who concluded that there was a fairly strong correlation between vitamin D deficiency/insufficiency and type 2 DM, and also demonstrates a negative correlation between vitamin D levels and HbA1c. Similarly, Clemente-Postigo, et al., (2015)[29] reported that serum 25(OH) vitamin D3 level was lower in prediabetic and diabetic subjects than in normoglycemic individuals and was found negatively correlated with glucose levels and HOMA-IR. In a cross-sectional analysis of a general population sample in eastern Finland, an inverse association was observed between 25(OH)D3 levels and fasting insulin, fasting glucose and results of 2 h glucose tolerance test, suggesting that low serum 25(OH)D3 may be associated with impaired glucose metabolism.[39] In another study, an inverse association of insulin resistance with 25(OH)D3 levels was observed which was mainly found at 25(OH)D3 levels between 16 and 36 ng/ml.[40]

In Type 2 DM, the role of Vitamin D was suggested from the presence of Vitamin D receptors (VDR) on the pancreatic β-islet cells.[41] Vitamin D facilitates the production and secretion of insulin from pancreatic beta cells via its action on the VDR, thus appearing to regulate insulin secretion.[42] Therefore vitamin D deficiency may be related to impaired insulin secretion in type 2 DM. In addition, as vitamin D stimulates the expression of the insulin receptor, vitamin D deficiency may be related with insulin resistance.[43] Several studies demonstrated a relationship between single-nucleotide polymorphisms in

the genes regulating VDR and Vitamin D binding protein and glucose intolerance and insulin secretion.[44-46] The present study, concluded that there is a tight relation between type 2 DM and obesity, where statistically significant increase in BMI and WC was found in type 2 diabetic Subjects comparing to control subjects. Among the studies consistent with our study are those done by Hertel, et al., (2011)[47] and Golay, et al., (2005)[48] influenced by the presence of fat mass and obesity associated gene and these studies also concluded that obesity increases the resistance to insulin.

This study showed that there was a statistical significant negative correlation between BMI and 25(OH) vitamin D3 level. The association between serum vitamin D status and obesity can be explained in two ways; an appreciation was that obesity is a cause of vitamin D deficiency due to decreased sun exposure (as a result of lack of confidence in obese) and increased fat deposition, since vitamin D stored in adipose tissue becomes less bioavailable even with adequate sun exposure compared to non-obese.[49,50] A potential confounder is that obesity is also linked to an unhealthier lifestyle, characterized by less physical activity, and poor eating habits and, hence, lower vitamin D levels and worse clinical outcomes. Bell, et al., (1985)[51] stated that vitamin D can cause obesity, arguing that vitamin D deficiency is associated with secondary hyperparathyroidism stimulating 1 alpha hydroxylase activity leading to increase in $1,25(OH)_2$ vitamin D, where both modulate Ca^{2+} signaling in adipocytes leading to stimulation of lipogenesis and inhibition of lipolysis.

A sensitive marker of low-grade inflammation, CRP is the most commonly measured marker of inflammation.[52] Previous studies has demonstrated negative associations between CRP levels and vitamin D status.[53,54] However, in the current study, there no significant correlation was found between CRP and vitamin D status. This finding is in consistent with a study done by Grossmann et al., (2015)[55] who concluded that the inflammatory and immune biomarker profile including white blood cells (WBCs), granulocytes, lymphocytes, monocytes, platelets, CRP, albumin, fibrinogen, and hematocrit concentrations varies with the development and progression of type 2 DM. Markers of inflammation and immunity enable differentiation between the early preclinical and clinical phases of the disease, disease complications, and progression.

CONCLUSION AND RECOMMENDATIONS

In conclusion, the present study demonstrated that 25(OH) vitamin D3 level was significantly lower in subjects with type 2 DM comparing to healthy normal controls in a sample of Egyptian population and was found to be negatively correlated with HOMA-IR and serum insulin. This suggest that low levels of 25(OH) vitamin D3 could be considered a potential risk factor for the development of type 2 DM. 25(OH) vitamin D3 deficiency was not associated with increased markers of inflammation. Vitamin D levels were related to glycemic control in diabetic subjects, thus vitamin D supplementation could have a therapeutic potential in prevention and management of type 2 DM. Further studies on the benefit of including vitamin D supplements in treatment protocol of type 2 DM are needed.

Limitations of the study

The study had some limitations; the sample size was small and the sunlight exposure of each individual varies on a daily basis.

Conflict of Interest: None to declare.

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