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RESEARCH ARTICLE

The Relation between Vitamin D Levels and Depression in Type 1 Diabetic Patients

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Abstract

Background and Aims: Recently, studies suggest vitamin D deficiency may be correlated with severity and frequency of type 1 diabetes (T1D) and depression. Prevalence of depression in diabetics is 2-3 times higher compared to non-diabetics. We aimed to assess vitamin D status in T1D patients and patients with depression, and its relation to diabetes control.

Methods: This study was conducted in the summer of 2013, on 120 subjects, divided into 4 groups: 30 healthy controls, 30 patients with T1D, 30 with depression and 30 with both T1D and depression. MADRS scale was used for diagnosis of depression. Serum 25-hydroxyvitamin D, FBS, 2hPG, and HbA1c were measured.

Results: Vitamin D levels were found insufficient in the control group while being deficient in all patients (62.43$\pm$ 24.86 vs.23.37 $\pm$ 18.14,16.35 $\pm$ 12.58, 22.14 $\pm$ 20.6 nmol/L respectively, $p<0.001$), but without significant difference between patient groups. Vitamin D was negatively correlated with FBS, 2hPG, HbA1c and MADRS score and positively correlated with weight and BMI. Depression, female gender and T1D were independent determinants for vitamin D level by multiple regression analysis.

Conclusion: Vitamin D status should be assessed in diabetics and in depression. Severe depression associated with poor control.

Introduction

Diabetes mellitus (DM) is one of the most common non-communicable diseases globally. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries. Diabetes is undoubtedly one of the most challenging health problems in the 21st century **[1].**

Vitamin D deficiency is an important public health problem because of its great impact on bone metabolism and the possible implication on cardiovascular outcomes, diabetes, cancer and mortality **[2].**It was shown that vitamin D levels are suboptimal in adolescents and adults in many countries, especially in the Middle East and Asia where vitamin D deficiency appears to be highly prevalent **[3].** Better understanding of the physiological role of vitamin D system, in particular its potential effect on inflammatory and autoimmune conditions as well as on insulin secretion

and possibly also on insulin resistance, increased the interest in its potential role in prevention and control of both type 1 and 2 diabetes [4].

The role of vitamin D in cognitive function and mental health has been reported. Vitamin D concentrations have been shown to be low in patients suffering from mood disorders and have been associated with cognitive dysfunction[5].Numerous studies have identified vitamin D receptor (VDR) in nearly all tissues of the body, including both neuronal and glial cells in the central nervous system [6].

A bidirectional association has been found between depression and diabetes mellitus [7]. Depression is a risk factor for diabetes[8], and diabetes increases risk for the onset of depression[9].Not only depression is common in patients with diabetes but also it contributes to poor adherence to medication and dietary regimens, physical inactivity, poor glycemic control, reduced quality of life, disability and increased health care expenditures [10].

There is evidence that a low serum 25(OH) D level increases the progression of depressive symptoms with time [11]. There is also observational evidence linking a low serum 25(OH) D level to the prevalence of depression [12].

Traditionally, vitamin D insufficiency has been mainly associated with high latitude and is attributed to reduced ultraviolet radiation exposure in regions far from the equator. [13] However, recent studies show that this problem is not limited to sun-deprived areas of the world but is also common in sunny regions such as Florida (USA), Turkey, New Zealand, Australia, Brazil, India, Lebanon, Tunisia, Jordan and Saudi Arabia. [14]

Aim of the Work

The primary aim was to assess vitamin D status in type 1 diabetic patients and patients with depression. Secondarily, we aimed to investigate the relation of vitamin D status to diabetes control and severity of depression.

Subjects and methods:

This is a case control study was conducted from May - October 2013, on 120 white Egyptians (Caucasian) subjects aged 16-40 years, collected from outpatient clinic of endocrinology and psychiatry units of Ain Shams University Hospital. Subjects had good nutritional intake and average sun exposure 4-5 times/week, for at least 20 minutes.

Exclusion criteria included history of hepatic, renal diseases and pregnant women. Patients receiving drugs that affect vitamin D levels such as vitamin D supplementation, anti-epileptic drugs and corticosteroids were also excluded. Selected subjects were divided into 4 groups:**Group 1:**30 healthy control subjects (15 males and 15 females), **Group 2:**30 patients with type 1 diabetes (13 males and 17 females), **Group 3:**30 patients with depression (10 males and 20 females) and **Group 4*:*** 30 patients with both T1D and depression (11 males and 19 females). Gender distribution was comparable among all four groups (p value = 0.565).

All subjects were subjected to full medical history emphasizing on the duration of diabetes mellitus, drug history and history of any medical condition. Clinical examination included weight, height and body mass index (BMI). BMI was calculated as body weight in kilograms divided by the height in meters squared (kg/m^2). A well trained psychiatrist confirmed the diagnosis of depression according to Diagnostic and Statistical Manual of Mental Disorder-fourth edition (DSM-IV) criteria using the Structured Clinical Interview for DSM Axis I Diagnosis – Clinician Version (SCID-CV) and severity was determined using the Montomegry-Asberg Depression Rating Scale (MADRS) which is a ten items rating scale including questions on the following symptoms: Apparent sadness, Reported sadness, Inner tension, Reduced sleep, Reduced appetite, Concentration difficulties, Lassitude, Inability to feel, pessimistic thoughts, suicidal thoughts. For diagnosis of depression the rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5) and then report the appropriate number. Thus the scoring choices lie on a likert scale from 0 to 6 and adding of individual scores yields the total score. Total score (0-10) Normal, (11-30) mild, (31-45) Moderate and (46-60) severe. The MADRS was compared with the Hamilton Rating Scale for Depression on clinical assessment of severity of Depression. The correlation of MADRS was 0.71. The authors reported inter-rater reliability that ranged from 0.89 to 0.97.[15].

Laboratory tests included fasting blood glucose (FBG) and 2hPG, which was measured using an automated glucose oxidase method using Behring Diagnostics Reagents (SVR Glucose Test; Behring, La Jolla, CA). HbA1c was measured by Stanbio Procedure No.0350 "Quantitative colorimetric determination of Glycohemoglobin in blood". 25-hydroxyvitamin D levels were measured by ELISA using immunodiagnostik AG, Stubenwald-Allee 8a, D-64625 Bensheim, Germany. This test kit is a competitive protein binding assay for the measurement of 25-OH vitamin D.

Based on the most recent Endocrine Society guidelines, vitamin D deficiency has been defined at 25 (OH)-vitamin D_3 levels below 50 nmol/L [20ng/dl] while insufficiency at levels of 51-74 nmol/L [21-29 ng/dl] and sufficient if it is ≥ 30 ng/dl [75nmol/L] [16].

This study was approved by the internal review board of Ain Shams University. All subjects provided written informed consent before the study.

Statistical analysis:

Data analysis was performed using the SPSS program (v.13.2, 2003, Echosoft Corp, Agoura Hills, CA). Data were expressed as mean ± standard deviation (SD) for parametric data and as median and interquartile range (IQR) for non-parametric data respectively. Parametric data were analyzed using one-way analysis of variance (ANOVA) was used when comparing between more than two groups. Pearson's correlation coefficient (r) test was used for correlating data. Correlation coefficient (r) was set as: [0.1 - 0.3] weak correlation, [0.4 - 0.6] moderate correlation and [> 0.7] strong correlation. **Mann Whitney U test** was used to compare quantitative variables, in non-parametric data. Multiple regression analysis was done to define the independent determinants of vitamin D.

Statistical significance was set at p value <0.05, while p <0.001 was accepted as highly significant.

Results:

The studied groups were age and sex matched. BMI was matched between patient groups, but was found lower in diabetics with depression compared to control group.

Vitamin D levels were found insufficient in the control group while being deficient in all patients. There was a highly statistical significant decrease in vitamin D levels in diabetics, in depressed subjects and in diabetics with depression in comparison to control group (23.37 ± 18.14,16.35 ± 12.58, 22.14 ± 20.6 nmol/L vs. 62.43 ± 24.86 respectively, p<0.001), but no significant difference between patient groups. All criteria of subjects included in the study are summarized in(table 1).

We found that severe depression is the most prevalent representing 20 patient (66.7%) in depressed group and 16 patients (53.3%) in type 1 diabetics with depression group, and it was of a highly statistical significant difference (p <0.001) in relation to moderate and mild depression (table 2).

Vitamin D levels were negatively correlated with FBS, 2hPG, HbA1c and MADRS score (r= -0.26, r= -0.25, r=-0.25 and r= -0.36, p<0.001) and positively correlated with weight & BMI (r=0.019, r= 0.19, p<0.05)(table 3).

Mean HbA1c level was higher in patients with severe depression (n=16) versus moderate depression (n= 12), and diabetics without depression (n=30) (9.2% vs. 8.2%, 8.5% respectively), yet there was no statistical significant difference (p = 0.12).

Comparing diabetic (n=60) to non-diabetic (n=60) patients, we found significant decrease in weight (70 vs.75Kg), BMI (24.49 vs.27.59 kg/m^2) and vitamin D levels (20 vs. 34.50 nmol/l) in diabetics (p=0.003) (Fig. 1) and a significant increase in FBG, 2hPG and HbA1c in diabetics (p<0.001).

Our results also demonstrated a statistical significant decrease in weight (70.5 vs.77.5 Kg), BMI (24.22 vs.26.97 kg/m^2) and vitamin D levels (16.5 vs.34.5 nmol/l) in depressed (n=60) compared to non-depressed (n=60) patients (p <0.001) (Fig. 2).

Multiple regression analysis for determinants of vitamin D level showed that of the variants included in the regression model, depression, female gender and type 1 DM were independent determinant for vitamin D level (P < 0.001, P= 0.017 and P= 0.018, respectively), but no effect for age or BMI (table 4).

Table (1): Comparison between the different studied groups regarding their demographic and laboratory data using ANOVA.

	Control (n=30)	Type I DM (n=30)	Depression (n=30)	Type I DM plus Depression (n=30)	
Variable	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**P value**

Age (yr)	27.53 ± 6.17	28.13 ± 6.76	29.57 ± 6.98	27.77 ± 7.02	0.650
Weight (kg)	82.00 ± 15.77	74.10 ± 8.59	74.43 ± 11.74	68.13± 13.15*	< 0.001
Height (m)	1.71 ± 0.11	1.67 ± 0.08	1.68 ± 0.07	1.67 ± 0.09	0.387
BMI (kg/m2)	28.01 ± 3.67	26.49 ± 3.17	26.21 ± 3.31	24.45± 4.67*	0.005
FBG (mg/dl)	86.8 ± 7.7	201.23 ± 74.04*†	92 ± 5.3	207.60 ± 67.91*†	<0.001
2hPG (mg/dl)	125.3 ± 10.7	241.97 ± 73.73*†	128.5 ± 8.2	242.37 ± 78.31*†	<0.001
HbA1c (%)	5.14 ± 0.32	8.50 ± 1.47*†	5.46 ± 0.46	8.8 ± 1.10*†	<0.001
Vitamin D (nmol/L)	62.43 ± 24.86	23..37 ± 18.14*	16..35 ± 12.8*	22..14 ± 20.61*	<0.001

*P < 0.001 vs. control group.

†P<0.001 vs. depressed group.

Table (2): MADRS score in the four study groups.

MADRS score	N, %	Control (n=30)	Type I DM (n=30)	Depression (n=30)	Type I DM plus Depression (n=30)	P value
Normal	N	30	30	0	0	<0.001
	%	100.0%	100.0%	0.0%	0.0%	
Mild depression	N	0	0	0	2	
	%	0.0%	0.0%	0.0%	6.7%	
Moderate depression	N	0	0	10	12	
	%	0.0%	0.0%	33.3%	40.0%	
Severe depression	N	0	0	20	16	
	%	0.0%	0.0%	66.7%	53.3%	

Table (3): Correlation between vitamin D level and other quantitative variables

	Spearman's rho (ρ)	P value
Age (yr)	0.008	0.927
Weight (kg)	0.197*	0.031
Height (m)	0.1140	0.215
BMI (kg/m^2)	0.199*	0.029
FBG (mg/dl)	-0.265*	0.003
2hPG (mg/dl)	-0.255**	<0.005
HbA1c (%)	-0.252**	0.005
MADRS score	-0.362**	<0.001
Duration of DM	-0.103	0.432

*. Correlation is significant at the 0.05 level.

**. Correlation is highly significant at the 0.01 level.

Table (4): Multiple regression model for determinants of vitamin D level

Independent variables	B	SE	T	P value
Type I DM*	-0.856	0.356	-2.405	0.018
Depression**	-1.361	0.365	-3.727	<0.001
Female gender***	-0.877	0.361	-2.427	0.017
Age (yr)	0.022	0.028	0.799	0.426
BMI (kg/m^2)	-0.013	0.042	-0.312	0.756
Constant	4.785			

B, regression coefficient, SE, standard error; t, t statistic.

*Referenced to non-diabetic.

** Referenced to non-depressed.

***Referenced to male gender.

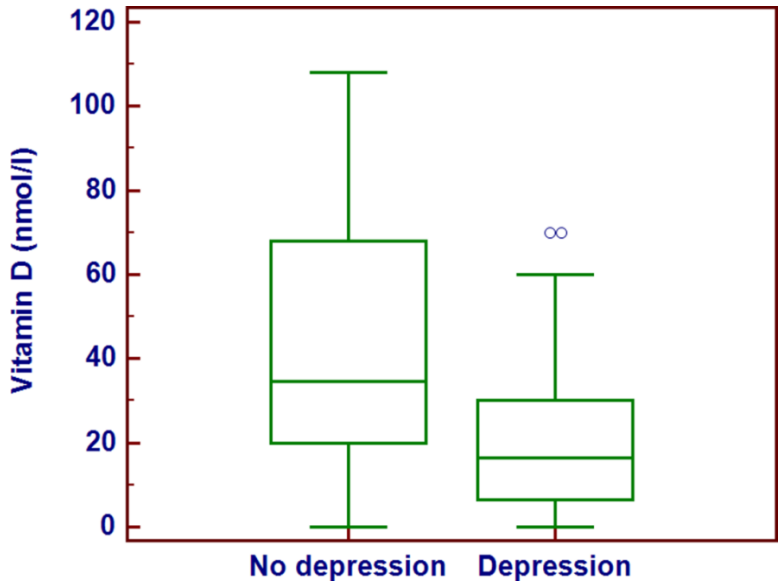

Figure (1): Boxplot showing Vitamin D level in patients with or without depression. All values are presented as median (Interquartile range).

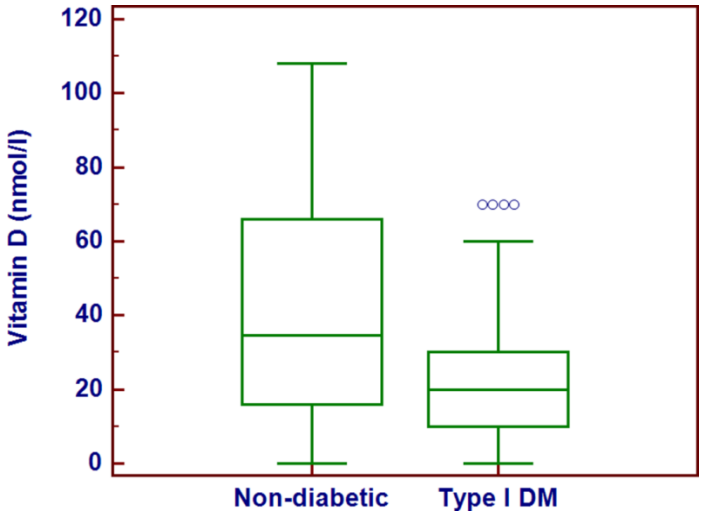

Figure (2): Boxplot showing vitamin D level in patients with or without type 1 DM. Central box represents interquartile range. Middle line represents median. Whiskers extend from minimum to maximum value, excluding outliers that are displayed as circles.

Discussion

Worldwide, vitamin D deficiency is a problem not only in diabetics but also in healthy subjects. To our knowledge, this is the first study that examines the association between type 1 diabetes mellitus, vitamin D status and depression. In our study, vitamin D levels were found insufficient in the control group. This is in agreement with results from Saudi Arabia found a marked deficiency in serum 25-hydroxyvitamin D levels in both male and female blood donors. The low level of 25-hydroxyvitamin D found in their study could not be explained by low intake or poor sun exposure, as a substantial proportion of the participants in that study (90% of males and 93% of females) reported a sufficient nutritional intake of vitamin D and nearly 67% of them had regular exposure to UV sunlight. A possible explanation for this markedly low 25-hydroxyvitamin D level in both males and females is a racial difference in vitamin D concentration or a genetic predisposition to vitamin D deficiency among Saudi Arabians[17].Although there is abundant sunshine, accumulating data from many countries of the Middle East shows an increased prevalence of vitamin D deficiency and insufficiency. A report on the global vitamin D status published by the scientific advisory committee of IOF [international osteoporosis foundation] revealed some earlier data from some middle east countries showing that 70-80% of adolescent girls in Saudi Arabia and Iran had vitamin D level 25 nmol/L while in Lebanon was 32% in same age group while studies in adults revealed a prevalence of 60% and 65% for vitamin D values < 25nmol/L in Lebanon , Iran and Jordan and 48% for cut-off below 37.5 nmol/L in Tunisia.[18]

The results of our study showed a highly statistically significant decrease of vitamin D levels among diabetics when compared to non diabetics. Similar results were obtained by various studies. The study by **Lisa et al.** measured serum 25-hydroxyvitamin D in 128 youth with type 1diabetes (T1D). Less than 25% of these patients were vitamin D sufficient. The majority had inadequate levels of vitamin D; 61% insufficient and 19% deficient[19]. Similarly, in a case control study from North India, 58% of T1D and only 32% of controls had 25-hydroxyvitamin D deficiency [20].

Furthermore, a study on pubertal type 1 diabetic patients showed altered vitamin D regulatory mechanisms with relative decrease in 1, 25 dihydroxy vitamin D plasma concentration and increased 24,25-dihydroxy vitamin D levels in diabetics compared to their healthy counterparts[21].This suggests that vitamin D deficiency results from diabetes. Another strong hypothesis suggests that vitamin D deficiency may lead to diabetes. Thus, vitamin D may have a protective role against diabetes[23].The pathophysiology of and how vitamin D deficiency can lead to diabetes are still a matter of debate.

Vitamin D level was significantly decreased among depressed compared to the non-depressed group. Also, a negative correlation was detected between vitamin D level and MADRS score. Our results were in agreement with **Vijay et al.,** and **May et al.** who reported that there is an association between vitamin D level and incident depression[5,23]. Moreover, **Milaneschi et al.** examined the relationship between 25(OH) D and depressive symptoms over a 6 year follow-up. It was part of a population-based cohort study in Italy and a total of 531 women and 423 men aged 65 years and older participated. The conclusion was that hypovitaminosis D is a risk factor for the development of depressive symptoms in people older than 65years[11]. Also, **Berdtone-Johnson et al.** conducted a cross-section and prospective analysis. They found that the intake of vitamin D from foods and supplements was negatively correlated to the risk of depressive symptoms. They also found that women with an intake of >800 IU vitamin D per day daily intake had a lower prevalence for depressive symptoms compared to women who reported a total intake of <100 IU vitamin D per day[24]. On the other hand, **Zhao et al.** found no significant association between serum concentrations of 25(OH) D and depression[25].

We found that vitamin D levels were significantly negatively correlated with FBS, PPBS and HbA1c. This is in agreement with Zoppini et al., who found that in type 2 diabetic patients, high HbA1C levels were associated with low concentrations of serum 25(OH) D independently of duration of diabetes or diabetic treatment.[26]

A positive weak correlation between vitamin D level and BMI was found. In contrast, Torun et al. found that obese children and adolescents had significantly lower 25-hydroxyl vitamin D concentrations compared with non-obese group[27].

In our study vitamin D level was significantly decreased in diabetics, in depressed patients and in diabetics with depression in comparison to healthy controls. However, comparing the three patient groups, no statistically significant difference was found.

A question is thus raised – whether diabetes or depression is associated with more profound deficiency of vitamin D. Thus, multiple regression analysis was done and showed that the main independent determinants for vitamin D level were depression followed by female gender and finally DM.

Female gender as an independent determinant of vitamin D deficiency may be explained by pregnancy and lactation in females which occurs repeatedly during this age group (16-40years). Other possible explanations for low 25(OH) D levels in female patients include high temperatures, which result in using sun block creams on exposed skin areas to protect from UV rays and the traditional Islamic veil worn by women in our society, which prevent penetration of UVB light needed for vitamin D synthesis. Certainly Hobbs et al. reported severe vitamin D deficiency in Arab–American women who wear the veil [28].

In the current study, HbA1c level was higher in diabetics with severe depression compared to diabetics with moderate depression, but with no statistical significance. This is in agreement with **Singh et al,** who found that higher HbA1c levels were significantly associated with worse mood in diabetic patients[29]. Depression in diabetes has been associated with poor medication adherence and poor glycemic control [30].Untreated depression in diabetes can increase the risk for diabetes-related complications such as heart disease, blindness, amputations, stroke, kidney disease, and sexual dysfunction [31].Moreover, death rates among individuals with both diabetes and depression were found to be three times higher than among diabetics without depression.[32]

To conclude, vitamin D levels were found insufficient in the control group while being deficient in all patients. Severe depression associated with poor control. The independent risk factors for increased prevalence of vitamin D deficiency were found to be depression, female gender and diabetes mellitus.

Conflict of Interest:

The authors have no conflict of interest nor financial or personal relationship to the study.

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