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Original Article

Serum 25-Hydroxyvitamin D in Patients with Major Depressive Disorder

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Abstract

Background: We investigated the association between serum 25(OH) D levels and depressive symptoms in patients with major depressive disorder (MDD).

Methods: Eighty-five adults, 44 drug free patients with MDD and 41 apparently healthy controls, participated in the study. The Hamilton Depression Rating Scale was used to assess severity of major depression. Mental health of the controls was assessed according to DSM-IV criteria. Stress level of the participants was assessed by the Holmes and Rahe stress scale. Serum 25(OH) D levels was measured by immunochemiluminescence assay. Vitamin D deficiency was defined as a serum 25(OH) D concentration of lower than 20 ng/ml.

Results: Depressed patients had the higher levels of stress. There was a positive correlation between stress level and disease severity (r= 0.32, *P*= 0.03). In total participants, mean percentage of vitamin D deficiency was 77.6% with 75% in patients and 80.5% in the healthy subjects. There were no differences between the two groups in serum 25(OH) D levels and percentage of subjects with the vitamin deficiency. A negative correlation was observed between disease severity and serum 25(OH) D level of patients with depression episodes < 2 y (r= -0.38, *P* = 0.08) and winter samples (samples collected and measured from December to march, r= -0.62, *P* = 0.004).

Conclusion: Serum 25(OH) D levels were not associated with depression. However, the inverse relationship between levels of vitamin D and depressive symptoms in current depression episodes and in sun-deprived season warrants further investigation.

Keywords: Vitamin D, Depression, Depression severity, Current depression

Introduction

Major Depressive Disorder (MDD) is a common mental disorder that affects persons' health related quality of life accompanied by reduced productivity. The disorder was known as the second global most important cause of disability in 2020 (1). It affects around 840 million people worldwide (2). The causes of depression are suspected to be a combination of biological, environmental, and psychological factors. Recent studies have given an increasing amount of attention to a possible role of vitamin D in cognitive function and mental health (3, 4). A unique neurosteroid hormone may have also an important role in the development of depression. Vitamin D receptor (VDR) and vitamin D activating enzyme ,1- alpha-hydroxylase, are widely distributed in human brain, particularly in the hypothalamus and also in the limbic system, which is assumed to be involved in pathophysiology of the depression (5, 6). Vitamin D is also involved in numerous brain processes including neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity

and brain development making it biologically plausible that this vitamin might be associated with the depression (7).

Over one billion people have either vitamin D insufficiency or deficiency (8). Improving epidemiologic evidences have indicated a possible correlation between vitamin D levels and depression (9), but clinical evidence is limited. Therefore, this study was designed to investigate the association between serum levels of vitamin D and depression in patients with MDD as compared to control subjects.

Materials and Methods

Participants

The study conducted during December to June 2013 and consisted of 85 participants (aged 18- 63 y), 44 drug- free patients with MDD (9 men and 35 women) and 41 healthy subjects as control (9 men and 32 women). Not all the patients were under any antidepressant treatments for at least 3 month prior the initial assessment. Healthy participants were characterized with no history of past or current chronic physical or mental disorders, including neurological diseases and were not taking any specific medications. Patients' depression level and mental health of the healthy controls was diagnosed according to DSM IV (10) by an experienced psychiatrist. Both the groups were sex and age-matched.

In addition, a written informed consent was obtained from all the participants. The study was approved by Ethical Committee at Tabriz University of Medical Sciences, Tabriz, Iran.

Demographic information and medical history of the participants were obtained during the clinic visit. The medical history included questions pertaining to any previous medications used to manage depression, anxiety, mood and other related issues, clinical manifestations of the disease, diagnosis history and smoking status. Physical activity level was determined by using a validated International Physical Activity Questionnaire (IPAQ) and expressed as a standard Metabolic Energy Turnover in MET-minutes/week (11). Three levels of physical activity were classified: low (<600 MET-minutes/week), moderate (from 600 to 2999 MET-minutes/week) and high (3000 MET-minutes/week or more). Dietary intake of vitamin D was evaluated by a 3-day food record, completed on non-consecutive days. Body weight was measured using a digital scale, with the examinee wearing a light gown. Height was measured barefoot using a wall-mounted stadiometer to the nearest 0.5 cm. Body mass index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Waist circumference (WC) was measured by a tape measure at the midpoint between the lower costal margin and iliac crest to the nearest 0.5 cm. Hip circumference was measured over light clothing at the widest point over the buttocks when viewed from the side. Waist hip ratio was obtained by dividing the waist circumference by hip circumference. Sunlight exposure was assessed by a question relating to the amount of daily exposure during weekdays.

Assessment of stress and depression level

The stress level of participants studied was assessed by means of the Holmes and Rahe stress scale. Stress level was defined as mild (score< 100), moderate (score= 100-150) and severe (score> 150).

To assess the severity of depression in patients, the 17-item Hamilton Rating Scale for Depression (HRSD) (12) was used by a well-trained rater. The severity of depression was categorized to mild (score= 10-13), moderate (score= 14-17) and severe (score> 17).

Determination of 25(OH) D levels in serum

Fasting blood samples were collected and sera were immediately collected after centrifugation at 5000 RPM for 3 minutes. Serum levels of 25(OH) D were measured using immunochemiluminescence assay. Serum 25(OH) D levels of <20 ng/ml defined as deficiency, >20 as desirable level and <10 as severe vitamin deficiency (13). Samples collected and measured from December to march considered as winter samples and samples from April to June as spring samples.

Statistical analyses

Demographic characteristics of the participants were summarized by either mean ± standard deviation (SD) for continuous data, or frequency (percentage %) for proportional data. Differences between the groups were assessed by Chi-square or Fisher's exact test for categorical variables, student's *t* test and Mann-Whitney U test for continuous variables. Pearson's or Spearman's coefficients correlations were performed for associations between variables. Regression analysis was done using multiple linear regressions. *P* values less than 0.05 were considered statistically significant.

Results

Demographic characteristics

Descriptive data of the study population are presented in Table 1. Average ages of patients and healthy subjects were 36.93 ± 12.05 and 36.97 ± 12.9 years, respectively. There was no statistical significant difference in age, gender, anthropometric parameters, physical activity level, educational level, marital status, dietary vitamin D intake, and daily sun exposure between the two groups (Table 1). In patients, the median of disease duration was 24.00 with a range of 12.00 to 60.00 months.

Table 1: Descriptive data of depressed patients and healthy controls

Variable	Patients	Control	*P* value
Number (total)[b]	44	41	0.87
Male	9 (20.5)	9 (22)	
female	35 (79.5)	32 (78)	
Age[a]	36.93 (12.05)	36.97 (12.97)	0.99
Physical activity[b]			0.18
Low	26 (59.09)	16 (39.02)	
Moderate	14 (31.82)	20 (48.78)	
high	4 (9.09)	5 (12.19)	
BMI (kg/m^2)[a]	27.58 (5.61)	28.08 (7.36)	0.72
Waist circumference (cm)[a]	93.69 (10.81)	93.85 (13.93)	0. 95
Waist/hip ratio[a]	0.85 (0.06)	0.87 (0.06)	0.49
Literacy level[b]			0.29
Under diploma	19 (43.18)	13 (31.71)	
Diploma	18 (40.91)	16 (39.02)	
College	7 (15.91)	12 (29.27)	
Marital status[b]			0.47
Married	35 (79.5)	31 (75.6)	
Single	7 (15.9)	7 (17.1)	
Divorced	2 (4.5)	0 (0)	
widowed	0	3 (7.3)	
Dietary vitamin D intake (µg)[c]	0 (0, 0.84)	0.12 (0, 2.55)	0.16
Sun exposure (minute/day)[c]	30 (5.25, 120)	30 (10, 60)	0.41

Data were expressed as [a] mean (SD), [b] frequency (percent), and [c]median (IQR)

Stress level and severity of depression

The stress score was discovered to be significantly higher in patients with depression as compared to the healthy controls (*P* = 0.03) (Table 2). Percentage of subjects with severe stress was significantly greater in depressed patients (31.8%, 14 of 44) as compared to the healthy subjects (14.6%. 6 of 41) (*P*= 0.03). Of patients, 54.8% (n= 23) were recognized with severe depression level (Table 2). As shown in Table 3, a positive correlation was observed between depression severity and stress levels (r= 0.32, *P*= 0.03). There were no significant correlations between anthropometric parameters with stress level or severity of the depression (Table 3)

Table 2: Stress mean score and rating in depressed patients and healthy controls

Variable	Controls N= 41	Patients N= 44
Stress (mean± SD)	76.83 ± 60.92	124.14 ± 98.56*
Mild n (%)	30 (73.20)	22 (50.00)
Moderate	5 (12.20)	8 (18.20)
Severe	6 (14.60)	14 (31.80)**
HRSD[a]		
Mild	-	11 (25.00)
Moderate	-	10 (23.70)
Severe	-	23 (52.30)

[a] Hamilton Rating Scale for Depression
* P <0.05 as compared to mean stress score of controls (total) using Man-Witney U test
** P <0.05 as compared to percentage of controls with severe levels of stress using chi-square test

Table 3: Correlation of serum 25(OH)D level, depression severity and stress with potential confounding factors

Variable	25(OH)D		HRSD		Stress	
	r	*P*	r	*P*	r	*P*
Age	0.24	0.03	0.10	0.53	-0.18	0.10
BMI	0.08	0.46	0.11	0.47	-0.11	0.32
Waist circumference	0.12	0.32	0.01	0.94	-0.12	0.28
Waist/hip ratio	0.09	0.41	-0.14	0.38	-0.12	0.27
Stress	0.06	0.61	0.32	0.03		
Disease duration	0.11	0.47	0.01	0.94	0.06	0.69

HRSD= Hamilton Rating Scale for Depression, P values less than 0.05 were considered statistically significant.

Vitamin D status

As shown in Table 4, median (interquartile range, IQR) serum 25(OH) D level of patients with depression was 10.54 (6.16, 19.35) ng/ml compared to 8.95 (6.33, 17.80) ng/ml in healthy controls with no statistically significant difference. Serum 25(OH) D levels did not differ between winter and spring subjects (Table 4). The vitamin level was non-significantly lower in currently depressed patients, patients with depression episodes less than 2 year (14), as compared to those who had depression ≥2 y (past depression) (Table 4). Totally, serum 25(OH) D levels below 20 ng/ml were observed in 77.6% (n= 66) of the participants. Vitamin D deficiency was observed in 75% (n= 33) of depressed patients and 80.5% (n= 33) of healthy subjects with no statistically significant difference (Table 4). Interestingly, percentage of male subjects (94.4%, 17 of 18) with vitamin D deficiency (<20 ng/ml) was remarkably greater than female subjects (73.1%, 49 of 67) (P = 0.06). However, a higher percentage of females (52.2%, 35 of 67) had severe vitamin D deficiency (<10 ng/ml) as compared to the males (22.2%, 4 of 18) (P = 0.03) (Table 4).

Totally, in patients, there were no significant correlations between disease severity and serum 25(OH)D levels, but in currently depressed patients a mild negative correlation was observed between the two variables (r= -0.38) (P = 0.08) compared to those who had depression ≥2 y (Table 5). In addition, a strong negative correlation was detected between the disease severity and serum 25(OH) D levels in the samples measured in winter (r= -0.62) (P = 0.004) as compared to those measured in spring (Table 5).

As shown in Table 3, a mild positive association was observed between age and serum vitamin D levels (r= 0.24, P = 0.03). There were no significant correlations between anthropometric parameters, stress level, and disease duration with serum 25(OH) D levels (Table 3).

Table 4: Vitamin D status on the base of disease duration, season, and gender

Variable	Controls (n= 41)	Patients (n= 44)	Total (n= 85)	*P*
Vitamin D level (ng/ml)[b]	8.95 (6.33, 17.80)	10.54 (6.16, 19.35)	-	0.73
winter subjects (n= 29)	-	-	10.58 (5.16, 19.60)	0.97
spring subjects (n= 56)	-	-	9.57 (6.33, 18.75)	
patients with current depression (n= 15)	-	7.16 (4.54, 12.70)	-	0.15
patients with past depression (n= 29)	-	10.58 (8.11, 21.20)	-	-
Vitamin D[a] < 20				
• total	33 (80.5)	33 (75)	66 (77.6)	0.61
• male	8 (88.9)	9 (100)	17 (94.4)	0.06
• female	25 (78.1)	24 (68.6)	49 (73.1)	-
Vitamin D[a] < 10				
• total	21 (51.2)	18 (40.9)	39 (45.9)	0.39
• male	1 (11.1)	3 (33.3)	4 (22.2)	0.03
• female	20 (62.5)	15 (42.9)	35 (52.2)	-

Data were expressed as [a] frequency (percent), and [b] median (IQR)

Table 5: Correlation of serum 25(OH) D level with depression severity (HRSD) in depressed patients

Variable	r	*P*
Total patients	-0.09	0.56
Patients with current depression[a]	-0.38	0.08
Patients with past depression[b]	0.22	0.33
Winter patients	-0.62	0.004
Spring patients	0.27	0.20

HRSD= Hamilton Rating Scale for Depression
[a] patients with depression episodes < 2 year; [b] patients with depression episodes ≥2 y

Discussion

Overall, we observed low serum 25(OH) D levels in the participants studied and over three-quarters of them (77.6%) were vitamin D deficient. The results are in agreement with findings from the previous studies in the country. 72.1% of male and 75.1% of female subjects in Iran are living with vitamin D deficiency (15). Hashemipour et al. reported low serum 25(OH) D levels in 79.6% of subjects, aged 20 to 69 years, in the capital city of Tehran (16). Environmental conditions such as geographical location, latitude and seasons along with personal characteristics such as age, gender, race, skin color, sun protective behaviors, inadequate dietary intakes, lifestyle and cultural factors can potentially affect the serum 25(OH) D level (17-23). Given that geographical location (38.0667 ° N, 46.3000 ° E) of Tabriz city provides wavelength necessary to get enough sunlight, therefore, other possible factors might play a role in serum vitamin D status. Limited exposure to UV due to lifestyle preferences, work schedule, and the fear of skin damage and cancer, skin-covering clothes and sunscreens are effective barriers for adequate exposure to UV rays, which impedes production of vitamin D in the skin. Hence, intake of vitamin D from fortified food sources to achieve adequate levels of vitamin D appear to be necessary.

The present study has also investigated association of serum levels of 25(OH)D with depressive symptoms in patients with MDD who attended to a psychiatry clinic and showed that, in total, serum 25(OH)D levels were relatively comparable in the depressed patients and healthy controls with any correlations between the vitamin levels and the disease severity. There are limited similar clinical trials in this matter and most of the studies were conducted on large general population samples with inconsistent findings. A growing body of epidemiological evidence suggests that hypovitaminosis D is associated with depressive disorders and its related clinical characteristics. Milaneschi et al. in a large cohort study on population aged 18-65 years indicated that low levels of 25(OH)D

were associated to presence and severity of the depressive disorders (24). Milaneschi et al. in a population-based cohort study on older persons suggested that hypovitaminosis D is a risk factor for development of depressive symptoms (25). Jaddou et al. in a national population-based household sample of 4,002 Jordanian participants, aged ≥25 years, demonstrated a significant association between depression and serum 25(OH) D level (26). However, there are some others indicating no associations between the two variables. Pan et al. in a population-based study on 3262 community residents, aged 50-70, found that depressive symptoms were not associated with 25(OH) D concentrations in middle-aged and elderly Chinese (27). Zhao et al. in a survey on 3916 participants aged ≥ 20 years could not determine any associations between serum concentrations of 25(OH) D and any rating of depression (28). Given that these studies have been performed on specific population groups in terms of age and race, together with variations in sample size, the measure used for diagnosis of depression and more importantly cut-off points used for vitamin D deficiency are key contributors to inconsistency of the findings. For example, the Institute of Medicine suggested serum concentration of equal or higher than 50 nmol l^{-1} (20 ng ml^{-1}) as optimal level of 25(OH) D. In addition, serum 25(OH) D lower than 25 nmol l^{-1} (10 ng ml^{-1}) and 25–50 nmol l^{-1} is considered as is considered vitamin D deficient and insufficient, respectively (13). However, some experts consider serum 25(OH) D >75nmol l^{-1} (30 ng ml^{-1}) as optimal (29). Hoang et al. considered 25(OH) D levels below than 20 ng/ml as deficient and levels between 20-30 ng/ml as insufficient (30) In addition, Milaneschi et al. divided 25(OH)D status into four quartiles: adequate, >75 nmol l^{-1}; desirable, 75–50 nmol l^{-1}; insufficient, <50 nmol l^{-1}; deficient,<25 nmol l^{-1} (24). Zhao et al. set 25(OH) D data in quartiles as follows: <15 ng/ml; , 15– 20 ng/ml; 20– 26 ng/ml; ≥26 ng/ml (28).

However, we could not show any significant associations between vitamin D and depression, but when sub-analyses was conducted on the data obtained from the participants with current depression; we observed a remarkable negative correlation between the disease severity and serum 25(OH) D levels as compared to the subjects with history of depression. The result is in agreement with previous findings indicating higher prevalence of vitamin D deficiency in currently depressed persons and inverse association of 25(OH) D with symptom severity (14, 24). The relationship observed between low levels of vitamin D and current depression episodes suggests that hypovitaminosis D may represent an underlying biological vulnerability in initial stage of MDD. In the present study, more analysis of data collected from patients in winter season showed a strong correlation between disease severity and serum 25(OH) D levels as compared to spring samples. The result was in accordance to findings of Nanri et al., which could not connect serum vitamin D levels with decreased depressive symptoms. However, when they did analysis by season, differential association emerged implying that a lower prevalence of depressive symptoms among persons with high serum 25(OH)D concentrations in assessments performed in November as compared to July (31). An earlier study has been reported that vitamin D supplementation might improve depressive symptoms during winter period (5). Our finding suggests a protective effect of vitamin D on depressive symptoms and might mitigate the disease severity.

Conclusion

Results of this study did not support a protective role of vitamin D in pathogenesis of depression. However, an inverse relationship observed between the levels of vitamin D and depressive symptoms in current depression episodes, albeit statistically non-significant, and in sun-deprived seasons warrants further investigation.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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