The Effect of 2 Different Single Injections of High Dose of Vitamin D on Improving the Depression in Depressed Patients With Vitamin D Deficiency

A Randomized Clinical Trial

Hassan Mozaffari-Khosravi, PhD, Lale Nabizade, MSc,* Seyed Mojtaba Yassini-Ardakani, MD,† Hossein Hadinedoushan, PhD,‡ and Kazem Barzegar, MSc§*

Abstract: The correlation between vitamin D deficiency and depression has recently been put forward and resulted in controversial findings. The present study was conducted to find out the effect of 2 single injections of 150,000 and 300,000 IU of vitamin D on improving the depression in depressed patients with vitamin D deficiency.

This clinical trial study was carried out during 2011–2012 in Yazd, Islamic Republic of Iran. A total of 120 patients who had a Beck Depression Inventory II score of 17+ and were affected with vitamin D deficiency were randomly assigned to 3 groups of 40. They included G300, G150, and NTG. G300 and G150 received an intramuscular single dose of 300,000 and 150,000 IU of vitamin D, respectively, and the NTG group received nothing. After 3 months of intervention, the depression state, serum vitamin D, calcium, phosphorus, and parathormone were measured.

The median of serum vitamin D after intervention were 60.2, 54.6, and 28.2 nmol/L ($P < 0.001$) for the G300, G150, and NTG, respectively. Percentages of vitamin D deficiency after intervention were 18, 20, and 91.2 for the groups, respectively. The serum calcium mean showed a statistically significant increase in just the 2 test groups receiving vitamin D. There was only significant difference in mean of Beck Depression Inventory II test score between G300 and NTG ($P = 0.003$).

The results of the study revealed that first, the correction of vitamin D deficiency improved the depression state, and second, a single injection dose of 300,000 IU of vitamin D was safe and more effective than a 150,000-IU dose.

Key Words: depression, vitamin D, Vitamin D deficiency

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From the *Department of Nutrition, Faculty of Health, †Department of Psychiatry, Faculty of Medicine, and ‡Department of Immunology, Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences; and §Department of General Course, Teaching English, Faculty of Medicine, Yazd Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

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Reprints: Hassan Mozaffari-Khosravi, PhD, Department of Nutrition, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran (e-mail: mozaffari.kh@gmail.com).

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Vitamin D is a fat-soluble vitamin that plays the dual role of vitamin and hormone. It is produced in the skin as a result of direct exposure to sunlight. The nutritional sources of this vitamin are limited, and its only rich source is cod liver oil. It is also found in small and varying amounts in butter, cream, yoke, and liver. Therefore, its relative deficiency is high, especially in countries where there are no food enrichment programs for vitamin D.[1] For this vitamin to be biologically activated, it must first be hydroxylated into 25-hydroxyvitamin D in the liver, and then converted to 1,25-dihydroxyvitamin D, the active from of this vitamin, in the kidneys.[1,2]

Vitamin D deficiency is a worldwide problem that has been common in one third to half of the adult population of both developing and developed countries.[3,4] It was previously thought in the past that most of the required vitamin D is provided via dermal synthesis. Yet, recent investigations have revealed that the dermal synthesis does not satisfy the daily need of the body to this vitamin, and various factors including latitude, insufficient exposure to sunlight, seasonal characteristics, use of sun-blocking creams, and type of clothing may cause insufficient intake of vitamin D.[5,6]

Studies conducted in Iran on vitamin D condition show the high prevalence of this vitamin in Iran, so that different investigations have reported its prevalence up to 80%.[7–9] The studies carried out in Yazd also reveal the high prevalence of vitamin D deficiency despite Yazd being a desert city with abundant sunlight. A study on female secondary school students in Yazd showed that 60% of them have vitamin D deficiency.[8] Also, 80% of mothers with gestational diabetes have this deficiency.[9]

The most well-known role of vitamin D is the regulation of blood levels of calcium and phosphorus for the normal mineralization of bones. Other capabilities of this vitamin have been recently discovered including its receptors in various tissues showing that it plays a significant role in many important metabolic processes not related to bones. Different studies have reported the role of vitamin D in disorders as osteoporosis, cancer, cardiovascular diseases, and diabetes.[10–15] Recently, the role of this vitamin in the improvement of cerebral functions including cognitive functions and mental health has been discovered.[16,17] The effect of cellular signaling can explain the relationship between vitamin D deficiency and the development of many of the aforementioned disorders.[16–20]

Depression is considered one of the common disorders in psychiatry and one of the most disabling and crippling disturbances in various communities.[21] Statistics show that one fifth of women and one tenth of men experience this disorder during their lives. Based on the statistics given in the United States, 18 million people are affected with depression.[22] Depression leads to a decrease in life quality, an increase in mortality, and an increase in the probability of affliction with various diseases. Lack of treatment of this disorder brings about many psychological

damages and socioeconomic consequences for the patients. It is estimated that depression will be the third disabling factor in 2020.[23] In a meta-analytic study that studied 24 related investigations, the prevalence of depression was reported to be 4.1%.[24] Depression can result from genetic, hereditary, biological, psychosocial, and nutritional factors.[25] One of the important factors contributing to depression is nutritional deficiencies specifically deficiency of niacin, omega fatty acids, iron, zinc, vitamin C, selenium, and folic acid.[26,27]

The relation between depression and vitamin D has been recently put forward, although the findings are contradictory.[18,28–40] Some of these studies have revealed that serum vitamin D level is lower in depressed persons compared to the normal ones.[18,38–40] Hoogendijk et al[38] showed that decreased serum level of vitamin D and increased serum parathormone (PTH) is correlated with the incidence of depression and its severity in the elderly. The results of a cohort study by Milaneschi et al[39] revealed that vitamin D deficiency is a risk factor for the appearance of depression symptoms in the elderly and that there was a higher correlation for the females compared with the males.

Various biological justifications have been offered for the probable role of vitamin D in the improvement of brain functioning. These include the presence of vitamin D receptor in various parts of the brain including the limbic system, cerebellum, cortex,[18] and the presence of the enzyme α1-hydroxylase in different regions of CNS as amygdala, a region that controls emotions and behavior in man.[20,41]

Based on the reasons given previously and some studies conducted in this regard, it seems that vitamin D deficiency plays a part in depression.[18,38–40] Regarding the evidence given above on the roles of vitamin D in cerebral functioning and the low level of serum level of vitamin D of depressed patients, the cooccurrence and high prevalence of depression and vitamin D deficiency in Yazd and some parts of the world, the hypothesis is made as whether the correction of vitamin D deficiency in depressed patients improves their disorder and whether the different doses of this vitamin will produce different results. Therefore, the present study focused on determining the effect of single injections of 150,000 and 300,000 IU of vitamin D in patients affected with this deficiency.

MATERIALS AND METHODS

Participants, Design, and Setting

The participants in this study were men and women aged 20 to 60 years who showed symptoms of depression at least 2 weeks before presenting to the psychiatrist. These patients, selected from specialist clinics of Yazd Shahid Sadoughi University of Medical Sciences in the spring and summer of 2011, possessed the required qualifications. The criteria for entrance into the study included the following: not being affected with other psychological disorders; absence of cardiovascular, renal, and hepatic diseases; special physiological conditions as pregnancy and lactation; lack of use of antidepressant drugs; and lack of use of nutritional supplements over the past 3 months. In addition, those facing problems such as mourning for the death of relatives or experiencing from the effects of divorce or job loss over the past 6 months were excluded from the study. Among the clients referred to psychiatry outpatient services for counseling, individuals who had inclusion criteria were enrolled in the study and were asked to fill out the Beck questionnaire; and if the test result was in favor of depression, this diagnosis was approved by a psychiatrist through interview. So depression was not specified, and what is important in this study was the change of score of depression after supplementation.

In the first stage, 211 of the patients having the inclusion criteria with a Beck Depression Inventory II test score of 17+ were identified, and their 25-hydroxyvitamin D level was measured. In the second stage, the clinical trial study was designed in which 120 of those affected with vitamin D deficiency (25-hydroxyvitamin D <40 nmol/L) participated. These individuals were randomly assigned to 3 groups of 40 using the random numbers table. G300 and G150 received 300,000 and 150,000 IU of vitamin D intramuscularly, respectively, and the NTG (nontest group) received no injection. The vitamin D was provided by Iran Hormone Drug Manufacturing Company in Iran. After recording the readings, injection of vitamin doses, and the passage of 3 months, the intended data were read and recorded again.

Measurements

To determine the status and severity of depression, the Beck Depression Inventory II test was used.[42] This is a self-report attitude questionnaire of 21 items used for assessing depression in individuals aged 13+ years. There are 4 statements in each item, and the individual is asked to mark the choice that best describes their feelings and status over the past 2 weeks. In this scale, zero stands for absence of any specific symptoms, and 3 stands for the highest degree of the presence of symptoms. The points are then added up to arrive at the total score on the questionnaire. The classification of depression in this scale is as follows: persons with a score of 0 to 10 are considered normal; 11 to 16, mild depression; 17 to 20, in need of psychological consultation; 21 to 30 relatively depressed; 31 to 40 severely depressed; and 40+, very severely depressed (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*).[43]

Individuals with the required criteria were asked to turn to the center while fasting for taking blood samples and recording of other variables. Five milliliters of venal blood was taken of each participant for measuring the serum level of 25-hydroxyvitamin D, PTH, calcium, and phosphorus before single-dose injection of vitamin and assignment to 3 groups. Their weight was measured using the Seca scales with a precision of 0.1 kg, and their height was measured and recorded using the standing measure of Seca in the standing position with a precision of 0.5 cm. Body mass index was calculated by dividing weight by the square root of height in meters.

To estimate the individuals' daily intake of vitamin D, calcium, phosphorus, and energy, use was made of the 24-hour dietary recall questionnaire. The data were analyzed using the Nutritionist IV (Nutritionist IV Diet Analysis, First Data Bank Division, Hearst Corp, San Bruno, CA). The participants were required not to change their physical activities during the intervention. Persons who started to use antidepressants or mineral vitamin supplements under psychiatrist's advice during the intervention were excluded from the study. The exclusion criteria included death of relatives, divorce, and job loss during the 3 months of study. These participants answered the items in the Beck Depression Inventory II questionnaire again after 3 months; and the previous studies for measuring 25-hydroxyvitamin D, calcium, phosphorus, and PTH were repeated, and the 24-hour dietary recall of participants were obtained.

Serum 25-hydroxyvitamin D was measured via immunoassay using enzyme-linked immunosorbent assay and an Immunodiagnostic Systems Ltd kit (IDS Ltd, Boldon, UK) with a sensitivity of 2 nmol/L. In this study, a 25-hydroxyvitamin D serum level of more than 40 nmol/L was considered normal, a level of 25 to 40 was considered a mild deficiency, a level of 12.5 to 25 was

considered a moderate deficiency, and less than 12.5 nmol/L was considered a severe vitamin D deficiency.[44] Parathormone was measured using the enzyme-linked immunosorbent assay and Biomerica kit made in Hannover, Germany. The serum calcium and serum phosphorus were measured by calorimetric method using AutoAnalyzer (Echo Plus Corporation, Rome, Italy) and Biosystems kit (Barcelona, Spain).

Ethical Considerations

Written informed consent was obtained from the patients to participate in the study. The patients were free to withdraw from the study. The proposal of this study was approved by the ethics committee for research in Shahid Sadoughi University of Medical Sciences. The clinical trial registration code was obtained from the center for registration of clinical trial, from the deputy of Research and Technology of the Ministry of Health, Treatment, and Medical Education (www.irct.ir). The participants paid no expenses, and the vitamin D cost was paid for by the researcher.

Statistical Analysis

To analyze the data, the SPSS package version 11 (SPSS Inc, Chicago, IL) was used. To determine data distribution, the Kolmogorov-Smirnov test was applied. To compare the means of quantitative data with normal distribution among the groups, use was made of the one-way analysis of variance, post hoc multiple comparison, and the Student *t* test. To carry out intragroup comparisons at the beginning and end of the study, the paired *t*-test and the Wilcoxon signed rank test were used. To present the data not having a normal distribution, the 25th, 50th, and 75th percentiles were used; and to compare these data among the groups, median test was used. To compare the frequency distribution of qualitative variables, the χ^2 test, the sign test, and the Fisher exact test were applied. Significance was set at $P = 0.05$.

RESULTS

Of the 211 individuals participating in the first phase of the study, 120 patients participated in the interventional phase of whom 109 individuals completed the intervention. Two patients withdrew from the study. In addition, 6 participants were excluded in the course of the study owing to their use of nutritional supplements or antidepressant drugs. One of them died in a car accident. One participant withdrew owing to the death of spouse, and one withdrew owing to divorce (Fig. 1).

The characteristics of the quantitative and qualitative variables before intervention are given in Table 1. At the beginning of the study, only the mean of serum phosphorus was statistically different among groups, this difference being between NTG and other test groups. Regarding the qualitative variables, only the literacy level variable was statistically different among the groups. There was no statistically significant difference among the 3 groups regarding the variables of daily dietary intake of energy, vitamin D, calcium, phosphorus, at the beginning and end of intervention.

The frequency distribution and vitamin D median of the participants before intervention are presented in Table 1. Table 2 presents frequency distribution of vitamin D status before and after intervention in the test groups and nontest group. There was no statistically significant difference in the frequency distribution of vitamin D status before intervention among the 3 groups ($P = 0.59$; Table 1). Yet, the groups showed a significant difference in this regard after the intervention ($P < 0.001$). As can be seen, vitamin D status has significantly improved in G300 and G150 before and after the intervention so that 82% and 80% of

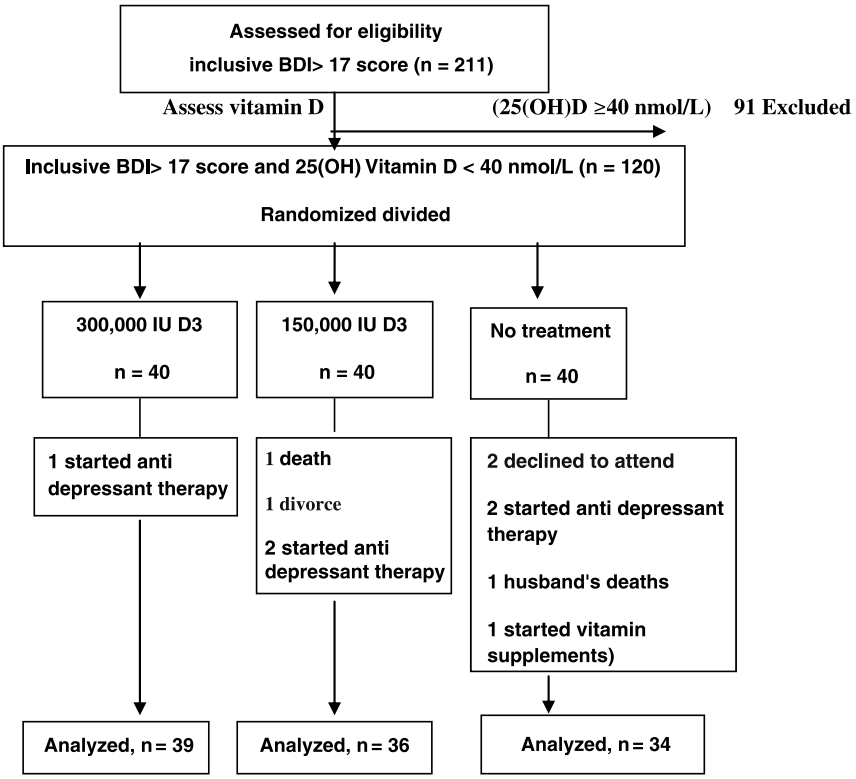

FIGURE 1. Flow of patients through the study.

TABLE 1. Comparison of Mean ± SD, Median, and Frequency Distribution of the Variables Before Intervention Among the 3 Groups

Variables	NTG (n = 34)	G150 (n = 36)	G300 (n = 39)	*P*
Age, y	33 ± 8.8	32.7 ± 8.4	32.1 ± 9.0	0.9*
Weight, kg	67 ± 10.7	68.5 ± 13.5	69.2 ± 14.8	0.7*
Body mass index, kg/m^2	25.9 ± 3.8	26.3 ± 5.1	26.2 ± 4.8	0.9*
Beck Depression Inventory II test score	26.4 ± 5.2	27.5 ± 8.4	26.7 ± 7.5	0.8*
Parathormone, Pgr/mL	35.1 ± 21.4	33.5 ± 21.4	37.2 ± 27.4	0.8*
Calcium, mg/dL	8.8 ± 0.3	8.7 ± 0.2	8.8 ± 0.5	0.4*
Phosphorus, mg/dL	3.2 ± 0.3	3.5 ± 0.6	3.5 ± 0.6	0.02*
25-hydroxyvitamin D percentile, nmol/L				
25	17.3	16.8	16.4	0.3†
50	25.4	23.0	21.3	
75	30.4	30.9	27.6	
25-hydroxyvitamin D, nmol/L	N (%)	N (%)	N (%)	0.59
<12.5	2 (5.9)	2 (5.6)	4 (10.3)	
12.5–25	15 (44.1)	19 (52.8)	23 (59)	
25–30	14 (41.2)	10 (27.8)	8 (20.4)	
35–40	3 (8.8)	5 (13.8)	4 (10.3)	
Education				
Below diploma	13 (40.6)	17 (48.6)	11 (28.2)	0.04‡
Diploma	9 (28.1)	10 (28.6)	6 (15.4)	
University education	10 (31.3)	8 (22.8)	22 (56.4)	
Body mass index, kg/m^2				
<18.5	1 (3.3)	2 (6.5)	0 (0)	0.23‡
18.5–25	11 (36.7)	12 (38.7)	16 (47.1)	
25–30	15 (50)	8 (25.8)	11 (32.4)	
30≤	3 (10)	9 (29)	7 (20.5)	
Sex				
Male	8 (23.5)	9 (25)	14 (35.9)	0.43‡
Female	26 (76.5)	27 (75)	25 (64.1)	
Profession				
Worker	2 (6.1)	2 (5.4)	2 (5.1)	0.62‡
Employee	3 (9.1)	3 (8.2)	9 (23.1)	
Housekeeper	20 (60.5)	23 (62.1)	18 (46.1)	
Free job	5 (15.2)	4 (10.8)	6 (15.4)	
University student	3 (9.1)	5 (13.5)	4 (10.3)	

*One-way analysis of variance test.
†Median test.
‡χ^2 test.

participants in G300 and G150 had a vitamin D rate higher than 40 nmol/L, whereas it was 8.8% for the NTG group, meaning that almost 91% of the participants in this group still had vitamin D deficiency (Table 2). There was no statistically significant difference in the median of 25-hydroxyvitamin D among the 3 groups before intervention. Yet, there was a statistically significant difference in this variable among the groups after intervention. The highest median belonged to G300, and the lowest median belonged to NTG. In addition, the highest significant increase compared to the beginning of intervention belonged to G300, and the lowest increase occurred in NTG (Table 3).

Frequency distribution and mean of serum calcium level of the participants are presented in Tables 2 and 3, respectively. As shown in Table 3, there was no significant difference in the mean serum calcium concentration among the 3 groups. However, this mean was significantly different among the groups after intervention, so that the mean of the vitamin D–receiving groups was higher than that of the NTG. On the other hand, the highest amount of significant increase compared with the beginning of the study was related to the 2 vitamin D–receiving groups and the lowest amount was related to the NTG. Similarly, a significant number of patients in just the 2 vitamin D–receiving groups who had previously a subnormal serum calcium level before intervention reached a normal calcium level, whereas this did not happen for the NTG (Table 2).

As given in Table 2, there was no statistically significant difference in the frequency distribution of various phosphorus levels before and after the intervention among all groups. In addition, as can be seen in Table 3, the mean of this variable was not significantly changed before and after the intervention among the groups.

Based on Table 2, there was no statistically significant difference in the frequency distribution of various PTH levels before and after intervention among groups. In addition, as can be seen

TABLE 2. Frequency Distribution of Status of Serum Calcium, Phosphorus, Parathormone, Beck-II Test Score and Vitamin D Before and After Intervention in Test and Non-Test Groups

	After		Before		
Groups	No. Patients	Percent	No. Patients	Percent	*P*
Beck Depression Inventory II test score					
G300					
<10	10	25.6	0	0	<0.001
11–30	26	66.7	25	64.1	
30≤	3	7.7	14	35.9	
G150					
<10	6	16.7	0	0	0.022
11–30	24	66.7	27	75	
30≤	6	16.6	9	25	
NTG					
<10	1	2.9	0	0	0.5
11–30	29	85.3	28	84.8	
30≤	4	11.8	5	15.2	
25-hydroxyvitamin D, nmol/L					
G300					
<12.5	0	0	4	10.3	<0.001
12.5–25	1	2.6	23	59	
25–40	6	18.4	12	30.8	
40≤	320	82.0	0	0	
G150					
<12.5	0	0	2	5.6	0.022
12.5–25	0	0	19	52.8	
25–40	7	20	15	41.7	
40≤	28	80	0	0	
NTG					
<12.5	0	0	2	5.9	0.5
12.5–25	15	44.1	15	44.1	
25–40	16	47.5	17	50	
40≤	3	8.8	0	0	
Calcium, mg/dL					
G300					
<8.8	3	7.7	22	56.4	<0.001
8.9–10.8	36	92.3	17	43.6	
G150					
<8.8	18	52.9	27	75	<0.001
8.9–10.8	16	47.1	9	25	
NTG					
<8.8	18	52.9	18	52.9	1
8.9–10.8	16	47.1	16	47.1	
Phosphorus, mg/dL					
G300					
<2.5	2	5.1	1	2.6	1
2.5–4.5	35	89.7	26	92.3	
45≤	2	5.1	2	5.1	
G150					
<2.5	3	9.1*	1	2.8	0.3
2.5–4.5	30	90.9	24	94.4	
45≤	0	0	1	2.8	
NTG					
<2.5	0	0	0	0	1
2.5–4.5	15	97.1	33	97.1	
45≤	1	2.9	1	2.9	
Parathormone, Pgr/mL					
G300					
<10.4	7	17.9	1	2.6	0.2
10.4–66.5	29	74.4	36	92.3	
66.5≤	3	7.7	2	5.1	
G150					
<10.4	7	20.6	1	2.9	0.1
10.4–66.5	25	73.5	31	94.1	
66.5≤	2	5.9	3	5.9	
NTG					
<10.4	5	14.7	1	2.9	0.3
10.4–66.5	27	79.4	32	94.1*	
66.5≤	2	2.9	1	5.9	

*Sign test.

in Table 3, the PTH concentration level did not significantly change before and after the intervention among the groups. There was no statistically significant difference in the frequency distribution of various PTH levels before and after the intervention in any group.

Frequency distribution and mean of the Beck Depression Inventory II test scores are shown in Tables 2 and 3, respectively. Based on Table 2, there was statistically significant difference only in the frequency distribution of the Beck Depression Inventory II test scores in the vitamin D–receiving groups after the intervention. As shown in Table 3, there was no a statistically significant difference in the mean of the Beck Depression Inventory II test scores before the intervention among the groups. Yet, there was a significant change in this score after intervention among the groups so that the lowest mean belonged to the G300 and the highest mean belonged to the NTG. On the other hand, the greatest significant decrease compared to the beginning of study belonged to the G300, and the least decrease belonged to the NTG. Based on least significant difference test among the groups after intervention, it was determined that the mean of the Beck Depression Inventory II test between the 2 groups, G300 and G150, was not significantly different compared with the NTG ($P = 0.1$). The G150 was not significantly different from the NTG ($P = 0.1$). The only significant difference was seen between the G300 and the NTG ($P = 0.003$).

DISCUSSION

The results of the study showed that after 3 months of prescription of the injection of 300,000 and 150,000 IU of vitamin D for the depressed patients affected by vitamin D deficiency, their symptoms of both disorders improved, and the 300,000 IU dose of vitamin D was even more effective and safe. The presence of correlation between depression and vitamin D deficiency has been reported in various epidemiological studies, although the

TABLE 3. Comparison of Mean ± SD and Median of Quantitative Variables Under Study Within and Among the Groups Under Study Before and After Intervention

Variable	NTG (n = 34)	G150 (n = 36)	G300 (n = 39)	*P*
Beck Depression Inventory II test score				
Before	26.4 ± 5.2	227.5 ± 8.4	26.7 ± 7.5	0.82
After	24.3 ± 6.2	20.6 ± 11.3	17.4 ± 9.8	0.01
Difference	2.1 ± 3.8	6.8 ± 7.9	9.3 ± 8.7‖	<0.001
P†	0.003	<0.001	<0.001	
Parathormone, Pgr/mL				
Before	35.1 ± 21.4	33.5 ± 21.4	37.2 ± 27.4	0.80
After	36.1 ± 14.7	39.8 ± 19.4	37.9 ± 16.3	0.67
Difference	−1 ± 17.1	−5.9 ± 24.7	−0.7 ± 28.5	0.60
P†	0.73	0.17	0.87	
Calcium, mg/dL				
Before	8.8 ± 0.3	8.7 ± 0.2	8.8 ± 0.5	0.43
After	8.8 ± 0.3	9.1 ± 0.2	9.1 ± 0.2	<0.001
Difference	0 ± 0.1	−0.3 ± 0.3	−0.32 ± 0.51	<0.001
P†	0.75	<0.001	<0.001	
Phosphorus, mg/dL				
Before	3.2 ± 0.3	3.4 ± 0.6	3.5 ± 0.6	0.02
After	3.2 ± 0.3	3.2 ± 0.5	3.4 ± 0.5	0.10
Difference	0	0.2 ± 0.7	0.08 ± 0.6	0.30
P †	0.69	0.13	0.38	
25-hydroxyvitamin D, percentiles 25th, 50th, and 75th, nmol/L				
Before	17.3, 25.4, 30.4	16.8, 23.0, 30.9	16.4, 21.2, 3.6	0.3
After	19.4, 28.2, 33.1	41.0, 54.6, 62.3	42.0, 60.2, 66.8	<0.001
Difference	−5.7	−33.2	−38.7	0.001§
P‡	0.001	<0.001	<0.001	

*One-way analysis of variance.

†Paired *t* test.

‡Wilcoxon signed rank test.

§Median test.

‖− indicates increase, and + indicates decrease.

findings are contradictory.[18,32–40] Some of these studies have reported that the presence of depression is related to low levels of vitamin D.[18,38–40] The results of the study by Hoogendjik et al[38] showed that a decrease in serum vitamin D level and an increase in serum PTH level was correlated with depression and its severity in the elderly. In addition, the study by Milaneschi et al[39] revealed that vitamin D deficiency is a risk factor for the appearance of depression symptoms in the elderly and that the correlation was higher for women than for men. Wilkins et al[32] and Ganji et al[40] also reported the correlation between low levels of serum vitamin D and depression.

Some studies have reported that there is no correlation between serum levels of vitamin deficiency and depression. Zhao et al[34] did not find any significant correlation between depression and vitamin D concentration in the middle aged and the elderly. Pan et al[45] also found no significant correlation between depression and vitamin D concentration in men and women aged 50 to 70 years in China. Of the clinical trial studies conducted so far on the relationship between depression and vitamin D, the findings of the present study are similar to those of Jorde et al.[36] In their study, supplementation of overweight and obese patients with 20,000 and 40,000 IU in 1 year improved their depression compared with the control group.[36]

Some studies investigated the effect of vitamin D on seasonal affective disorder, a kind of depression common in winter, and reported the positive effect of vitamin D on the improvement of the symptoms of this kind of depression.[46,47] In the study by Veith et al,[46] vitamin D supplementation with a daily dose of 4000 IU during 2 winters improved the symptoms of depression compared to the group receiving vitamin D with a daily dose of 600 IU. Also Lansdowne et al[47] reported the positive effects of vitamin supplementation for 5 days in winter in a randomized double-blind interventional study.

Contrary to the present study, the randomized double-blind clinical trial by Dean et al,[48] which studied the effect of vitamin D on cognitive and emotional functions in normal individuals, reported no significant difference in the depression state of the group that received a daily dose of 5000 IU of vitamin D for 6 weeks compared with the control group who received placebo. Furthermore, another study reported no statistically significant difference between the control group and the group of women older than 70 years who received a megadose of 500,000 IU of vitamin D annually for 5 years.[49]

There are many biological reasons regarding the probable role of vitamin D in the improvement of brain function and depression. One important evidence is the presence of 1,25-dihydroxyvitamin D, that is, the active form of this vitamin, in the brain tissue and the presence of vitamin D receptor and the activating enzyme of this factor, that is, 1-α hydroxylase, which catalyzes hydroxylation vitamin D into the active form of it, in various sites of CNS

including the amygdala. Amygdala is the region that controls the emotions and behavior in humans.[21] As another evidence, mention may be made of the way vitamin D affects the monoamines, which probably play a role in the rising of depression. It seems that vitamin D regulates the gene expressions that encode tyrosine hydroxylase and the precursor of neurotransmitters of norepinephrine and epinephrine in the adrenal gland and in this way play a role in the pathophysiology of mood disorders.[19] On the other hand, vitamin D may contribute to brain function and probably to the creation of depression by supporting neurons and acting against the dopaminergic poisons by regulating the glial cell line–derived neurotrophic factor and also by regulating the factors that affect neurotransmission and synaptic flexibility.[19,50,51] It is also observed that vitamin D has a neuroprotective role for the nervous system owing to its effect on the synthesis of special calcium-bonding proteins and antioxidation characteristics.[52]

One of the limitations of the present study was the short period of follow-up. If we increased the intervention period or even if the vitamin D doses were repeated once more, we might have specially obtained different results because even after intervention, some individuals in the test groups had vitamin deficiency. Another limitation was the point that the study was not double blinded, as the group that did not receive vitamin D was different from the other 2 groups regarding vitamin D injections. This weakness could be overcome if one injection was used as a placebo. It is recommended that new studies be conducted in which single doses higher than 300,000 IU of vitamin D are given to depressed patients with vitamin D deficiency. Even the prescription of vitamin supplements for those who have deficiency is of high significance.

The findings of this study showed that first, vitamin D deficiency in patients with depression has a high prevalence; second, the correction of vitamin deficiency improves depression in these patients; and third, the single dose of 300,000 IU of vitamin D is safe and more effective than 150,000 IU. Based on the findings of this study, and similar studies, and also noting the vitamin D status and the correction of vitamin D deficiency in depressed patients, we can gain better results in treating this group of patients.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interests.

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