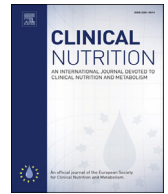




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Randomized Control Trials

Effect of vitamin D supplementation on depression in elderly patients: A randomized clinical trial[☆]

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SUMMARY

Background & aims: Treatment of depression in elderly population is a crucial issue. The effect of vitamin D supplementation on treatment of depression in older adults was investigated in this clinical trial.

Methods: It was an 8-week, randomized clinical trial of vitamin D supplementation and placebo in the treatment of depression in 3 psychiatric clinics. The study sample included 78 older adults aged over 60 years with moderate to severe depression. Subjects were randomly allocated to receive 50,000 U vitamin D3 pearl weekly for 8 weeks or placebo (39 subjects in each group). Main outcome measures comprised Geriatric Depression Scale-15 (GDS-15) questionnaire and 25-hydroxyvitamin D3 [25(OH)D3]. The analysis utilized Mann Whitney U test, Wilcoxon signed ranks test, chi-square and multiple regression analysis.

Results: The mean baseline 25(OH)D3 concentration was 22.57 ± 6.2 ng/ml in vitamin D group and 21.2 ± 5.8 ng/ml in placebo group ($p = 0.16$). The Vitamin D increased to 43.48 ± 9.5 ng/ml in vitamin D and 25.9 ± 15.3 ng/ml in placebo group. The depression score decreased from 9.25 to 7.48 in vitamin D group ($p = 0.0001$), while there was a non-significant increase in depression score in placebo group. The multiple regression analysis showed that the vitamin D group and the score of depression before study were the variables that could explain 81.8% of depression score after intervention.

Conclusion: The findings indicated that vitamin D supplementation can improve the depression score in persons aged 60 and over.

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1. Introduction

Depression is a common problem in older adults [1], with many consequences such as loss of appetite and energy, insomnia, and loss of interest in usual activities [2]. These patients feel anxious and dissatisfied with their lives [3]. Depression has adverse effects on physical performance and the quality of life of older adults [4,5]. A meta-analysis of 83 studies from all around the world showed that the prevalence of depression and depressive symptoms in adults aged 60 years and over was 27% whereas the highest depression prevalence of 34% was reported in persons older than 80 years [6]. It is also estimated that 8–16% of older adults have

clinically significant depressive symptoms, and 5% experience major depression [7]. In Iranian Turkmens the elderly depression prevalence was 20% [8]. In nursing homes the prevalence can increase up to 95.64% [9].

Vitamins play an important role in the functions of the body [10]. Vitamin D is accessible in enriched nutritional and supplements as ergocalciferol-D2 and cholecalciferol-D3. Central nervous system, including the amygdala -the area that controls emotions and behaviors in humans- has receptors for vitamin D and its enzyme activators. Some believe that vitamin D might affect depressive symptoms [11]. An experimental study showed that mice that were fed a vitamin D deficient diet for 10 weeks had reduction in the enzymes involved in GABA synthesis and displayed altered behavior, and an enhanced response to aversive stimuli such as heat and sound. This was accompanied by alterations in amino acid metabolism within the brain [12].

Vitamin D can be supplied through sun exposure, but studies show that vitamin D deficiency is very common [13,14], and many

[☆] This clinical trial has been registered on the Iranian Registry of Clinical Trials website with the number: IRCT201604252758N1. <http://www.irct.ir/trial/22570>.

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need vitamin D supplementation [15]. The studies about the relationship between vitamin D and depressive symptoms have different results. A study in the United States, suggested that low vitamin D levels were associated with depression although the subjects were between 15 and 39 years old [16]. The cross-sectional study in older adults, showed that the prevalence of depression was twice in seniors with low vitamin D levels compare to those without deficiency [17]. But two major studies in adults in United States and China showed no relationship between vitamin D level and depression [18,19]. In a cohort study in the Netherlands there was no effect of vitamin D levels on the course of depression or remission rates in older persons [20]. Almeida showed that Vitamin D deficiency was associated with current depression, although this study did not support the role for vitamin D in the causation of depression [21]. Given the conflicting and different results about the relationship between vitamin D and elderly depression, a meta-analysis was conducted by Anglin in 2013. In this study a slight association between depression and low levels of vitamin D was found. The researchers noted that studies on the impact of vitamin D intervention in the treatment or prevention of depression are necessary [22].

There are few clinical trials about the effect of vitamin D on depressive symptoms in older adults. In a systematic review in 2014, all the intervention studies on the effect of vitamin D on depression were evaluated. Only seven clinical trials were found. The results of the meta-analysis showed that the total effect of vitamin D was negligible and not significant. The researchers concluded that this issue needs further investigation [23]. Another meta-analysis in 2015, reported no significant reduction in depression following vitamin D supplementation [24]. The most recent review in elderly population showed an inverse association between vitamin D blood level and depression in observational studies but only one clinical trial showed the significant difference in depression after vitamin D prescription [25].

It seems that there are several meta-analysis and systematic reviews in this field that have used the limited number of repeated and inconsistent studies for their conclusions. The older adults have not been target population, and the duration of the intervention has not been adequate in many studies. Some researchers have used the daily supplement of vitamin D that decrease the compliance of the subjects and to our knowledge there was no clinical trial about vitamin D and depression in older adults in Iran.

Prevention and treatment of depression in elderly population is a crucial issue and vitamin D might have a potential impact on depression. Few randomized placebo-clinical trials (RCTs) have been done to examine the effect of vitamin D supplement in treatment of depression in older adults, so the aim of this clinical trial was to investigate the effect of vitamin D supplementation on the severity of depression in elderly population in 2016–2017.

2. Materials and methods

2.1. Participants

This randomized placebo-controlled trial was conducted in 3 psychiatric clinics, during March 2016 to February 2017. For estimating sample size, the type 1 (α) and type 2 errors (β) of 0/05 and 0/20 (power = 80%) were calculated respectively. We reached the sample size of 40 participants for each group using the suggested formula for parallel clinical trials. In this study we included patients aged over 60 years who were under treatment for depression. Other inclusion criteria were Iranian citizenship, the ability to speak Farsi and answer the questions, no history of mental illness other than depression, no history of physical disability, and GDS- Geriatric Depression Scale- score above 5 that represents moderate to severe

depression. The subjects that were uncooperative and refused to continue the treatment and those with severe stress such as hospitalization or death of relatives were excluded from the study.

The eligible patients were randomly assigned to vitamin D group ($n = 40$) or placebo ($n = 40$) for 8 weeks. Random assignment was done by computer-generated random numbers. Randomization and allocation were concealed from researcher and participants until the main analyses were completed. A trained nurse at the psychiatric clinic, assigned participants to intervention and control groups randomly.

Ethical statement: This study was done according to guidelines published in the Declaration of Helsinki. This study was approved by the ethics committee of the X University of Medical Sciences with the grant NO: 93160 and registered on the Iranian Registry of Clinical Trials website with the number IRCT201604252758N1. Written informed consent was obtained from all study subjects before commence recruitment.

2.2. Study design

Individual in vitamin D group received 50,000 units of vitamin D3 pearl weekly for 8 weeks at the mealtime. Individuals in the placebo group received placebo weekly in the same time. The vitamin D3 supplement and its placebo were produced by Osvah pharmaceutical corporation, Tehran, Iran. Routine treatments for depression were continued for both groups. The appearance of the supplement and placebo was identical (i.e. Size, packaging and shape). Vitamin D3 and their placebo were packed in the same packages and coded by the producer to insure blinding. Participants were asked not to change their routine physical activity or usual dietary intakes during the study. Adherence to vitamin D3 supplement checked by asking the patients to bring the medication containers, and counting the remained pearls.

2.3. Measurements

For vitamin D measurement, at the baseline and after 8 weeks of the intervention, 5–6 ml non-fasting venous blood samples were taken at the University laboratory. Serums were sent to the Vakili's Laboratory. The 25-OH vitamin D3 was determined by DiaSorin LIAISON 25 OH Vitamin D TOTAL Assay uses chemiluminescent immunoassay (CLIA), (brand: Diasorin S.P.A, Italy, build number: 133193 and expiration date: 19/4/2017). The 25-OH vitamin D level less than 30 ng/ml was considered as deficiency and 30–100 ng/ml as normal range [26].

Geriatric Depression Scale-15 (GDS-15) was used for assessment of depression. GDS has been developed by Yesavage and Brink in 1983, and it has been translated and used extensively in different countries [27]. The GDS-15 has been translated into Farsi by Malakouti. In his study on 204 older adults in Iran, its internal consistency (alpha-cronbach index), and split-half coefficients were reported to be 0.9, and 0.89 respectively. The factor analysis also approved the construct validity of this questionnaire [27]. This instrument has been used in some other studies in Iran [28–30]. This scale has 15 dichotomous items. One can get the score between 0 and 15 from this scale. The score above 5 suggests mild to moderate depression, and score above 10 is indicating severe depression [31].

2.4. Statistical analysis

The normality of the variables was evaluated by using Kolmogorov–Smirnov test. The demographic characteristics of the participants in vitamin D and placebo groups such as sex and education were compared with chi-square test, the depression severity as category was analyzed by Fisher's exact test. Vitamin D

level and depression scores were used as outcome variables. The vitamin D level before intervention in vitamin D group, depression before intervention in placebo group and difference in vitamin D and depression in both groups were not distributed normally so the differences of vitamin D levels, and GDS scores between groups were analyzed using Mann Whitney U test, and values before and after intervention were analyzed using Wilcoxon signed ranks test.

Depression score after intervention had normal distribution and it was considered as dependent variable in multiple regression analysis. The other variables that showed correlation with dependent variable or theoretically could explain the depression were entered to the multiple regression analysis. These variables were depression before intervention, vitamin D levels before and after intervention, group of intervention, sex, gender and duration of depression. All analyses were conducted with SPSS version 16 (SPSS Inc., Chicago, Illinois). $p < 0.05$ was used to identify statistical significance.

3. Results

Only one individual in each group declined to participate in the study and finally 78 individuals (vitamin D [N = 39] and placebo [N = 39]) completed the trial (Fig. 1). For those who completed the trial (n = 78), the pearls counts showed 100% adherence in both groups.

The mean \pm SD age of subjects in vitamin D Group was 68.7 years (± 7) and 67 years (± 6.3) in placebo group, and almost half of each group were female. The vitamin D and placebo groups had no significant difference in sex, age, the history of diabetes and

hypertension, and severity of depression. The participant's characteristics can be seen in Table 1.

All the patients had vitamin D deficiency (vitamin D level less than 30 ng/ml) before intervention. The mean baseline 25(OH)D3 concentration was 22.57 ± 6.2 ng/ml in vitamin D and 21.2 ± 5.8 ng/ml in placebo group ($p = 0.16$). The Vitamin D increased to 43.48 ± 9.5 ng/ml in vitamin D and 25.9 ± 15.3 ng/ml in placebo group. Both groups showed significant increase in vitamin D concentration although the increase was about 4 times greater in vitamin D Group (Table 2). After intervention 36 subjects (92.3%) in vitamin D group and 11 subjects (29.7%) in placebo group had normal level of vitamin D concentration.

The Depression score decreased from 9.25 to 7.48 in vitamin D group ($p = 0.0001$), while there was a non-significant increase in depression score in placebo group ($p = 0.867$). Before intervention the severe depression (GDS > 10) was not significantly different in the groups. After intervention no patients in vitamin D group showed severe depression but 10 patients (25.6%) in placebo group had severe depression ($p = 0.001$) (Table 3). The analysis showed that vitamin D supplementation was associated with improvement in depression score in elderly patients. No adverse effects were reported during the trial.

The multiple regression analysis showed that the intervention group and the score of depression before study were the variables that could explain 81.8% of depression score after intervention ($R = 0.905$, R square = 0.818, Adjusted R Square = 0.8, p value = 0.0001). The other variables did not make a significant contribution (Table 4).

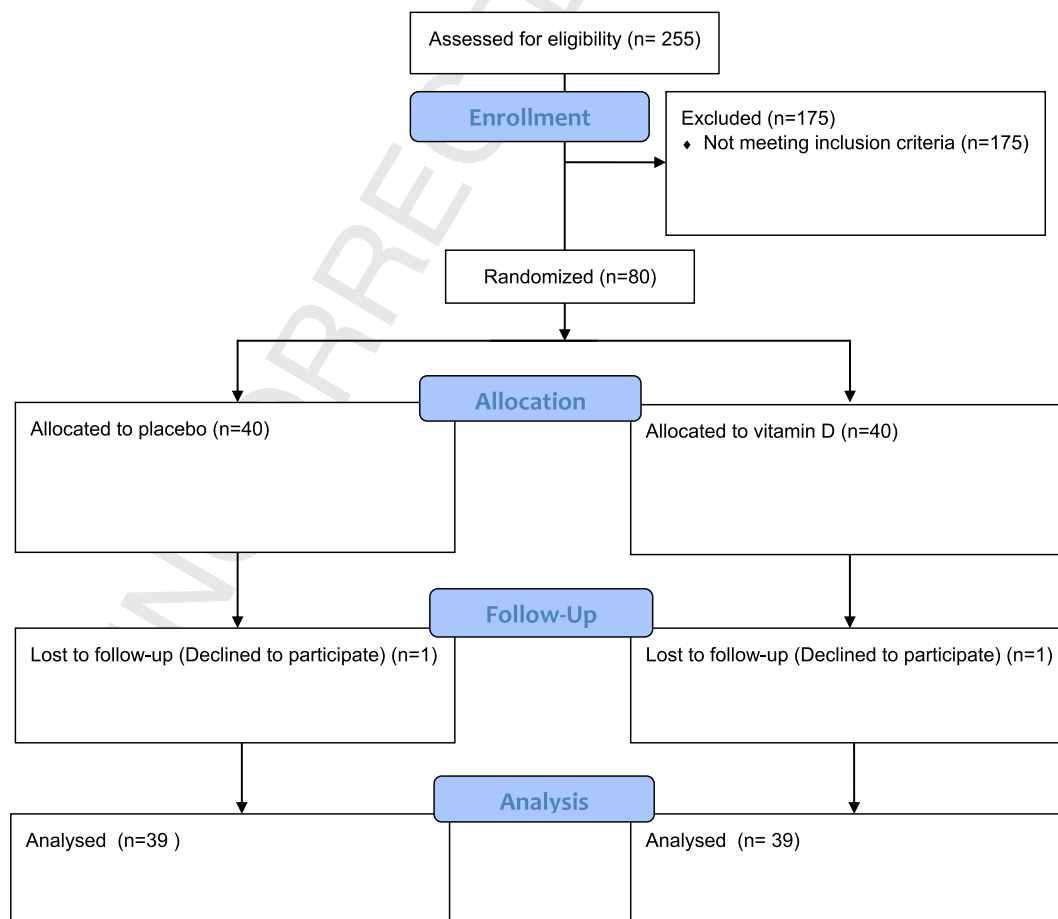


Fig. 1. Summary of participant's flow diagram. Individual in the vitamin D group Received 50,000 U vitamin D3 pearls weekly for 8 weeks, and those in placebo group received placebo.

Table 1
The patients' characteristics in Intervention and control groups.

Variables	Vitamin D supplementation	Placebo	P value
Sex N (%)			
Male	20 (51.3)	19 (48.7)	0.821
Female	19 (48.7)	20 (51.3)	
Education N (%)			
Illiterate	18 (46.2)	14 (35.9)	0.783
Under diploma	17 (43.6)	19 (48.7)	
Diploma and higher	4 (10.3)	6 (15.4)	
Hypertension N (%)	20 (51.3)	26 (66.7)	0.167
Diabetes N (%)	15 (38.5)	22 (56.4)	0.112
The history of depression N (%)	20 (51.3)	14 (32.9)	0.171
Age (mean ± sd)	68.7 ± 7	67 ± 6.3	0.313
Duration of depression (mean ± sd)	3.4 ± 3.5	3.1 ± 2.4	0.833

Table 2
Pre and post data for vitamin D status and Geriatric Depression Scale-15 (GDS-15) in vitamin D supplementation and placebo groups.

Groups	Vitamin D supplementation (mean ± sd)	Placebo (mean ± sd)	P value
Vitamin D plasma concentration before Intervention (ng/ml)	22.57 ± 6.2	21.2 ± 5.8	0.160
Vitamin D plasma concentration after Intervention (ng/ml)	43.48 ± 9.5	25.9 ± 15.3	0.0001
P value	0.0001	0.021	
vitamin D plasma concentration Difference (ng/ml)	20.9 ± 9.7	4.9 ± 13.5	0.0001
GDS-15 Scores before intervention	9.25 ± 2.4	8.9 ± 2.3	0.607
GDS-15 scores after intervention	7.48 ± 1.66	9 ± 2.1	0.002
P value	0.0001	0.867	
GDS-15 scores difference	-1.76 ± 1.28	0.027 ± 0.95	0.0001

4. Discussion

In this study vitamin D supplementation could improve the depression scores. There are many vitamin D receptors in hippocampus that is associated to the depression, and vitamin D metabolites can cross the blood–brain barrier. So vitamin D concentration may be effective in treatment of depression. There are some systematic reviews about the vitamin D and depression. In a recent one that has been published in 2016, twenty observational (cross-sectional and prospective) studies and 10 randomized trials were reviewed by Okereke. There was an inverse association between vitamin D blood level and depression in 13 observational studies but only one clinical trial showed the significant difference in depression after vitamin D prescription [25].

RCTs are important to determine whether vitamin D supplementation is an effective treatment for depression. The available

studies have inconsistent results. This may relate to design limitations (small sample size, different age range of subjects, vitamin D dosage and method of administration, and depression measures). Such limitations make it difficult to generalize findings across studies. In 2009, the seminal integrative literature review on vitamin D and the occurrence of depression on older adults determined the relationship between vitamin D and depression to be largely circumstantial [30]. So the details in the methodology of clinical trials and the precise protocol of systematic review have crucial role in the findings and should be considered in any interpretation [32]. Farrington in her systematic review suggested that further research is needed with tightly controlled variables related to age, gender, diet, seasonality, geographic location, measurement strategies, and existing clinical treatment of geriatric depression [30]. Current research might be valuable for geriatric practitioners because we limited our study to elderly patients with recognized depression that were currently under treatment.

Table 3
Number (%) of patients diagnosed with moderate/Severe depression according to the GDS-15 score values (Geriatric Depression Scale-15 score 5–10 = Mild to moderate depression; >10 = Severe depression).

GDS-15 Scores*	Vitamin D supplementation N (%)	Placebo N (%)	P value
Before intervention			
Moderate depression	26 (66.7)	27 (69.2)	0.678
Severe depression	13 (33.3)	12 (30.8)	
After intervention			
Moderate depression	39 (100)	29 (74.4)	0.001
Severe depression	0	10 (25.6)	

Table 4
Multiple linear regression analysis using post-intervention Geriatric Depression Scale-15 (GDS-15) scores as dependent variable.

Independent Variables	B	Standard Error	Beta	t	P value
Constant	-0.387	1.521		-.254	.800
GDS-15 scores before intervention	.696	.047	.808	14.748	.000
Intervention group (Vitamin D and Placebo)	1.571	.265	.384	5.931	.000
Vitamin D plasma concentration before intervention	.000	.020	.000	-.006	.995
Vitamin D plasma concentration after intervention	-.008	.010	-.057	-.781	.437
Age	.001	.017	.004	.066	.948
Sex	-.025	.223	-.006	-.111	.912
Duration of depression	.043	.039	.063	1.095	.277

Recent studies focus on comparing the effects of an antidepressant and vitamin D supplementation with the patients receiving only an antidepressant [33]. Current study also used the same design and patients continue to receive their usual antidepressant treatments.

In a cohort study in England the researchers found that participants with common mental disorders (depression, anxiety, panic, phobia) showed inverse associations of vitamin D level with depression and panic at 45 years old. The association between vitamin D and risk of depression was non-linear in other age groups [34]. This study showed that there might be more complex relationship between vitamin D and depression than thought before. We limited our study to the patients aged over 60 years; this might help to limit the effect of age on the results because most of the previous studies were used wider age groups.

In current study the researchers were successful in improving the vitamin D blood levels in intervention group. One of the reasons might be the weekly prescription of the supplement that is easy and increase the compliance of the patients. Many interventional studies have used the daily usage of vitamin D that can decrease their effects [35–38]. There was a significant increase in vitamin D level in placebo group. The study started in March that is concurrent with the long and sunny days. Most of the patients were recruited to the study in spring and summer time so the increase in vitamin D level in control group might be due to sun exposure, although the increase was far less than intervention group. The mild increase in vitamin D level in control group did not show significant effect on depression score and its severity. It might show that there must be a certain level of vitamin D concentration, before expecting any antidepressant effects.

Vitamin D supplementation is a cost-effective method with rare side-effects and with potential antidepressant effects according to our findings. Vitamin D have other benefits such as improvement of muscle and skeletal performance, and relieving fatigue [39]. A clinical trial showed that vitamin D supplementation can decrease the musculoskeletal pain [40]. We recommend the evaluation of vitamin D serum levels in older adults with depressive symptoms and prescription of vitamin D supplements for at least 8 weeks in patients with deficiency, it is a safe recommendation since vitamin D toxicity (above 100 ng/ml) [41] is rare and this prescription might have other benefits for older people. Practitioners also can safely instruct their patients to have more sun exposure.

This study had some limitations; first there were some confounding variables that we could not control sufficiently such as the severity of depression, the depression treatment, sun exposure of the subjects, history of depression, cross contamination between intervention and control group, and possible use of supplements by control group. We tried to control these variables by random allocation of the subjects to placebo and intervention groups.

In conclusion vitamin D supplementation significantly decreased GDS score in older adults. According to our findings the older adults who are under treatment of depression could clinically benefit from vitamin D prescription. Although, there is a need for more well designed randomized clinical trials in this field.

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Statement of authorship

All persons who meet authorship criteria are listed as authors, and all authors have participated sufficiently in the work to take public responsibility for the content, including participation in the

concept, design, analysis, writing, or revision of the manuscript. Negin Masudi Alavi prepared the final draft. Saeed Khademalhosseini contributed to data collection. All authors read and approved the final version of the paper.

Conflicts of interest

The authors declare that there is no conflict of interest reacted to this manuscript.

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