REVIEW ARTICLE
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Effect of vitamin D supplementation on depression treatment

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INTRODUCTION

Depression is a mental disorder that has drawn attention because of its high incidence. The World Health Organization (WHO) reported that the number of cases of depression increased by 18% between 2005 and 2015; 322 million people have depression globally, and most of them are women. In Brazil, depression affects 11.5 million people (5.8% of the population)[1].

Depression is characterized by the impairment of the physical and mental states of an individual. Its main symptoms are constant sadness, lack of energy, irritability, anxiety, and loss of interest in activities that usually produce a feeling of pleasure, low self-esteem, and changes in sleep and appetite. For the diagnosis of depression, symptoms should persist for at least 2 weeks[2,3].

Depression is also associated with serious disabilities, mortality, and medical expenses. Despite the development of biological, psychological, and environmental theories, the underlying pathophysiology of depression is still unknown and may involve several mechanisms[4,5].

There has been a long-standing interest in the role of nutrition and its relationship to depression; some studies have shown a strong relationship between vitamin D and depression. Several dietary factors have been implicated in the development and treatment of depression. The changes in vitamin D receptors impact several brain neurotransmitters and, therefore, suggest a potential role of vitamin D in causing and correcting mood disorders[6].

Vitamin D is involved in several brain processes, including neuroimmune regulation, neurotrophic factor regulation, neuroprotection, neuroplasticity, and brain development. Therefore, biologically speaking, this vitamin may be related to depression, and its supplementation may play an important role in the treatment of the disease[7,8]. Therefore, this study aimed to review the recent literature on the effect of vitamin D supplementation in the treatment of patients with depression.

METHODS

A systematic review of vitamin D supplementation in patients with depression was performed. For the guiding question, the PICO strategy was used, which represents the population (P) to be studied, the intervention (I), comparison (C), and outcome (O). The question to be raised was whether vitamin D supplementation, compared with placebo, helps in the treatment of patients with depression. Each PICO item represents an element: (P) patients with depression, (I) vitamin D supplementation, (C) placebo, and (O) improvements in patient health.

The review was carried out from September to December 2020 and included all articles published up to the time of the research retrieved from the PubMed, SciELO, and ScienceDirect databases. The following combination of descriptors was used in the search for articles: supplementation and (depression or depressive symptoms) and vitamin D registered in the Medical Subject Headings.

Original articles and randomized (RCTs) and placebo-controlled clinical trials addressing vitamin D supplementation

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in patients with depression with different clinical conditions and at different ages were included. Duplicate original articles and articles that could not be accessed were excluded. The research was registered with the Research Coordination of the UNINOVAFAPI University Center under case number 104/2020.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was used to ensure the quality of this study. For the quantitative analysis and risk of methodological bias, the Jadad scale was used to classify articles from 0 to 5 based on the methodological criteria and adequacy of results, and the Cochrane collaboration tool was used to classify articles with a low risk of bias, high risk of bias, and uncertain risk of bias.

RESULTS

The bibliographic research, according to the pre-established strategy, resulted in 830 articles. Of these, 46 were from the PubMed database, 784 were from ScienceDirect, and 0 were from SciELO. After the duplicate article selection and removal process, six original RCTs were identified as eligible for this systematic review. Figure 1 shows the flowchart of the search results for the sources of information and the selection and inclusion of original articles in the systematic review, according to the PRISMA protocol.

The clinical trials showed a homogeneous methodological quality based on the risk of bias assessment using the Cochrane tool (Table 1)[9-14]. Random generation and allocation concealment were adequately reported in 83.35% (5/6) of the studies; blinding of participants and professionals was reported in 100% (6/6) with a low risk of bias; blinding of the outcome evaluators was reported in 50% (3/6) with a low risk of bias; incomplete outcomes were reported in 66.66% (4/6) with a low risk of bias; selective outcome reporting was reported in 100% (6/6) with uncertain risk of bias; and other sources of bias were reported in 16.6% (1/6) with low risk of bias. Table 1[9-14] presents the results of the quality assessment of the articles analyzed according to the Jadad scale. Regarding the items assessed, all articles adequately described the aspects assessed using that scale.

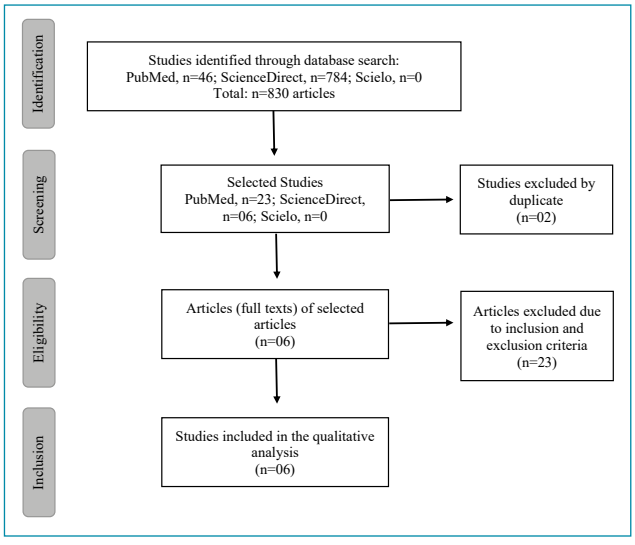

Figure 1. Flowchart for the database search and screening, eligibility, and inclusion of articles in the systematic review.

The data presented in Table 2[9-14] integrate the results of the articles reviewed, including authors, year of publication, study sample size, dose, assessment instrument, duration of supplementation, and main outcomes. The supplemental doses of vitamin D ranged from 2,800 to 50,000 IU, and the duration of intervention ranged from 8 weeks to 2 years.

The main variable investigated was the relationship between vitamin D supplementation and depressive symptoms. Three studies showed a positive effect of supplementation on disease activity, and three studies showed no improvement in disease activity after supplementation.

DISCUSSION

Of the clinical trials present in this review, three found improvements with the use of vitamin D supplementation in depression symptoms: Alavi et al.[11], Omidian et al.[13], and Zheng et al.[14] Three other studies found no improvement: Hansen et al.[9], Marsh et al.[10], and Kjærgaard et al.[12]

Hansen et al.[9] randomized patients with depression into two groups (intervention or control) in blocks of four to receive vitamin D (70 µg vitamin D3 [2,800 IU]) or placebo for 12 weeks. At baseline, 23 patients had a normal 25-hydroxyvitamin D (25(OH)D) concentration (≥50 nmol/L), 22 had insufficiency (<25 nmol/L), and 17 had deficiency (25–50 nmol/L). At the end of the treatment, vitamin D supplementation did not reduce the symptom scores among the patients with depression. The study may not have shown significant outcome data, as they did not reach the estimated sample size and did not exclusively include patients with low vitamin D content.

In the study by Marsh et al.[10], the participants were allocated in a 1:1 ratio. The participants received 5,000 IU vitamin D3 (cholecalciferol) capsules daily or placebo for 12 weeks. The mean serum 25(OH)D concentration increased by 9.9±8.2 ng/mL in vitamin D in the supplemented group and by 1.3±4.3 ng/mL in the placebo group for 12 weeks. At the end of the experiment, there was no improvement in the symptoms of depression with treatment relative to placebo. The absence of

Table 1. Analysis of methodological quality and risk of bias according to the Cochrane collaboration and Jadad scale.

Cochrane tool						
Variables	Hansen et al.[9]	Marsh et al.[10]	Alavi et al.[11]	Kjaergaard et al.[12]	Omidian et al.[13]	Zheng et al.[14]
Random Sequence Generation	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Uncertain bias risk	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants and professionals	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of outcome evaluators	High risk of bias	Uncertain bias risk	Uncertain bias risk	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcomes	Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	Low risk of bias
Selective outcome report	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk	Uncertain bias risk
Other sources of bias	High risk of bias	Low risk of bias	High risk of bias	Uncertain bias risk	Uncertain bias risk	High risk of bias
Jadad scale						
Variables	Hansen et al.[9]	Marsh et al.[10]	Alavi et al.[11]	Kjaergaard et al.[12]	Omidian et al.[13]	Zheng et al.[14]
Was the study described as randomized?	Yes	Yes	Yes	Yes	Yes	Yes
Has randomization been described and is it adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any comparisons between the results?	Yes	Yes	Yes	Yes	Yes	Yes
Have comparisons and results been described and are they adequate?	Yes	Yes	Yes	Yes	Yes	Yes
Have losses and exclusions been described?	Yes	Yes	Yes	Yes	Yes	Yes
Total	5	5	5	5	5	5

results in the study may be related to the small number of participants, low concentrations of vitamin D supplementation, and the short period of the study.

Alavi et al.[11] randomly assigned eligible participants to receive vitamin D (n=40) or placebo (n=40) for 8 weeks. The vitamin D group received 50,000 units of vitamin D3 weekly for 8 weeks at mealtime, and the control participants received a placebo weekly at the same time. All patients had vitamin D deficiency (vitamin D concentration of less than 30 ng/mL) before the intervention. The mean baseline 25(OH)D3 concentration was 22.57±6.2 ng/mL in the vitamin D group and 21.2±5.8 ng/mL in the placebo group (p=0.16). Vitamin D increased to 43.48±9.5 ng/mL in the vitamin D group and 25.9±15.3 ng/mL in the placebo group. Both groups showed a significant increase in vitamin D concentration, although the increase was approximately fourfold greater in the vitamin D group. After the intervention, it was observed that vitamin D supplementation was effective in reducing depression scores in people aged 60 years or older. The results of the study may have been positive, as all participants had vitamin D deficiency

Table 2. Synthesis of studies evaluated regarding the effect of vitamin D supplementation in aiding the treatment of depression.

Authors	Sample	Variables analyzed	Intervention	Outcome
Hansen et al.[9]	n=62	- To examine whether vitamin D3 supplementation in patients with depression would result in improved disease activity. - Assessment instrument: International Classification of Diseases (CID-10) (F32.X).	- Randomization: 2,800 IU of vitamin D3 or placebo. - Duration: 12 weeks.	- No significant reductions in depression scores were found.
Marsh et al.[10]	n=33	- To examine improvements after vitamin D3 supplementation in bipolar depression activity. - Reduction in mood elevation or anxiety symptoms. - Assessment instrument: Hamilton Anxiety Rating Scale, Young Mania Rating Scale.	- Randomization: 5,000 IU vitamin D3 or placebo. - Duration: 12 weeks.	- There was no significant reduction in depressive symptoms. - Vitamin D supplementation did not improve reduction in mood elevation or anxiety symptoms.
Alavi et al.[11]	n=78	- To examine the effect of D3 supplementation in the treatment of depression in the elderly population. - Assessment tool: Geriatric Depression Scale-15 questionnaire and 25-hydroxyvitamin D3 to assess the level of depression.	- Randomization: 50,000 IU vitamin D3 or placebo. - Duration: 8 weeks.	- Vitamin D supplementation can improve depression scores in people aged 60 years and older.
Kjaergaard et al.[12]	n=344	- To examine improvements after vitamin D3 supplementation in patients with low serum levels of 25-hydroxyvitamin D. - Low and high serum levels of 25-hydroxyvitamin D. - Assessment instrument: Beck Depression Inventory, Hospital Anxiety and Depression Scale, Seasonal Pattern Rating Scale, and Montgomery-Åsberg Depression Rating Scale.	- Randomization: 40,000 IU vitamin D3 or placebo. - Duration: 6 months.	- No significant effect of vitamin D supplementation was found on depressive symptom scores. - Low serum 25-hydroxyvitamin D levels are associated with depressive symptoms, but no effect was found with vitamin D supplementation.
Omidian et al.[13]	n=68	- To examine the effect of vitamin D3 supplementation in type 2 diabetes mellitus patients with depressive symptoms. - Assessment instrument: Beck Depression Inventory-II (BDI-II-PERSIAN).	- Randomização: 4,000 IU vitamin D3 or placebo. - Duration: 12 weeks.	- Vitamin D supplementation in diabetes mellitus type 2 patients may protect these patients against the onset of major depressive disorder.
Zheng et al.[14]	n=413	- To examine the effect of vitamin D3 supplementation in patients with knee osteoarthritis with depressive symptoms. - Assessment instrument: Patient Health Questionnaire (PHQ-9, 0-27).	- Randomization: 50,000 IU vitamin D3 or placebo. - Duration: 8 weeks.	- Vitamin D supplementation can improve depression scores in people aged 60 years and older.

before the intervention, and the supplemented dose was higher than in other studies.

Kjærgaard et al.[12] studied participants with low and high serum 25(OH)D concentrations and a randomized clinical trial comparing placebo or 40,000 IU vitamin D supplementation for 6 months. In this intervention study, there was no significant effect of high-dose vitamin D on depressive symptom scores. The study had some limitations that may have contributed to its negative results, such as a short study period, distribution of participants in groups, and the exclusion of participants with high scores for depression from the intervention. Consequently, most participants had no or only mild depressive symptoms. This may have influenced the results, as participants who were not sick were more likely to respond to the placebo.

In a study by Omidian et al.[13], randomized type 2 diabetes mellitus patients with depressive symptoms were divided into two groups to receive 4,000 IU vitamin D or placebo. The results of this study showed that vitamin D supplementation is effective in improving depressive symptoms in patients with type 2 diabetes and mild-to-moderate depressive symptoms. Vitamin D supplements significantly improve depressive symptoms, and they also significantly decrease HbA1c, insulin, and TG concentrations in diabetic patients with vitamin D deficiency. A suggested mechanism for this effect may be related to vitamin D and insulin secretion, as vitamin D facilitates the release of insulin from beta-cells.

Zheng et al.[14] studied randomized patients to verify the effect of vitamin D supplementation on depressive symptoms in patients with knee osteoarthritis (OA). The participants were randomized in a 1:1 ratio to receive a 50,000 IU vitamin D3 oral capsule or placebo monthly for 24 months. The serum 25(OH) D concentrations increased from 43.7±11.8 to 84.5±17.3 nmol/L in the vitamin D group and increased from 43.8±12.7 to 50.6±17.5 nmol/L in the placebo group. The study concluded that vitamin D supplementation and the maintenance of vitamin D at sufficient concentrations above 24 months may have beneficial effects on depression symptoms in patients with knee OA. The study results suggest that vitamin D supplementation may have a positive effect on depressive symptoms when serum vitamin D concentrations become optimal. The study hypothesized that vitamin D may have a neuroprotective effect on the brain when vitamin D deficiency is corrected.

The studies analyzed in this review show that the initial vitamin D status (deficient or normal) may have been one of the factors that most influenced the improvement of depressive symptoms in patients. In addition, the severity of depressive symptoms, sample size, age of the individuals, dose of vitamin D offered, and duration of the intervention may have contributed to the outcome of the results.

CONCLUSIONS

The results of the studies indicated that vitamin D can improve depressive symptoms; however, this improvement depends on several factors such as dose and duration of supplementation as well as the initial state of health of the patient before supplementation. We emphasize the need for more clinical studies to verify the most efficient forms of supplementation for different clinical conditions.

AUTHORS' CONTRIBUTIONS

RTM: Project administration, Conceptualization, Data curation, Formal analysis, Investigation, Methodology Writing – original draft, Writing – review & editing. **LARLR:** Project administration, Conceptualization, Data curation, Formal analysis, Investigation, Methodology Writing – original draft, Writing – review & editing. **LMF:** Data curation, Formal analysis, Investigation, Writing – review & editing, Supervision. **JMC:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **LCCL:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **OSRF:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing. **KMGF:** Data curation, Formal analysis, Investigation, Supervision, Writing – review & editing.

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