Review Article

Depression and vitamin D deficiency: A review

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ABSTRACT

Depression is the most common of all mood disorders. It has a neurobiological basis. Recently, vitamin D deficiency has been proposed as one of the contributors to the etiology of depression. Evidence has been favoring vitamin D deficiency as a causative reason for depression. Limitations in the studies that have been done so far warrant further research defining the role of vitamin D deficiency in depression. Management of depression in vitamin D deficiency consists of supplementation of the vitamin and antidepressants. Careful consideration should be done while choosing antidepressants as some of the antidepressants have been found to be associated with osteoporosis.

Key words: Antidepressants, Depression, Supplementation, Vitamin D deficiency

INTRODUCTION

Unipolar depression is the most commonly reported mood disorder. It may manifest as a single episode or as recurrent episodes. It presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Depression has a high lifetime prevalence ranging from 2% to 15% and is associated with substantial disability.[1] Depression affects an estimated 350 million people today. The World Mental Health Survey conducted in 17 countries found that on average about 1 in 20 people reported having an episode of depression in the previous year. At its worst, depression can lead to suicide. Almost 1 million people commit suicide yearly which translates to 3000 suicide deaths every day. For every person who completes a suicide, 20 or more may attempt to end his or her life.[2]

Vitamin D deficiency is defined as a serum 25-hydroxyvitamin D (25(OH)D) level of <20 ng/mL (50 nmol/L), and insufficiency is defined as a serum 25(OH)D level of 20-30 ng/mL (50-75 nmol/L). Today vitamin D deficiency is still a nutritional deficiency which is under-diagnosed and under-treated despite being of pandemic proportions.[3] Studies across India have reported vitamin D deficiency as high as 70-100% of apparently healthy individuals. Even apparently well young soldiers and sportswomen with adequate intake (AI) of calcium, sun exposure, and regular exercise were vitamin D deficient.[4-6]

NEUROBIOLOGY OF DEPRESSION

Psychological and biological factors both could enter into the causation of depressive and other mental disorders. Adolf Meyer coined the term psychobiology to emphasize this. Over the years, many theories have been proposed to emphasize the biological basis of depression.

Norepinephrine-containing neurons are involved in many functions that are profoundly disturbed in melancholia such as mood, arousal, appetite, reward, and drives. A formal hypothesis connecting depletion or imbalance of biogenic amines (specifically norepinephrine) and clinical depression has been proposed.[7,8] A serotonin counterpart of this model has also been proposed. Both catecholamine and indoleamine hypotheses were essentially based on two sets of pharmacological observations. First, reserpine precipitates clinical depression in some patients. Second, antidepressant medications, which alleviate clinical

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depression, raise the functional capacity of the biogenic amines in the brain.[9,10] Furthermore, a permissive biogenic amine hypothesis in which serotonin deficits permit the expression of catecholamine-mediated depressive, or manic states have also been explained.[11]

It has been hypothesized that neurotransmitter deficits may underlie the disinhibition of the hypothalamic–pituitary–adrenal axis, characterized by steroidal overproduction in depression. Impaired glucocorticoid and mineralocorticoid receptor function have been shown in these disorders.[12]

Coppen collected data that appear to be compatible with the hypothesized movement of excess sodium into the neuron during an episode of mood disorder and redistribution toward the pre-illness electrolyte balance across the neuronal membrane during recovery. Intraneuronal sodium leakage is postulated in both depressive and manic disorders but is regarded to be more extreme in mania.[9] Lithium is known to replace intracellular sodium and hyperpolarize the neuronal membrane, thereby decreasing neuronal excitability. Goodwin and Jamison first showed that a substantial minority of depressed patients with a bipolar substrate respond to lithium salts, which further supports the concept of a neurophysiological common denominator to mania and depression.[13]

European studies have shown that depressed patients are phase advanced in many biological rhythms, including the latency to the first rapid eye movement (REM) in sleep. Shortened REM latency has been proposed as another laboratory "test" for depressive disorder.[14]

Yet another hypothesis states that the electrophysiological substrates could be so kindled that an oligoepisodic disorder initially triggered by environmental stressors could assume an autonomous and polyepisodic course. It was hypothesized that neuronal perturbations in the early course of mood disorders get incorporated into the DNA.[15]

VITAMIN D, NEUROPHYSIOLOGY AND DEPRESSION

Vitamin D is a unique neurosteroid. Its deficiency can lead to depression by various mechanisms (Table 1). However, all evidence are not in favor of vitamin D deficiency causing depression, and the matter is far from settled (Table 2).

Various brain processes such as neuroimmunomodulation, regulation of neurotrophic factors, neuroprotection, neuroplasticity, and brain development involve vitamin D.[16] Those areas of the brain such as the cingulate cortex and hippocampus which have been implicated in the pathophysiology of depression have been shown to have receptors for vitamin D.[17]

Furthermore, vitamin D regulates the expression of important neurotrophic factors that affect neurotransmission and synaptic plasticity.[18] Moreover, vitamin D has been shown to be neuroprotective, notably by inducing the synthesis of calcium-binding proteins or by antioxidant mechanisms.[18,19] Vitamin D receptor gene polymorphisms in humans have been associated with cognitive impairment and depressive symptoms.[20] Finally, the immunomodulatory activity of vitamin D has been related to recent evidence that inflammation may play a causal role in depression: Vitamin D has been shown to down-regulate inflammatory mediators, such as nuclear factor-B, which have been linked to sickness behavior, psychosocial stress, and depression.[18,21]

LIMITATIONS OF THE STUDIES

Limitations of meta-analysis

a. In the only meta-analysis mentioned in this review as at the time of review, there was no randomized controlled trial (RCT) of vitamin D for depression. The review was therefore restricted to observational studies, which usually yield lower-quality evidence than RCTs
b. The majority of the cross-sectional studies and cohort studies in the meta-analyses had significant heterogeneity and lacked precision.

Limitations of other studies

a. Studies used variable definitions of vitamin D deficiency, and therefore, the analysis was performed using the lowest versus highest vitamin D categories and different cut-off points rather than adhering to a strict definition of deficiency
b. The depressive symptoms were evaluated based on self-reports (not clinically diagnosed depression) and thus were subject to recall bias
c. The sample was relatively homogeneous in terms of race and ethnicity, potentially limiting the generalizability, or external validity of the findings
d. Some studies used only rating scale to assess the severe of the symptoms without making a prior diagnosis of clinical depression
e. The cross-sectional designs of some studies cannot determine a causal association between vitamin D levels and depressive symptoms

Table 1: Evidence in favor of vitamin D deficiency causing depression

Authors	Type of studies included	Number of patients	Conclusion
Anglin *et al.*, 2013[22]	Meta-analysis	31,424 participants	Increased odds ratio of depression for the lowest versus highest vitamin D categories
Kjaergaard *et al.*, 2012[23]	Nested case-control study and RCT	357 participants in nested case-control study and 243 in RCT	Participants with low 25(OH)D levels at baseline were more depressed (P<0.05) than participants with high 25(OH)D levels
Vieth *et al.*, 2004[24]	Double-blind RCT	110 participants	Improved wellbeing (reduced depression) in patients with vitamin D supplementation
Lansdowne and Provost, 1998[25]	Randomized double-blind study	44 healthy subjects	Vitamin D3 significantly enhanced positive affect and there was some evidence of a reduction in negative affect
Gloth *et al.*, 1991[26]	Prospective, RCT	15 subjects with SAD. Eight received 100,000 I.U. of vitamin D and 7 received phototherapy	Vitamin D status improved in both groups (74% vitamin D group, P<0.005 and 36% phototherapy group, P<0.01). Improvement in 25(OH)D was significantly associated with improvement in depression scale scores (r^2=0.26; P=0.05)
Tolppanen *et al.*, 2012[27]	Prospective cohort study	2752 children	Higher concentrations of 25(OH) D3 assessed at mean age 9.8 years were associated with lower levels of depressive symptoms at age 13.8 years (adjusted RR: 0.90; 95% CI: 0.86-0.95)
Bertone-Johnson *et al.*, 2011[28]	Observational study	81,189 women aged 50-79 years	Women who reported a total intake of ≥800 IU vitamin D had a prevalence odds ratio for depressive symptoms of 0.79 (95% CI: 0.71-0.89; P trend <0.001) compared with women who reported a total intake of <100 IU
Milaneschi *et al.*, 2010[29]	Population-based cohort study	531 women and 423 men aged 65 year and older	Women (hazard ratio: 2.0; 95% CI: 1.2-3.2; P=0.005) and men (hazard ratio: 1.6; 95% CI: 0.9-2.8; P=0.1) with low vitamin D had higher risk of developing depressive mood over the follow-up
Hoogendijk *et al.*, 2008[30]	Population-based cohort study	1182 community residents aged 65 to 95 years	Levels of 25(OH) D were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder compared with levels in 1087 control individuals (P<0.001)
Jorde *et al.*, 2008[31]	Cross-sectional study and randomized double-blind controlled trial	441 subjects (body mass index 28-47 kg/m^2, 159 men and 282 women, aged 21-70 years)	Subjects with serum 25(OH)D levels <40 nmol/L scored significantly higher than those with serum 25(OH)D levels ≥40 nmol/L on the beck depression inventory. In the two groups given vitamin D, but not in the placebo group, there was a significant improvement in BDI scores after 1 year
Hoang *et al.*, 2011[32]	Cross-sectional study	12,594 participants	Higher vitamin D levels were associated with a significantly decreased risk (odds ratio: 0.92; 95% CI: 0.87-0.97) of current depression based on CES-D scores

RCT: Randomized controlled trial, SAD: Seasonal affective disorder, CI: Confidence interval, RR: Risk ratio, BDI: Beck Depression Inventory, CES-D: Center for Epidemiologic Studies Depression, 25(OH)D: 25-hydroxyvitamin D

Table 2: Evidence not in favor of vitamin D deficiency causing depression

Authors	Type of studies included	Number of patients	Conclusion
Sanders *et al.*, 2011[33]	RCT	102 participants	No significant differences between the vitamin D and placebo groups
Bertone-Johnson *et al.*, 2012[34]	RCT	36, 282 postmenopausal women	After 2 years, women randomized to receive vitamin D and calcium had an odds ratio for experiencing depressive symptoms of 1.16 (95% CI: 0.86-1.56) compared with women in the placebo group. The findings do not support a relation between supplementation of vitamin D3 along with calcium and depression in older women
Dumville *et al.*, 2006[35]	Double blind RCT	2117 women	No significant difference between the scores of control and intervention group
Nanri *et al.*, 2009[36]	Health survey	527 workers	Depressive symptoms were not appreciably associated with serum 25(OH)D concentrations

25(OH)D: 25-hydroxyvitamin D, RCT: Randomized controlled trial, CI: Confidence interval

f. Some of the studies had sample sizes that were not sufficiently large to detect a modest association with statistical significance
g. All the cohort studies had problems with bias
h. Some other studies had substantial attrition over time with those who continued to attend the follow-up clinics being more likely to be from higher socioeconomic backgrounds
i. Some studies had a very short time frame to investigate depression, which is a condition that may develop slowly and last for several years, and that only one assessment might not be sufficient since depression often fluctuates over time
j. One of the studies was performed in a general population where people with high scores on the depression scales were excluded from the intervention, and accordingly, the majority of the participants had no or only mild depressive symptoms. This could have influenced the results, since participants, who are not ill, are more likely to respond to placebo, as seen in our *post-hoc* analyses, and not to active therapy.

MANAGEMENT OF VITAMIN D DEFICIENCY

Prevention of vitamin D deficiency

The Institute of Medicine has recommended AI as current daily intake of 200 IU for infants, children, and adults younger than 51 years; 400 IU for adults 51-70 years of age; and 600 IU for adults older than 70 years.[37-39] However, based on recent research suggestions that current AI recommendations for children and adults may be too low to maintain optimal levels (above 30 ng/mL), the American Academy of Pediatrics recently recommended doubling the minimum daily intake for children and adolescents to 400 IU.

Replenishment of vitamin D deficiency

Oral ergocalciferol at 50,000 IU/week for 8 weeks is economical way to replenish vitamin D in deficient individuals. The goal is to achieve a minimum level of 30 ng/ml. If serum 25(OH)D levels have not reached or exceeded the minimum level after this, a second 8-week course of ergocalciferol should be prescribed. If the serum 25(OH)D levels still have not risen malabsorption should be suspected and consultation with a gastroenterologist should be considered. After vitamin D levels are replete, maintenance dosages of cholecalciferol should be instituted at 800-1000 IU/day from dietary and supplemental sources.[40-42]

Treatment of depression

Antidepressant drugs acting on the serotonin system have been linked to reduce the bone mineral density and lead to osteoporosis. Serotonin receptors have been found on all major types of bone cells indicating an important role of the neuroendocrine system in bone. The presence of depression itself increases fracture risk, in relation with decreased bone mineral density (BMD) and an increase in falls. The majority of depressed patients receive antidepressants, mostly selective serotonin reuptake inhibitors (SSRIs) and some of them receive tricyclic agents. These have been associated with decreased BMD and increased fracture risk. This risk is reported to be greatest in the early stages of treatment with a peak within 1 month of initiation for tricyclics and 8 months for SSRIs. It has therefore been suggested that SSRIs and tricyclics should be considered as risk factors for osteoporotic fractures.[43] These risks associated with antidepressants should be kept in mind while prescribing antidepressants to depressed subjects with vitamin D deficient individuals.

CONCLUSION

Depression is the most common mood disorder. Recent findings emphasize the neurobiological basis for this psychiatric illness. Vitamin D has been shown to have receptors on the parts of brain which regulate emotions. Therefore, recent reports of vitamin D deficiency being associated with depression are likely to have a neurobiological basis. Although some studies have refuted this hypothesis, most studies have provided evidence implicating a possible role of vitamin D deficiency in at least some cases of depression. Managing vitamin D deficiency along with depression in these cases is of paramount importance as it seems to be etiologically associated in some cases. The choice of antidepressants in these cases should be carefully considered as some them have been implicated in osteoporosis.

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