Effectiveness of Vitamin D in the Treatment of Mood Disorders: A Literature Review

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Abstract *Depression is a mood disorder that has a significant negative impact on the lives of many individuals. Since vitamin D deficiency is prevalent in the North American population, recent scientific research is investigating the connection between insufficient vitamin D and the pathogenesis of mood disorders, as well as the nutrient's potential as a therapeutic agent. Several epidemiological studies have shown a relationship between low levels of vitamin D and the presence of depression. A small number of intervention trials have found a potential trend toward the reduction of depressive symptoms from vitamin D supplementation; however, many of the studies had limitations which restrict the conclusions that can be drawn. Further research in the field is warranted.*

Background: Vitamin D

Vitamin D is a steroid hormone that plays several important physiologic roles. Some of these actions, including an impact on mood health, have been recently hypothesized and are the subject of investigation. Vitamin D can be obtained from dietary sources such as fish liver oils, fatty fish, egg yolks and fortified milk and it can be synthesized in the skin in response to sun light exposure.[1] While most vitamin deficiencies are rare in the developed world, vitamin D is the only one that remains prevalent.[2,3] People living at northern latitudes receive less sun exposure during the winter. Additionally, cultural trends of increasingly sedentary lifestyles, more indoor activities, and increasing awareness about the risk of excess sun exposure, contribute to vitamin D deficiency.[4]

The main function of vitamin D is the maintenance of blood calcium and phosphorous concentrations to facilitate cellular, neuromuscular and ossification functions through enhancing absorption of these ingested nutrients in the small intestine and by mobilizing bone stores.[1] The consequence of severe deficiency is a condition called rickets which is characterized by severe bone deformation. While fortification of milk has served to decrease the incidence of rickets,[1] many studies have found large percentages of the population to have deficient or insufficient levels of serum vitamin D.[5-7] Inadequate levels have been associated with chronic diseases including osteoporosis, cancer, diabetes, neurodegenerative, autoimmune and infectious diseases.[1] In older adults, de-

ficiency has been associated with decreased physical function, increased risk of fractures, frailty and mortality.[5] In addition to correcting deficiency and treating osteomalacia and rickets,[1] evidence supports the use of vitamin D supplementation in hyperparathyroidism, hypothyroidism,[2] psoriasis,[8] osteoporosis,[9] muscle weakness/pain,[10] fall prevention,[11] immunomodulation,[12] multiple sclerosis,[13] and prevention of cancer[1] and heart disease.[14] The Canadian guidelines for recommended dietary intakes of vitamin D are 600 international units (IU) for individuals aged 1 to 70 and 800 IU for those 71 or older, although higher doses are used in the treatment of some conditions.[15]

Newer research on vitamin D has identified possible mechanisms through which it could affect mood. Vitamin D is able to pass through the blood-brain barrier and its receptors are found widely throughout the brain including the cortex, cerebellum and limbic system.[16] It has been shown to stimulate serotonin, down-regulate glucocorticoid receptor genes which are up-regulated in depressed states and provide a neuroprotective effect.[17] Low vitamin D leads to elevation of parathyroid hormone which is associated with depression. The depression tends to resolve after treatment of the hyperparathyroidism.[18]

Mood disorders

Depression and other mood disorders are a major health concern globally. These disorders have significant impact on quality of life, morbidity and mortality and it has been estimated that by 2020, depression will rank second in global health burden to heart disease based on disability-adjusted years.[16]

Depression is characterized by persistently low mood and feelings of sadness and hopelessness. In Major Depressive Disorder (MDD), this low mood lasts longer than two weeks and is accompanied by other symptoms that include decreased interest or pleasure in activities, changes to weight and sleep, fatigue and impaired concentration and feelings of worthlessness or guilt. People experiencing depression may feel overwhelmed and exhausted, and, as a result, stop participating in their routine activities. Commonly, they may withdraw from family and friends. Patients may also have thoughts of death or suicide.[19] Patients with dysthymia also suffer from chronically low mood lasting at least two years although their symptoms are not as severe as in MDD.[9]

A recent study identified 8.2 percent of Canadians and Americans meet the criteria for MDD. Conventional treatment for depression uses a combination of anti-depressant pharmacotherapy targeted at modulating neurotransmitters and psychotherapy.[19] There is also significant research to support the use of exercise as an effective intervention.[20] Complementary and alternative medical interventions for depression include omega-3 essential fatty acids, tryptophan, S-adenosylmethionine, folic acid, vitamin B_{12} and zinc.[21]

Seasonal Affective Disorder (SAD), another type of depression, is characterized by the development of recurrent depression during the fall or winter. While many of the emotional and cognitive symptoms are similar to those of depression, vegetative symptoms such as increased sleep, appetite, carbohydrate cravings and weight gain are more common in SAD patients compared to a decrease in sleep, appetite and weight in depression patients. Studies have estimated the prevalence to be 1-9% based on different populations and methodologies.[22] It has been hypothesized that changes in serotonin contributes to SAD pathogenesis.[23] While SAD is most often treated with phototherapy, pharmacotherapy and cognitive behavioural therapy have also shown benefit.[24]

Insufficiency and/or deficiency of vitamin D may play a role in the pathogenesis of mood disorders. Supplementation could be an effective antidepressant therapy.[25]

Methods

The Medline (PubMed) database was searched for articles published prior to February 2011 that matched any combination of the following keywords: vitamin D, vitamin D deficiency, 25-hydroxyvitamin D, depression, generalized anxiety disorder,

Figure 1. Observational Studies

Reference	Type of Study	Sample Size	Topic	Results	Conclusion
Berk M, Jacka FN, Williams LJ, et al: Is this D vitamin to worry about? Vitamin D insufficiency in an inpatient sample. *Aust NZ J Psychiatr,* 2008;42:874-878.	Cross-sectional	53	Chart review audit of patients in psychiatric facility where serum 25-hydroxyvitamin D (25OHD) levels were routinely tested	58% of patients had insufficient 25OHD levels and 11% had moderate deficiency (68% and 12% respectively when tested in the winter) compared to 30% and 7.2% of healthy controls	High rates of Vitamin D insufficiency in psychiatric inpatients
Armstrong DJ, Meenagh GK, Bickle I et al: Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol,* 2007;26:551-554.	Cross-sectional	75	Relationship between current levels of 25OHD and anxiety, depression, fibromyalgia-related disability	No relationship between 25OHD status and Fibromyalgia Impact Questionnaire score; Mean Hospital Anxiety and Depression Score among deficiency patients was 31, among insufficient patients was 22.5 and among patients with normal levels was 23.5 ($p<0.05$)	Higher rates of anxiety and depression in fibromyalgia patients were associated with deficient serum 25OHD levels
Wilkins CH, Sheline YI, Roe CM et al: Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatr,* 2006; 14:1032-1040.	Cross-sectional	80	Study of patients with mild Alzheimer's disease and non-demented controls looking for associations between current 25OHD levels and cognitive, mood and physical health	After adjustment was made for age, sex, race and season, significant increase in presence of active mood disorders seen among patients with deficient and insufficient 25OHD compared to controls with adequate levels ($p=0.022$ for deficient and $p=2.54$ for insufficient)	Vitamin D deficiency was associated with lower mood and poorer cognitive performance
Nanri A, Mizoue T, Matsushita Y et al: Association between serum 25-hydroxyvitamin D and depressive symptoms by survey season. *Eur J Clin Nutr,* 2009; 63: 1444-1447.	Cross-sectional	527	Relationship between low 25OHD and depressive symptoms. Serum 25OHD and Center for Epidemiological Studies Depression Scale (CES-D) score assessed in participants from office A in July and participants from office B in November	No significant difference in level of depressive symptoms between the two offices. Among participants in office B, prevalence of depressive symptoms decreased with increasing 25OHD; however, the results did not reach statistical significance	Author concluded that vitamin D was not protective in the pathogenesis of depression

Figure 1. Observational Studies, cont'd

Reference	Type of Study	Sample Size	Topic	Results	Conclusion
Hoogendijk WJ, Lips P, Dik MG, et al: Depression Is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatr*, 2008; 65: 508-512.	Cross-sectional	1,282	Association between depression and serum 25OHD and parathyroid hormone (PTH) levels in older adults	Vitamin D levels were 14% lower in patients with minor depression or major depressive disorder ($p<0.001$). Depression severity (CES-D score) was significantly associated with the decreasing 25OHD and increasing PTH according to quartile of blood levels (both: $p<0.001$)	There was an association between lower levels of vitamin D/higher levels of PTH and higher incidence and severity of clinical depression
Lee DM, Tajar A, O'Neill TW: Lower vitamin D levels are associated with depression among community-dwelling European men. *J Psychopharmacol,* 2010 [Epub ahead of print].	Cross-sectional	3,151	Association between depressive symptoms, serum 25OHD and PTH	Serum 25OHD was significantly lower in men with Beck Depression Inventory-II (BDI-II) scores ≥ 14 (depressed men)	Lower levels of 25OHD were associated with higher BDI-II scores
Reed SD, Laya MB, Melville J et al: Prevalence of Vitamin D Insufficiency and Clinical Associations among Veiled East African Women in Washington State. *J Womens Health* (Larchmt), 2007; 16: 206-213.	Cross-sectional	71	Association between low 25OHD and fatigue, musculoskeletal complaints and depressive symptoms in veiled women	All women had insufficient vitamin D levels: 12.3% severe, 40.9% moderate and 44.9% mildly deficient. When comparing the mean vitamin D levels of pa tients with or without mild/moderate depression symptoms, pain, fatigue and muscle weakness no difference was found	No association exists between the severity of vitamin D deficiency and the presence of depression; however, because all participants were deficient, study could not compare depression levels to those of controls with adequate 25OHD
Stewart R, Hirani V: Relationship Between Vitamin D Levels and Depressive Symptoms in Older Residents From a National Survey Population. *Psychosom Med,* 2010; 72(7): 608-12.	Cross-sectional	2,070	Relationship between low serum 25OHD and depression in the elderly	Patients with <10 ng/mL 25OHD had significantly higher frequency of depression than control	There was an association between low vitamin D levels and depressive symptoms/ clinically signifi cant depression in elderly patients

anxiety disorder, comorbidity, diagnosis and treatment, hypovitaminosis. Articles were screened and those that reported on the relationship between vitamin D insufficiency/ deficiency and psychiatric disorders or related psychiatric conditions were included in **Figures 1** and **2**, (p.129-133).

Discussion

There were 14 studies that fit the criteria parameters; see Figures 1 and 2 (10 cross-sectional, one cohort, one quasi-experiment, four RCTs). Of the 10 cross-sectional studies, eight reported a significant correlation between low levels of 25OHD and the

Figure 1. Observational Studies, cont'd

Reference	Type of Study	Sample Size	Topic	Results	Conclusion
Milaneschi Y, Shardell M, Corsi AM, et al: Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. *J Clin Endocrinol Metab,* 2010;95:3225–3233.	Cohort	639	Cohort study assessing for the development of depression 3 and 6 years after assessment of 25OHD deficiency	Patients with 25OHD levels in the lower two tertiles at baseline had larger increases in CES-D scale than those in the higher tertile. Lower 25OHD levels associated with higher probability of developing depression during follow-up period	Lower levels of serum vitamin D in elderly patients increased the risk of developing depression in the future
Schneider B, Weber B, Frensch A, et al: Vitamin D in schizophrenia, major depression and alcoholism. *J Neural Transm,* 2000; 107:839-842.	Cross-sectional	120	Role of vitamin D status in schizophrenia, alcoholism and major depressive disorder	25OHD and 1,25-dihydroxyvitamin D3 were significantly lower in psychiatric patients than in healthy controls when considering the group as a whole ($p<0.02$). Patients with schizophrenia and depression had lower levels of 1,25-dihydroxyvitamin D3 than patients with alcoholism or healthy controls	Vitamin D status among psychiatric patients had no relationship to the pathogenesis of depression, which was likely the result of confounding factors, such as malnutrition or inadequate sun exposure
Jorde R, Sneve M, Figenschau Y, et al: Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med*, 2008;264:599-609.	Cross-sectional & Randomized Cotrolled Trial (RCT)	441	Relationship between baseline serum 25OHD levels and baseline Beck Depression Inventory (BDI) scores, including subscales 1-13 (mental symptoms) and 14-21(somatic-vegetative symptoms)	When comparing participants with 25OHD <40 nmol/L to remaining participants, the deficient participants had a significantly higher mean BDI score (6.0 vs 4.5) and BDI 1-13 subscale score (2.0 vs 1), ($p<0.01$)	There was a relationship between lower serum 25OHD and increased depression in overweight and obese individuals

presence of mood disorders. Several of these studies involved a large number of subjects, included control subjects and used well validated evaluation tools like the BDI-II. Of the two remaining cross-sectional studies, one showed an inverse relationship between 25OHD and mood, but did not reach statistical significance. The other cross-sectional study compared the severity of vitamin D deficiency with depression, but did not use non-deficient controls as a point of comparison. While these studies suggest a relationship between 25OHD and mood, they do not necessarily give credence

Figure 2. Intervention Studies

Reference	Type of Study	Intervention	Subjects	Assessment of Intervention	Result	Conclusion
Jorde R, Sneve M, Figenschau Y, et al: Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med*, 2008; 264: 599-609.	RCT	Weekly dose of 40,000 IU, 20,000 IU or 0 IU of vitamin D3 plus 500 mg of calcium per day for one year	441 patients with BMI of 28-47, age 21-70	BDI at baseline and after one year of supplementation.	Both vitamin D supplementation groups had significant reductions in mean BDI and subscale scores after one year. In the placebo group, a significant reduction in BDI 14-21 subscale was seen. When comparing BDI change over 12 months in vitamin D vs placebo groups, significant improvement seen in BDI 1-13 score ($p<0.05$) but not using intention to treat analysis ($p= 0.051$)	Supplementation with vitamin D for one year might have a positive effect on depression in overweight and obese individuals 1998; 135: 319-323.
Lansdowne AT, Provost SC: Vitamin D_3 enhances mood in healthy subjects during winter. *Psychopharmacol*, 1998; 135: 319-323	RCT	800 IU, 400IU or 0 IU of vitamin D_3 plus 8000 – 10 000 IU vitamin A for 5 days during the winter	44 healthy participants age 18-43	The positive and negative affect score	Significant improvement in positive affect score in both vitamin D groups ($p<0.001$). The outcomes from the different vitamin D3 doses did not differ significantly. Improvements seen in the negative affect score did not reach statistical significance	Vitamin D supplementation in healthy controls during winter improves positive affect and may decrease negative affect
Shipowick CD, Moore CB, Corbett C, et al: Vitamin D and depressive symptoms in women during the winter: A pilot study. *Appl Nur Res*, 2009; 22: 221-225	Quasi-experimental pre-test, post-test design	5000 IU vitamin D3 per day for 8 weeks during the winter; no control or blinding	6 patients with vitamin D deficiency (<40 ng/mL), age 23-55	BDI-II completed at baseline and after 8 weeks of supplementation	Mean BDI-II score decreased from 31 to 21 ($p = 0.020$)	Supplementation of Vitamin D in deficient population during the winter may decrease depressive symptoms

to the hypothesis that vitamin D deficiency plays a role in the pathogenesis of mood disorders or its potential as a therapeutic agent. It is well known that depressed individuals are more likely to be less physically active[26] and as a result may have lower sun exposure. Additionally, depressed individuals often experience a decrease in appetite and eat poorly, which may result in broad-spectrum nutrient deficiencies, including vitamin D_3.

Figure 2. Intervention Studies, cont'd

Reference	Type of Study	Intervention	Subjects	Assessment of Intervention	Result	Conclusion
Sanders KM, Stuart AI, Williamson EJ, et al: Annual high-dose vitamin D_3 and mental well-being: a randomized controlled trial. *Br J Psychiatry*, 2011; 198: 357-364.	RCT	Annual dose of 500,000 IU of Vitamin D3 or placebo in autumn/ winter	2,317 community dwelling Australian women, at least 70 years of age selected for a trial on fractures	12-item Short Form Health Survey (SF-12) assessing physical and mental components of health; WHO Well-being Index was done in subset of 150 patients	12-item Short Form Health Survey: no difference in physical (41.4 vs. 41.2, p= 0.66) or mental (52.5 vs. 52.6, p= 0.75) scores between treatment and placebo groups. WHO Well-being Index in patient subset: no differences in questionnaire scores or use of medication between treatment and placebo groups and no trend between serum 25OHD and scores	The mental well-being of older women in Australia did not appear to benefit from annual high dose vitamin D supplementation
Vieth R, Kimball S, Hu A, Walfish PG: Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4,000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr J,* 2004; 3: 8.	RCT	95 mcg/ week (600 IU/ day) or 700 mcg/ week (4000 IU/day) of vitamin D3 for one year	112 patients with vitamin D deficiency	Completed brief questionnaire based on screening for depression; 6 questions on mood, energy, sleep, pleasure, concentration, and weight change	In the 4000 IU group, the correlation between wellbeing score and months of being on vitamin D was statistically significant (p=0.002). Although improvements were observed for the 600 IU group, they were not statistically significant. Neither group had changes in serum calcium	Vitamin D supplementation improves wellbeing; 4000 IU is safe for 1-year and produces a greater therapeutic response than 600 IU

One cohort study addressed the issue of causality.[5] This study observed serum 25OHD levels at baseline in 639 non-depressed elderly patients and monitored for the development of depression after three and six years. One limitation of this study was the timing of follow-up. Because depression symptoms were only assessed on two occasions, depressive episodes that occurred at other times over the six year period were not factored in the statistical analysis. Despite this, participants with lower baseline 25OHD levels reported greater increases in scores on the CES-D suggesting that ad-

equate vitamin D may be protective.

Among the RCTs, results varied. The largest study was conducted on elderly women in Australia as part of a study on hip fractures and falls. While this study failed to show a benefit in well-being there were several weaknesses in the study.[27] Because the study took place in a country known for its high sun exposure, a very small percent of the participants were deficient at baseline. Surprisingly, the treatment group experienced a 15% increased risk of falls and a 26% increased risk of fractures. It is well established that these events have significant adverse effects on elderly individuals' wellbeing, which may have negated any psychological benefits from vitamin D supplementation. While the population of patients receiving the intervention was large, the subgroup in which well-being was assessed was relatively small. Additionally, a large annual dose of vitamin D is not typically used in clinical practice. It is more common for patients to be given therapeutic doses of vitamin D_3 daily.

There were smaller intervention trials that showed positive outcomes, but these trials had methodological problems. One trial contained only six participants and did not utilize blinding or control subjects, which prevented the favourable findings (i.e., large improvements in BDI-II scores) from being generalizable to larger populations.[28] Another trial randomized patients to receive adequate or high doses of vitamin D_3, and showed that the high dose conferred significant antidepressant benefits; however, the assessment tool that they used was a six item questionnaire rather than a validated assessment tool.[29] A study in healthy volunteers revealed an improvement in positive affect among those supplementing with vitamin D_3, but these results do not necessarily mean that vitamin D_3 can treat depressive disorders.30 One large trial showed significant improvements in BDI scores following vitamin D3 supplementation.[31] The study participants were overweight or obese, which limited the generalizability of the results. There was also a high dropout rate, which prevented the results from reaching statistical significance.

Of the six intervention trials, five showed a trend towards reduced depression with vitamin D_3 supplementation. While methodological challenges existed in all of the studies, the results suggest that the vitamin might be beneficial.

Conclusion

The results suggest an association between vitamin D insufficiency and deficiency and the presence of mood disorders. Vitamin D_3 supplementation might also be helpful in the treatment of mood disorders. More RCTs are warranted to determine the level of insufficiency and deficiency that places an individual at risk for mood disorders, and to determine the optimal dosage of vitamin D_3 yielding sufficient antidepressant effects in healthy and at-risk populations.

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