Review Article

Vitamin D and depression: mechanisms, determination and application

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Depression is the most common debilitating psychiatric disease, the pathological mechanisms of which are associated with multiple aspects of neural function. While recent evidence has consistently suggested that a suboptimal vitamin D status is frequently observed in patients with depression, the results concerning whether vitamin D insufficiency is a causal factor of depression or is secondary to depressive behavior are conflicting; additionally, the lack of consistency of the method of vitamin D determination between labs has further worsened this confusion. Herein, we reviewed the neuroactivities of vitamin D that may be associated with depression and the current studies and clinical investigations to provide a full overview on the use of vitamin D in the treatment and prevention of depression.

Key Words: depression, vitamin D, pathological mechanisms, neuroactivities, determination

Depression is a public health concern with no current effective treatment, and approximately 1 out of 10 people are currently suffering from depression worldwide. Depression is also called major depressive disorder or clinical depression, and it is a common debilitating psychiatric illness that is marked by sadness, worthlessness, hopelessness, a loss of interest, and sometimes, feeling as if life is not worth living.[1,2] Depression is more than just about of the blues, depression is not a weakness and you cannot simply "snap out" of it. Depression may require long-term treatment. However, do not get discouraged. Most people with depression feel better with medication, psychological counseling or both. Unfortunately, it is not known what exactly causes depression, and as with many mental disorders, a variety of factors may be involved, such as biological differences, brain chemistry, hormones and inherited traits. Because of these uncertainties, researchers are trying to find the underlying mechanism involved in depression.

Recently, researchers found that there is a slight link between vitamin D and depression; however, the link is not completely understood.[3] Additionally, this link does not prove whether a low level of vitamin D causes depression or if depression causes a low level of vitamin D. The only certainty is that the risk of depression may be further exacerbated by low serum levels of vitamin D.

Vitamin D is a fat-soluble vitamin, which is also known as the "sunshine" vitamin. Vitamin D3 (cholecalciferol) and D2 (ergocalciferol) are the main precursors of the active vitamin D hormones. Vitamin D3 can either be obtained from the diet, or it can be synthesized from 7-dehydrocholesterol upon sun exposure of the skin. Both vitamin D3 and D2 can enter the blood circulation and can bind to the vitamin D binding protein (VDBP). Initially, vitamin D is transported to the liver, where it is hydroxylated at C-25 by the cytochrome P450 enzyme (CYP2R). In the kidneys, a second hydroxylation at the C1-position by cytochrome P450 [5(OH)D-1α-hydroxylase; CYP27B1] occurs. Then, the best nutritional status indicator of vitamin D, 25-hydroxyvitamin D (25(OH)D2 or 25(OH)D3), is produced. Next, 25(OH)D3 is metabolized to 1, 25-dihydroxyvitamin D (1, 25(OH)2D3), which is the most active form of vitamin D, and it is then transported to the target tissues.[4,5] The whole vitamin D metabolic process is shown in Figure 1.

An accumulating number of studies have indicated that vitamin D also acts as a neuroactive steroid,[6,7] which plays a key role in the expression of neurotransmitters, the regulation of neurotrophic factors, neuroimmunomodulation, the production of antioxidants and neurotropic factors , making it biologically plausible that vitamin D might be associated with depression. Currently, the results concerning whether vitamin D insufficiency is a causal factor of depression or secondary to depressive behavior are conflicting, and the lack of consistency in the vitamin D determination methods between labs has

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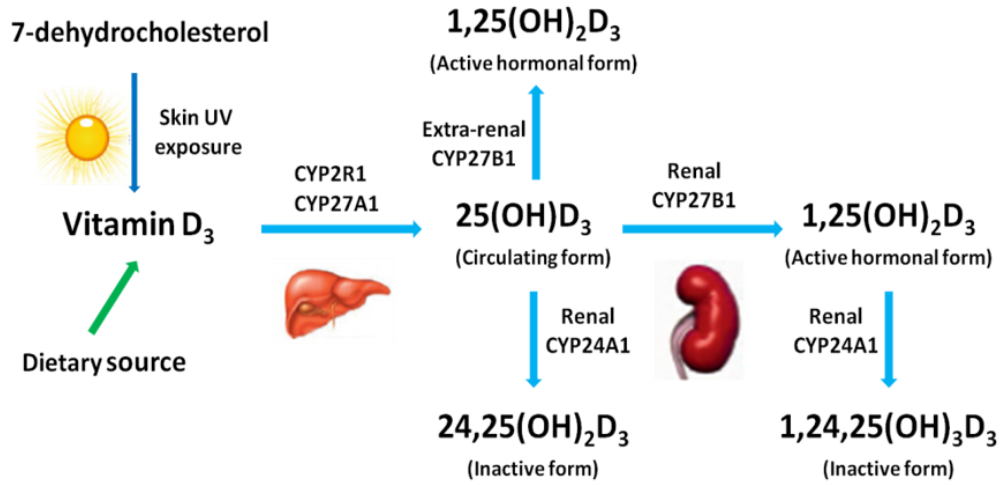

Figure 1. The process of vitamin D metabolism.

further worsened this confusion. Herein, we reviewed the neuroactivities of vitamin D that may be associated with depression as well as the current studies and clinical investigations to provide a full overview of the use of vitamin D in the treatment and prevention of depression.

METHODS

Depression: Underlying mechanisms involving Vitamin

Although the underlying pathophysiology of vitamin D in depression is still not fully understood, the main mechanisms of depression that are associated with vitamin D are as follows.

Vitamin D and neurotrophic hypothesis

Vitamin D receptors (VDRs) were initially found in the central nervous system (CNS) by immunohistochemical studies, providing the first real clue that vitamin D might have a role in brain function. The VDR and vitamin D activating enzyme 1-alpha-hydroxylase are widely distributed in multiple brain regions and in many different types of cells, particularly in the neurons in the amygdala and the glial cells in the hypothalamus,[8,9] thus adding further support for the hypothesis that vitamin D signaling might be involved in the pathophysiology of neuropsychiatric disease. VDR is widely distributed throughout the brain, particularly in the neuroepithelium and proliferating zones, whereas expression is not confined to these regions. Previous studies have indicated that 1,25(OH)2D3 could cross the blood-brain barrier to bind to VDR in specific brain regions, including the hippocampus, which raises the possibility that vitamin D is either directly or indirectly involved in brain and cognitive function.[10] Meanwhile, hippocampal structure could control memory, the emotional function of other brain regions, and the atrophy of the hippocampus and other limbic structures. In addition, hippocampal structure abnormalities have also been validated to take place in humans when they are suffering from chronic depression. The hippocampus plays a key role in the mechanisms of depression, and therefore, the discovery of VDR within the hippocampus has prompted many researchers to study the effects of vitamin D on hippocampal structure or function in rodents.[11] Numerous studies have also been conducted with the in vitro culturing of hippocampal cells, and even on the brains of adult rodents in vivo, and the results have shown that vitamin D deficiency could change the structure or function during hippocampal development.

Increasing evidence has revealed that vitamin D is a potent modulator of the expression of neurotrophic agents, such as nerve growth factor (NGF), brain-derived neurotrophin factor (BDNF) and neurotrophin (NT)-3. Neurotrophic factors are essential for the survival, growth and migration of neurons, which exert their biological function by combining with their cognate tropomyosin-related kinase (Trk) receptors, including NGF/TrkA, BDNF/TrkB, NT-3/ TrkC and the common neurotrophin receptor p75 (p75NTR).[12] An extensive body of research has demonstrated that 1,25(OH)2D could increase the expression of BDNF, NGF and NT-3, whereas NT-4 is downregulated in astrocytes in the brain,[13,14] thus providing further evidence that vitamin D could modulate neuronal survival and differentiation during development. BDNF plays an important role in the long-term survival, differentiation, and function of newborn neurons in the adult hippocampus. Therefore, restoring the levels of BDNF might be beneficial for the treatment of depression. Neurogenesis is also important for depression, suggesting that the discovery of TrkB ligands might open new avenues for the treatment of this disorder. NT-3 and NT-4 are vital to the survival of developing neurons, including the proliferation and differentiation of neural progenitor cells, thereby directly or indirectly influencing depression. Therefore, vitamin D could modulate neurotrophic agents, the abnormal function of which is believed to be associated with various psychiatric diseases.

Vitamin D and monoamine neurotransmission hypothesis

The classic monoamine neurotransmission hypothesis suggests that monoamine deficiency may be a cause of depression; more precisely, depression is related to serotonin (5-HT), dopamine (DA) and norepinephrine (NE). The common clinical antidepressant drugs, such as tricyclic drugs, function by inhibiting the 5-HT and NE transporters. 5-HT, a monoamine neurotransmitter, is synthe-

sized from the amino acid tryptophan, and the hypotheses regarding the role that 5-HT plays in the pathophysiology of depression were formed as early as the 1960s. Some evidence has verified that 5-HT plays an important role in the brain functions that are involved with the regulation of mood.[15] However, a lack of vitamin D could affect the synthesis of 5-HT, leading to the abnormal development of the brain and serotonergic neurons. Additionally, 5-HT also acts on the hippocampus, where the generation of new neurons and synaptic plasticity has been implicated as possible factors in the development and treatment of depression. The VDR is expressed in dopaminergic neurons in the human and rat hippocampus, substantia nigra and prefrontal cortex, which are involved in depression.[16] VDR expression in the substantia nigra could delay DA cell differentiation and could cause DA-mediated behavioral deficits upon vitamin D deficiency,[17] and it further indicates that vitamin D deficiency could affect the development of dopaminergic neurons and has serious implications for the development of depression. Therefore, vitamin D might be involved in depression by directly or indirectly influencing the levels of 5-HT, DA and NE.

Vitamin D and neuroimmunomodulation

With a renewed interest in vitamin D, new pharmacological effects of vitamin D in autoimmune diseases and inflammation have been discovered. Accumulating evidence has suggested that 1, 25(OH)2D3, a key transcriptional regulator of components of the immune system, can inhibit the abnormal activation of the immune system, thereby having a neuroprotective effect.[18] Our previous basic research and that of others have shown that vitamin D insufficiency could elevate inflammatory markers in chronic mild stress (CMS)-induced depressive rats, specifically interleukin (IL)-1βand IL-6.[19] Thus, vitamin D insufficiency might contribute to inflammation. However, the underlying mechanisms are not clearly understood and are topics of ongoing investigation. Vitamin D supplementation could reduce elevated [$Ca2^{+}$]i via the CRAC and P2X7 channels and could decrease the expression of the cell surface P2X7 receptors in early chronic kidney disease (CKD).[20] As we and others previous researchers have shown,[21] vitamin D insufficiency exacerbated the depressive symptoms caused by P2X7R/NLRP3 activation; therefore, we think vitamin D may play a neuroimmunological role by regulating the activity and expression of P2X7R, thus preventing the excessive activation of the immune system that is caused by long-term stress, protecting nerve cells and producing antidepressant effects. Therefore, more researches related to this important potential mechanism is highly warranted.

Serum vitamin D concentrations and depression

Increasing attention has been paid to the levels of serum vitamin D; in the mid- to late-1980s, total serum 25(OH)D concentrations were usually used to characterize the vitamin D levels, as circulating 25(OH)D was deemed the best nutritional status indicator for vitamin D. Accumulating studies have shown that the levels of 25(OH)D are related to many diseases, such as cardiovascular disease, cancer, diabetes, obesity, and asthma.[22] It should be noted that vitamin D could regulate the expression of neurotrophic factors and interleukins. Thus, the role of vitamin D in the prevention and treatment of depression has gained more attention. Several studies still have not achieved a general consensus regarding whether lower levels of serum 25(OH)D are significantly associated with depression.[23,24] In contrast, recent studies have failed to demonstrate a correlation between serum 25(OH)D levels and depression in female subjects[25] or in older subjects.[26] The small numbers of subjects, and sociodemographic factors, including sex differences, genetics, body-mass index, residence, family affluence, parental education levels, subjective academic achievement, diet, drinking and smoking, have not been comprehensively considered, resulting in discrepancies arising when validating the previously observed correlations. There is no doubt that lowered serum vitamin D levels present a non-significant but increased risk of depression (OR 1.31, 95% CI 1.00-1.71).[27] Thus, the most important thing that we can do currently is to summarize the best available evidence to date to clarify the mechanism of vitamin D in the prevention and treatment of depression.

Vitamin D determination

Currently, for the diagnosis of vitamin D deficiency, a doctor or health professional will ask about your diet and the time spent in the sun. After this, the doctor will order a 25(OH)D blood test to check the level of vitamin D in your body. A number of hospitals and laboratories already include vitamin D testing as a part of clinical routine testing, and vitamin D levels are also a testing item for therapeutic drug monitoring (TDM). There are a variety of assays used to measure 25(OH)D, such as immunoassays (e.g., radio-labeled, enzyme, or chemiluminescent),[28] electrochemistry assays and chromatographic assays that use different detectors, e.g., ultraviolet (HPLC-UV) or tandem mass spectrometry (LC-MS/MS).[29,30] The immunoassays, such as the Siemens ADVIA Centaur Vitamin D total assay and Roche Elecsys Vitamin D total assay, cannot distinguish 25(OH)D from its analogue or its metabolites, indicating that these assays lack specificity. Chromatographic assays, such as LC-MS/MS, are considered to be the gold standard with the advantage of having high sensitivity and specificity and the ability to simultaneously measure 25(OH)D2 and 25(OH)D3. The concentration measurements are accurate, but LC-MS/MS is a very complicated assay, and thus, it is not suitable for routine clinical use by hospitals or laboratories for serum samples. Therefore, the inconsistency among the various conclusions regarding whether vitamin D deficiency is a cause of depression may be due to the inconsistencies in the quantitative methods, which make it hard to make sense of the data.

The inadequate accuracy or the cumber some techniques of the methods used to measure 25(OH)D not only hamper the ability to interpret data in patient care and public health research but also the diagnosis and treatment of hypovitaminosis D. To solve the problem of inter laboratory and inter assay discrepancies, vitamin D standardization efforts are ongoing, and the Vitamin D Standardization Program (VDSP) was established in 2011.[31,32] Due to these efforts, the National Institute of Standards and Technology (NIST), in collaboration with the US

Office of Dietary Supplements (ODS), has developed Standard Reference Materials (SRM 2972 and 972), and these materials have been certified by the Reference Materials Procedures (RMPs) for 25(OH)D testing in human serum.[33] Based on a method evaluation study on the new follow-up version of a chemiluminescence immunoassay (CLIA) and a new enzyme-linked immunosorbent assay (ELISA), both methods are aligned with the NIST SRM 2972, and the LC-MS/MS method is aligned with the new NIST SRM 972a.[34] Both the 25(OH)D2 and 25(OH)D3 concentrations are measured, with the sum gives the total serum 25(OH)D concentration. Even if the new NIST SRM 972a Standard is a relatively accurate measurement and assessment method, various discrepancies (e.g., region, ethnicity and diet) can make it difficult to determine whether the vitamin D level is normal. Despite the many shortcomings in the determination methods that remain, their use can still provide an idea of the 25(OH)D level, which is beneficial for the prevention and treatment of depression in some individuals.

Vitamin D supplementation for depression treatment

There is no absolute agreement as to whether there is inter human and inter region diversity in the ranges of the serum 25(OH)D concentration. Recent reviews have reported that children, young, middle-aged, and older adults worldwide, especially depressed individuals, are all at risk for having vitamin D deficiency.[35] Based on all of the information that has been collected, most experts now agree that a 25(OH)D level of <20 ng/mL indicates vitamin D deficiency and vitamin D insufficiency is now recognized as a 25(OH)D level of 21-29 ng/mL. Many experts now say that the ideal levels for 25(OH)D are >30 ng/mL. With aging, the skin's ability to synthesize vitamin D significantly decreases. A study indicated that the capacity of the skin to synthesize vitamin D at 70 years of age is reduced by more than 50% compared to at 20 years of age. However, aging does not affect the intestinal absorption of vitamin D,[36,37] and another study revealed that approximately two-thirds of the population in northern climates are considered deficient for vitamin D, with average serum 25(OH)D levels of 30 ng/mL;[38] thus, vitamin D supplementation is urgently required to reduce the risk of vitamin-related disease, to improve the quality of life and to prolong the lifetime of humans.

Vitamin D supplementation in combination with fluoxetine is more effective than fluoxetine alone in reducing depressive symptoms of patients with depression in the general population; therefore, the efficacy of vitamin D supplementation in depression has raised much interest. In three small pilot studies, vitamin D supplementation had a positive effect on the well-being, and the symptoms of depression were improved when high doses of vitamin D (≥100 μg D3 daily) were given for 1 to 3 months.[39] A study with a large sample size (n=441) demonstrated a similar significant improvement in the Beck Depression Inventory (BDI) scores in the treatment groups receiving 70 μg and 140 μg vitamin D supplementation compared to those of the placebo group during a 1-year period.[40] In addition, several studies have also shown that vitamin D supplementation is more effective and relevant in high-risk participants who have low serum 25(OH)D and have apparent depressive symptoms or reduced physical functioning.[41-43] In conclusion, the treatment of depression with vitamin D supplementation could have a profound influence, as vitamin D is not only an effective antidepressant but is also a cost-effective treatment for depression. However, while people with very low levels of vitamin D could benefit from vitamin D supplementation, people with a sufficient amount of vitamin D in the blood would not benefit from vitamin D supplementation and would not experience a decrease in depression. A serum 25(OH)D level >150 ng/mL is associated with hypercalcemia, hypercalciuria and hyperphosphatemia, which is called vitamin D intoxication. Therefore, the relationship between vitamin D supplementation and depression is complicated for the following reasons. First, different doses of vitamin D have been used for supplementation for different lengths of time in different studies. Second, different parameters are used to define vitamin D sufficiency and the efficacy of treatment. Third, different tools are used to evaluate mental health and depression. Finally, previous studies have administered vitamin D at different frequencies. Furthermore, serum 25(OH)D concentrations should be determined first, and then, according to the serum 25(OH)D concentrations, depressed patients might be treated with vitamin D supplementation in combination with other therapeutic schedules. To verify whether vitamin D supplementation improves depressive symptoms, large, randomized and controlled clinical trials are highly warranted.

Conclusion

In our paper, we reviewed the current underlying mechanisms of depression that are involving vitamin D, as well as vitamin D determination, supplementation and application. Although the data regarding the relationship between vitamin D and depression are conflicting, lower serum 25(OH)D levels are associated with an increased risk for depression, and depressive symptoms could be eased in people with very low levels of vitamin D through vitamin D supplementation. Additionally, in some cases, monitoring serum 25(OH)D concentrations can help us to learn about health status and can provide new insights into depression. Furthermore, we have structured our thoughts into the review and believe that the effective and safe protocols for dealing with depression will be developed. We hope that every depressed patient will receive personalized treatment.

EDITORS' NOTE

The Editors wish readers of this paper to be aware that serum vitamin D's association with affective disorders like depression may be as an indicator of sunlight (UV) exposure in its own right or in association wit UV-dependent cutaneous vitamin D synthesis. Similarly, the association may be attributable to participant food intake or food pattern from which vitamin D is derived.

AUTHOR DISCLOSURES

All authors declare no conflict of interest, financial or otherwise.

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