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Is Vitamin D Important in Anxiety or Depression? What Is the Truth?

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Abstract
Purpose of Review Depression and anxiety are mood disorders that affect health and therefore quality of life and increase the global burden of disease. One of the possible mechanisms in the pathophysiology of these mood disorders has been reported as oxidative stress and inflammation. In the light of this information, it is important to determine the relationship between antioxidant nutrients (such as vitamin D) and these diseases. There are points where the brain regions involved in the pathophysiology of depression and anxiety and vitamin D metabolism intersect.
Recent Findings Low vitamin D levels are associated with increased symptoms of depression and anxiety. For this reason, vitamin D screening should be performed in the prevention and treatment planning of these mood disorders.
Summary Vitamin D, which has antioxidant properties and activity in brain tissue, is important for mood disorders preventions or treatments but serum levels must be followed.

Keywords Depression · Anxiety · Mood disorders · Vitamin D · Antioxidant · Cholecalciferol

Introduction

Depression and anxiety are mood disorders that affect individuals' daily lives and health status with their social and economic dimensions, which are frequently observed. Identifying the factors that cause these mood disorders is a cornerstone to prevent or delay their occurrence. It is important to provide disease management for individuals diagnosed with mood disorders.

It has been determined that oxidative stress and inflammation are involved in the pathophysiology of these mood disorders along with many diseases [1]. Thereupon, the relationship between antioxidant and immunomodulatory nutrients and these diseases was examined. In this review, it is aimed to explain the place of vitamin D in the pathophysiology of depression and anxiety, the effect of vitamin D supplementation, and its interactions with the drugs used.

Vitamin D

Vitamin D is a fat-soluble vitamin that has been reported to have efficacy in many tissues, as well as its effects on calcium-phosphate homeostasis and bone health. Approximately one-fifth of vitamin D is provided by dietary intake, and the remaining 80% is synthesized from 7-dehydrocholesterol in the skin by ultraviolet rays [2]. Then, calcidiol, which is the serum form of the vitamin, is hydroxylated in the liver with the enzyme 25-hydroxylase (CYP2R1), and calcidiol is re-hydroxylated in the kidney and brain with the enzyme 1-α-hydroxylase (CYP27B1) and turns into 1,25 $(OH)_2$ cholecalciferol, also called calcitriol, which is the active form of the vitamin [3]. Vitamin D synthesis and active form formation stages are presented in Fig. 1. This active form binds to vitamin D receptors located on cell membranes of many tissues to mediate gene transcription and non-genomic reactions [2].

Serum 25(OH) cholecalciferol (calcidiol) level is taken into account to evaluate the sufficiency status for vitamin D. However, there is no international consensus on the cut-off points of this parameter for proficiency/inability. The

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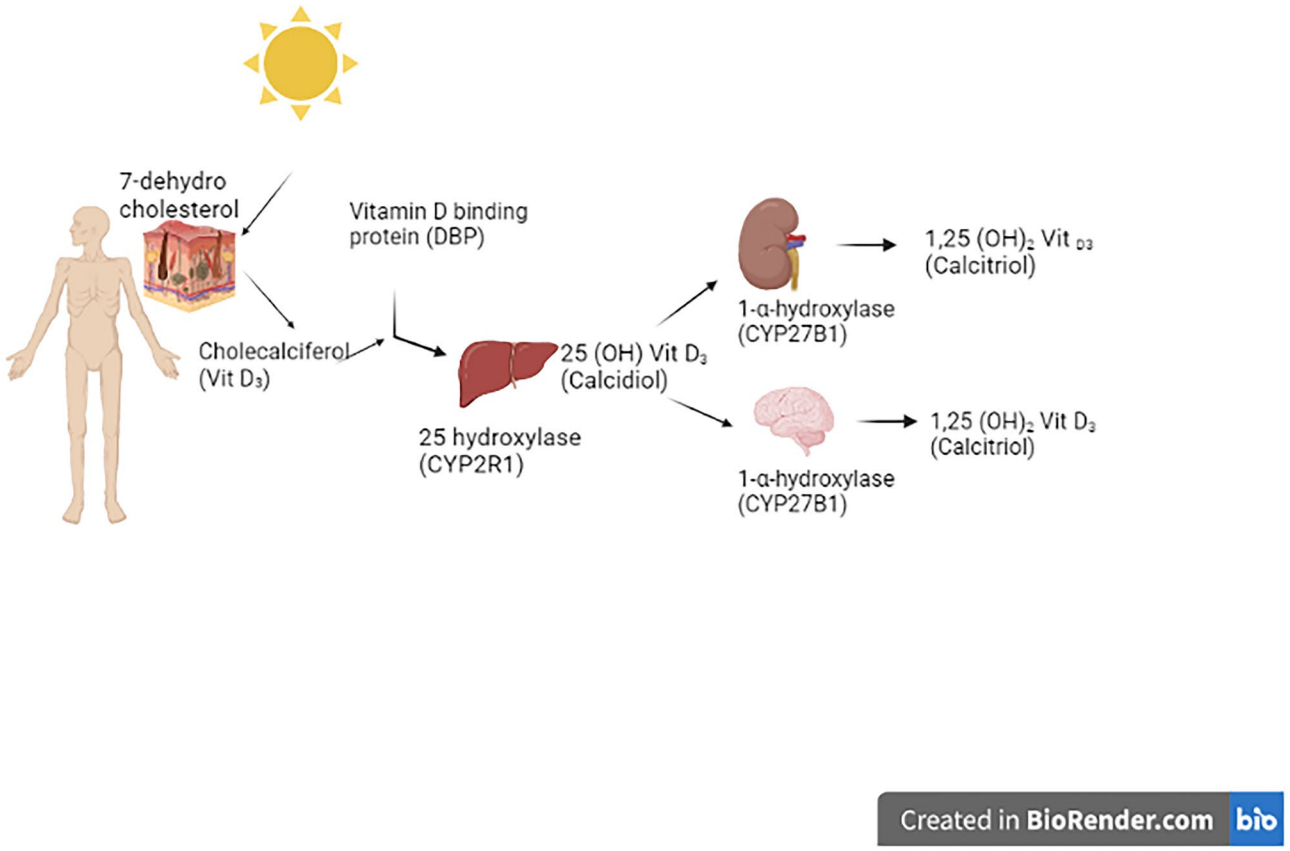

Fig. 1 Vitamin D synthesis and active form formation stages

cut-off points determined by different authorities vary. The data generated on this subject are presented in Table 1 [4, 5].

When the causes of vitamin D deficiency are examined, it may be caused by decreased exposure to sunlight, decreased endogenous synthesis with the deterioration in liver-kidney functions, malabsorption (cystic fibrosis, short bowel syndrome, gastric bypass, chronic pancreatic insufficiency, etc.), the drugs used (phenobarbital, carbamazepine, dexamethasone, nifedipine, spironolactone, clotrimazole, and rifampin), increased catabolism, and genetic resistance to vitamin D [5].

Adequate intake of vitamin D is particularly dependent on sunlight. Synthesis occurs with short-term (15–20 min) direct exposure to sunlight. In longer exposure to sunlight, compounds called lumesterol and which do not show vitamin D activity are formed. However, vitamin D synthesis levels in exposure to sunlight are affected by various factors such as skin pigmentation, sunscreen use, latitude, season, and age, and dietary or supplemental intake does not directly contribute to 25(OH) cholecalciferol levels. It is emphasized that factors such as body mass index, body fat percentage, and calcium intake are also effective on serum vitamin D levels [6]. When the prevalence of vitamin D insufficiency is examined, it is reported that 40% of Europe has vitamin D insufficiency, and 13% of them have severe insufficiency [7].

Table 1 Definitions of vitamin D deficiency and sufficiency according to different authorities [4]

Plasma 25(OH)D concentration (nmol/L)	IOM	Endocrine Society	EFSA	SACN	ECTS
< 25/30	Deficient	Deficient	Deficient	Deficient	Severely deficient
25–50	Uncertain	Insufficient	Deficient	-	Deficient
50–75	Sufficient	Insufficient	Sufficient	-	Sufficient
> 75	-	Sufficient	-	-	-

IOM Institute of Medicine, *EFSA* European Food Safety Authority, *SACN* Scientific Advisory Committee on Nutrition, *ECTS* European Calcified Tissue Society

Vitamin D receptors located in many tissues are also located in the brain specifically in the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra. These regions are of extra importance for this research as they are defined in the pathophysiology of depression [8]. It has also been determined that the vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) is widely distributed in many different cell types of many brain regions, especially in neurons in the amygdala and glial cells in the hypothalamus. This distribution strengthens the relationship between vitamin D and neuropsychiatric diseases. It is reported that the active form of vitamin D can cross the blood–brain barrier, which increases the possibility of vitamin D being directly or indirectly involved in brain and cognitive functions [9].

There are many studies in the literature reporting that vitamin D deficiency was associated with symptoms of depression and anxiety [10–14]. Although the cause and effect relationship of vitamin D and related diseases has not been clarified, it has been reported that vitamin D deficiency exacerbates the symptoms specific to these diseases [9]. Therefore, it is important to detect vitamin D deficiency and to plan appropriate treatments.

Depression

The global burden of the disease is generally assessed by the World Health Organization (WHO) based on disability-adjusted life years (DALY). From this point of view, mood disorders are reported to be at the top of the global disease burden [15]. Depression, one of the mood disorders, results from the complex interaction of social, psychological, and biological factors and is a common disease globally. According to 2019 data, it is reported that 5.0% of adults, 5.7% of individuals over the age of 60, and 3.8% of the global population suffer from depression [16, 17]. Although depression is different from the usual mood swings and short-term emotional reactions to the difficulties in daily life, it can deeply affect the lives of individuals, especially with the accompanying major depression [16].

The presence of five or more symptoms over a 2-week period is essential for the diagnosis of a major depressive episode according to DSM-5 criteria. At least one of the symptoms must be depressed mood or anhedonia, and secondarily, it may include appetite or bodyweight changes, sleep difficulties, psychomotor agitation, fatigue, decreased cognitive abilities, feelings of worthlessness, and extreme guilt. These symptoms are rated as always (1) or never (0) [18]. DSM-V assumes that depression can be accepted as one-dimensional and suggests that major depression can be determined by the sum of these degrees of change. However, it has been reported that depression may have different dimensions. It is stated that grouping the changes determined by DSM-V and mentioned above as somatic (insomnia, changes in appetite or body weight, decreased cognitive abilities, fatigue, and psychomotor agitation) and non-somatic (depressed mood, anhedonia, feelings of worthlessness, and suicidal thoughts) changes is the best representative. No correlation has been identified between the number of changes and the severity of depression. Scales are used for the severity of depression, and it has been reported that the most frequently used one is the Hamilton Depression Scale (HDS) [19].

Depression can lead to cardiovascular events and stroke due to these changes that affect daily life and lifestyle changes, and as a result, it can increase mortality and morbidity [20]. In addition, depression can extend to suicide, and it has been reported that the fourth cause of death for individuals aged 15–29 is suicide [16, 19]. When all these are evaluated together, the prevention, diagnosis, and treatment of depression are important. The WHO highlights the steps needed to provide appropriate interventions for many mental disorders, including depression, in the Mental Health Action Plan 2013–2030 [21].

The underlying biological mechanisms for depression have not been fully elucidated. However, some possible pathways are indicated. It mainly focuses on 3 hypotheses, including the effects of vitamin D on neurotrophy, monoamine neurotransmission, and immunomodulation [9, 20, 22].

It has been stated that the determination of the role of inflammation in the pathophysiology of depression may provide hope for anti-inflammatory agents for this mood disorder. Changes involving oxidative stress and neuroinflammation may cause activation of peripheral macrophages and central microglia, dysfunction of the hypothalamus–pituitary–adrenal (HPA) axis, and hypercortisolemia. As a result of all these, dendritic growth, synaptic plasticity, and deterioration in synaptic communication can be seen. It has been stated that the effect of vitamin D on the pathophysiology of depression may also be due to its immunomodulatory properties [6]. It is reported that with this feature, it can show a neuroprotective effect by preventing the abnormal function of the immune system [20, 22]. However, it was emphasized that these results were not at the level of evidence that could be used in clinical guidelines [6].

It is thought that increased expression of region-specific vitamin D receptors (VDR) in brain regions known to play an important role in mood regulation (such as prefrontal and cingulate cortices) may be effective on the progression of depression [20, 22]. Because the hippocampal structure can control memory, emotional functions in other brain regions, and limbic structure atrophy, it has been determined that individuals with disorders in this hippocampal structure suffer from chronic depression. After detecting the presence of VDR in the hippocampus, the activity of vitamin D in this

structure was examined, and it was revealed that vitamin D is a potent modulator of the expression of neurotrophic agents such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT)-3. Neurotrophic factors are necessary for the viability, growth, and migration of neurons that display their biological functions by combining with cognate tropomyosin-related kinase (Trk) receptors, and vitamin D can increase the expression of these neurotrophic factors. It is emphasized that neurons that secrete neurotransmitters, and therefore neurogenesis, are important in depression and that vitamin D has an important role in maintaining the vitality of neurons [9].

Calcitriol, also called neurosteroid hormone due to its immunomodulatory and neurotrophic roles, is effective in the synthesis of neurotransmitters (serotonin, dopamine, noradrenaline, adrenaline) that play a role in the pathophysiology of mood disorders by activating the gene expression of the tyrosine hydroxylase enzyme, reported as the rate-limiting step in catecholamine synthesis [14, 23]. Vitamin D both protects serotonergic neuron health with its neurotrophic effect and supports serotonin synthesis by providing gene expression of enzymes that are active in synthesis. Alteration of serotonin synthesis in case of vitamin D deficiency is also evident [22]. In addition to the synthesis, it is also stated that vitamin D takes part in the metabolism of these neurotransmitters and prevents their depletion [14, 20]. Vitamin D is also thought to be a factor in the onset of depression with its potential roles in correcting this calcium and glutamate-γ-aminobutyric acid (GABA) imbalance by regulating intracellular calcium stores and cellular signals [22]. Considering all this, it is reported that vitamin D provides modulation of the HPA axis [20]. It is emphasized that vitamin D is neuroprotective for neurons that secrete neurotransmitters (especially dopamine), but it may show neurotoxic effects when plasma levels exceed the threshold value [23].

The results of preclinical studies examining the relationship between vitamin D and depression were found to be inconsistent. It was determined that high-dose vitamin D administration (5 mg/kg/day) for 14 days in ovariectomized rats ($n=96$) showed antidepressant-like behavior in depression caused by ovariectomy [24]. Low levels of vitamin D have also been observed in the offspring ($n=15$) of mothers exposed to low levels of vitamin D from pre-pregnancy to the end of the lactation period. In addition, low vitamin D levels were found to cause anhedonia, an important marker of depression in offspring [25]. It has been reported that the administration of vitamin D_3 for 7 days effectively prevents depressive-like behavior caused by corticosteroid exposure and brain oxidative stress markers, and this antidepressant effect may also be due to oxidative stress modulation [26]. Another study showed that intraperitoneal treatment with 1,25$(OH)_2$ vitamin D_3 (5, 10 μg/kg, twice a week) for 5 weeks effectively ameliorated anhedonia with chronic mild stress [27]. However, there is also a study in the literature reporting that vitamin D deficiency does not affect the proliferation or survival of neurons in rats [28].

When the epidemiological and clinical studies were examined, cross-sectional and cohort studies were encountered that revealed an inverse relationship between plasma 25$(OH)D_3$ and depression symptoms and major depressive disorder [29–33]. In these studies, the cut-off points considered for vitamin D adequacy, insufficiency, and deficiency, the group in which the study was conducted and the scale used to determine depressive symptoms, show heterogeneity. However, it is emphasized in all studies that individuals with high vitamin D levels are less likely to develop depressive symptoms/depression. In a 4-year follow-up cohort study, which was planned especially in a large sample and aimed to reveal the causality between vitamin D and depression, it was determined that individuals with vitamin D deficiency were 75% more likely to develop depression when compared to individuals with adequate levels [29].

There are also studies evaluating the polymorphism, reporting that the relationship between plasma vitamin D levels and depression is not significant [34, 35]. Although these studies were planned as case control, vitamin D classification was not made, and interpretations were made on the averages of plasma 25 (OH) vitamin D levels.

In addition to these studies, there are also studies in which vitamin D therapy has been used as a therapeutic agent alone or as an adjuvant to classical pharmacotherapy in major depressive disorder [14, 36–42]. In a cell culture study examining the effect of vitamin D on serotonin reuptake transporters (SERT), which is the target of serotonin reuptake inhibitors (SSRI) used in the treatment of depression, and monoamine oxidase (MAO), which catalyzes the destruction of serotonin, it was determined that 10 nmol vitamin D application could suppress the expression of SERT and MAO (59%, 51%, respectively). However, it was also emphasized that there was no statistically significant difference for other doses (1 nmol/100 nmol) [14]. Epidemiological studies in which vitamin D supplementation was carried out were conducted on the effect of depressive symptoms observed due to the presence of chronic diseases such as diabetes, ulcerative colitis, and Chron's rather than individuals with a diagnosis of depression. Therefore, it was thought that the positive outcomes of vitamin D supplementation obtained from studies on depressive symptoms may be related to its effect on metabolic and inflammatory markers as an immunomodulator. In a placebo-controlled double-blind randomized clinical study evaluating the effect of vitamin D supplementation (50,000 IU for 2 weeks) on plasma 25 (OH) vitamin D levels and some neurotransmitters in individuals (n = 56) with mild and moderate depression, it was reported that serum 25 (OH) vitamin D levels

increased significantly in the intervention group, and the severity of depression decreased. In the same study, it was reported that no significant change was observed in platelet serotonin levels [13]. In the meta-analysis of 25 studies ($n = 7534$) evaluating the effectiveness of vitamin D supplementation on depression, it was reported that vitamin D was effective in individuals with major depressive disorder and plasma 25(OH)D levels ≤ 50 nmol/L and this effect was achieved with supplements less than 4000 IU for ≥ 8 weeks [11]. However, there is also a study in the literature that vitamin D supplementation does not affect depressive symptoms [43].

Anxiety

Anxiety disorders (generalized anxiety disorder, phobia, panic disorder, and others) are defined as a negative, uncertain, and unpleasant emotional state resulting from the anticipation of a potential danger with multifactorial causes. It represents a group of common mental health disorders that negatively affect daily life and well-being. Anxiety disorders involve excessive and persistent fear, worry, and/or avoidance of perceived threats in the external (e.g., social situations) or internal (e.g., bodily sensations) environment, often accompanied by panic attacks [44]. Anxiety and depression or other mental health disorders can also be observed together [6, 45]. Although the developmental ages of the subtypes of anxiety disorders vary, it is reported that they are mostly onset in childhood and adolescence. It has been reported that DSM-V and ICD-10 criteria are used in the classification of anxiety disorders, and these two classifications are similar [44].

In the meta-analysis study on the global prevalence of anxiety, it was reported that the prevalence of anxiety in Asia was 32.9% (13 studies), while the prevalence of anxiety in Europe was 23.8% (3 studies) [46]. However, this current study is given depending on the COVID-19 process. Anxiety, like depression, is among the mental disorders that affect the quality of life and therefore daily life and health costs [44, 47]. It has been determined that anxiety is in the second place in terms of DALY burden. Although anxiety, which is attributed to the 4.2% burden in DALY, is observed to be low, this burden increases with comorbidity depression [44]. Therefore, the prevention and treatment of anxiety disorders are important.

Some hypotheses have been defined in anxiety disorders. In the hypothesis defined for the neural circuit, it is reported that fear and anxiety are regulated by a mixture of bidirectional connections in the amygdala, ventromedial prefrontal hypothalamus, and anterior cingulate cortex with the functional effect of the hippocampus. It is emphasized that the discord between these centers plays a role in anxiety disorders (hyperactivation in the amygdala, decreased activation in the ventromedial prefrontal hypothalamus) [44]. It has been reported that amygdala hyperactivation, especially in response to a threat, is associated with the risk of developing anxiety in later years [48]. Another hypothesis is a defect in the HPA axis, which is also involved in the pathophysiology of depression [44]. Vitamin D activity should be considered due to the increased expression of the vitamin D receptor in these regions and the presence of the 1-α-hydroxylase enzyme. It has been reported that there are irregularities in the HPA axis in vitamin D deficiency [13]. This information supports the relationship between vitamin D and anxiety. It is stated that the deficiency of substrates such as dopamine, serotonin, and norepinephrine is also involved in the pathophysiology, but it is generally associated with reduced inhibitory signalling by GABA or hyperexcitability caused by increased excitatory glutaminergic neurotransmission. In addition, it is thought that vitamin D may also be a factor in anxiety due to oxidative stress and inflammation in the pathophysiology [6].

In a study on ovariectomized rats ($n = 96$), in which anxiety was evaluated as well as depression, it was found that low-dose vitamin D administration (1 mg/kg/day) for 14 days had an anti-anxiolytic effect, in contrast to depression [24].

The results of epidemiological studies conducted to determine the relationship between anxiety and vitamin D show a negative correlation similar to depression [10, 12]. In a study evaluating the relationship between vitamin D levels and anxiety in individuals with rheumatoid arthritis ($n = 161$), it was concluded that there was an inverse relationship between vitamin D levels and the presence of anxiety [30]. In the systematic review of fourteen studies published by Fallah et al., it was determined that 10 studies reported a direct relationship between vitamin D levels and anxiety, and one study reported an indirect relationship [49].

In a randomized controlled clinical study evaluating the efficacy of vitamin D supplementation on anxiety, it was reported that the administration of 1600 mg of vitamin D for 6 months improved anxiety symptoms [43]. In the study in which different vitamin D supplements applied to individuals ($n = 34$) in the remission stage of Crohn's disease were examined, it was reported that only high-dose (10,000 IU) vitamin D supplementation significantly increased serum vitamin D levels, but both doses improved the symptoms of depression and anxiety [40].

Conclusion and Recommendations

In conclusion, vitamin D has immunomodulatory, neuroprotective, and neurotrophic properties and may affect the brain tissues involved in the pathophysiology of depression and anxiety. The results of studies in the literature on

the relationship of vitamin D levels with supplementation, depression, and anxiety are inconsistent. It is thought that the reason for the inconsistency in studies examining vitamin D levels may be due to the use of different cut-off points regarding vitamin D adequacy, the differences in the groups in which the studies were conducted, and the differences in the tools used to determine depression and anxiety. It is thought that many factors may have contributed to the inconsistency in the studies in which vitamin D supplementation was evaluated, including the difference between the groups applied, the severity of depressive symptoms, the presence of comorbidities, initial $25(OH)D_3$ level, vitamin D supplement dose, supplement form, and duration. In addition, studies in the literature include not only individuals with symptoms of major depression or anxiety but also individuals with chronic inflammatory diseases such as ulcerative colitis, Crohn's, and diabetes. Therefore, positive outcomes in individuals with these diseases can be associated with the effect of vitamin D as an immunomodulator on metabolic and inflammatory markers. Although the cause and effect relationship of vitamin D with depression and anxiety has not been clarified in the literature, it is emphasized that low vitamin D levels cause an increase in the symptoms of these diseases. It is important to screen for vitamin D deficiencies regarding mood disorders, to plan appropriate treatments, and to determine the optimal dose. Because although there are studies in the literature reporting that the level of side effects and toxicity of vitamin D is low, it is also reported that the course of vitamin D levels above the threshold value is neurotoxic. Therefore, the necessity of monitoring vitamin D levels in planned vitamin D supplements is also clear. Besides, vitamin D is not included in the guidelines in the literature on mood disorders. For this disease group, cohort studies are needed to determine the effectiveness of vitamin D levels, supplement dose, and form.

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Declarations

Conflict of Interest The authors declare no competing interests.

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