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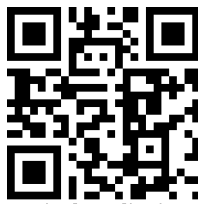
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# Depression and its Association with Vitamin D Deficiency: A Review

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## Abstract

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Depression is a common psychological disorder and a major health issue. Many socioeconomic, environmental and genetic factors contribute to the onset and progression of depression. In recent years, the deficiency of vitamin D has emerged as a possible predisposing factor responsible for the manifestation of depression. In this review article, the causes of depression are briefly reviewed with a special focus on the association between vitamin D and depression. In recent years, the association between vitamin D and depression has been extensively investigated; still, the mechanism that governs this association is not fully understood. An understanding of the underlying biological processes and mechanisms through which vitamin D exerts its role will help in understanding the predisposition towards depression and the amelioration of depressive symptoms.

**Keywords:** depression, vitamin D deficiency, mental health, neuronal differentiation, neurotransmitters

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## 1. Introduction

Depression is a major public health issue due to its high prevalence, dysfunction, suffering, morbidity and economic constraints. The Global Burden of Disease reported the rate of occurrence of the unipolar depressive episodes is 3.2% for women and 1.9% for men. The estimated prevalence for one year for women was 9.5% and for men it was 5.8%. The burden of depression was predicted to increase up to 5.7% of the total burden of disease by the year 2020, if the current trends of the epidemiological and demographic shifts persist. With such an increasing prevalence, depression would be the second major cause of disability-adjusted life years (DALYs) after ischemic heart disease [1].

Two-third of the suicide burden was attributed to mental and substance use

disorders in 2010, tallying their global burden to a further 22 million DALYs [2]. The fact that people with depressive disorders are not diagnosed properly and rarely or never receive any treatment further aggravates the issue. Only about 30%–35% of adults benefit from the modern therapeutic approaches of remitting the disease; however, two-third of the disease burden still remains intact [3]. Important predictors of the onset of depressive episodes include female gender, old age, lower social status, inadequate income, comorbidities, marital status and the feeling of loneliness. A study on geriatric homes reported that the depressive disorder represented about 37% of the mental disorders [4]. Moreover, the prevalence of depression was reported to be very high among medical students. One-third of the

medical students are affected by depression, globally [5, 6].

During the ongoing COVID-19 pandemic, the frequency of depression has increased worldwide because of social isolation. A study on healthy old people aimed to explore the impact of COVID-19 and its related social isolation on their physical and mental well-being reported that 12.8% of the participants showed the signs of depression associated with poor sleep and the feelings of loneliness. Subjective loneliness showed a significant relationship with both anxiety and depression [7]. The risk of psychotic disorders in children has increased during the COVID-19 pandemic as it has driven them into a state of crisis [8]. Mental health is adversely affected by the separation from friends, school and colleagues. It increases the risk of developing psychosis, mood disorders and suicide in adults [9]. Moreover, the patients with mental illnesses are considered more vulnerable during a pandemic [10].

This review focuses on research on the causes of depression and the association between vitamin D and depression. For this purpose, a thorough internet search was conducted using keywords such as depression, mental disorder, causes of depression, vitamin D and others in various combinations. Multiple search engines such as PubMed, Sciondirect, Google Scholar and Scopus were used.

## 2. Causes of Depression

Modern theories of depression support the notion that stress is the primary cause which initiates the cognitive and biological processes that increase the risk of depression. The fact that the best predictors of an impending onset of

depression are major traumatic events of life further strengthens these theories.

Although the link between stress induced depression and cognitive processes has been explicitly studied, very little information is available about its connection with the biological processes which along with affective and cognitive processes can lead to depression. The impact of tools developed for assessing the activities of neurons, gene expression, genetic variation and peripheral biology has played a crucial role in recognizing the pathways that may explain the association of the external social environment and the internal biological processes which have the capability of promoting depression [3].

### 2.1. External Factors Contributing to the Onset of Depression

Studies report a strong association of clinical depression with the perceived quality and frequency of social relationships [11]. A study conducted in Saudi medical colleges showed a link between depressive symptoms and students facing unstable socioeconomic conditions and doing smoking [12, 13]. Indeed, certain life events such as those involving social rejection confer a 21.6% increase in the risk of the onset of the major depressive disorder [3]. Another study reported its prevalence at 15.2% among students and the prevalence of suicidal attempts at about 7.7%. A significant association was found between the perceived economic burden, negative influence of night shifts, and physical inactivity. [13]. A study conducted among medical students showed how socio-demographic factors contribute in the onset and progression of depression and its high prevalence [14].

## 2.2. Physiological Basis of the Onset and Progression of Depression

### 2.2.1. Serotonin transporter gene.

Polymorphisms in the promoter region of the serotonin transporter gene (5-HTTLPR) are anticipated to play a part in the pathogenesis of depression by modulating transcription which in turn affects the hippocampal volumes. In subjects with homozygous for long allele (L/L), the later age of the onset of depression and smaller hippocampal volumes were associated. Moreover, there was an association between smaller hippocampal volumes and the early age of the onset of depression in subjects homozygous for short allele (S/S genotype) [15]. A study reported that depression might be linked to the presence of the promoter region of the serotonin transporter gene (5-HTTLPR) [16].

**2.2.2. Stress induced activation of the hypothalamus-pituitary-adrenal axis (HPA axis).** Corticotropin-releasing hormone (CRH) is known as the stress hormone released from hypothalamus under psychological stress. This hormone plays a vital role in the stimulation of the pituitary corticotropin secretion that in turn stimulates the cortisol secretion from the adrenal gland [17]. Abnormalities of the corticotropin / cortisol axis in subjects makes them more liable towards depression [18]. The elevated plasma levels of cortisol may be responsible for the development of depression and its associated complications [19].

### 2.2.3. Inflammatory theory.

Inflammation is a vital biological event that, similar to the conventional psychological reasons, might raise the risk of major depressive episodes. The hypothalamic-pituitary-adrenal axis (HPA axis) is activated by various

inflammatory cytokines such as tumor necrosis factor- $\alpha$ , interleukin-1 $\alpha$  and interleukin-6. This activation leads to the onset of depression. Peripheral infection stimulates innate immune cells to produce pro-inflammatory cytokines. These cytokines act on the brain and produce sickness. In autoimmune diseases, cancers or other infections, the persistent activation of the peripheral immune system results in a continuous immune signaling to the brain. It can exacerbate the sickness and may also cause the development of the symptoms of depression in vulnerable persons. This phenomenon explains the high prevalence of depression among physically ill people [20].

Although inflammation is normally supposed to be the body's primary response to any infection or physical injury, studies have reported that inflammatory activity can be triggered by psychological stress even in the absence of any physical injury. This triggering of inflammation profoundly alters the behaviour and induces the onset of the symptoms of depression such as fatigue, anhedonia, sad mood, social-behavioral withdrawal and psychomotor retardation. These results consequently support the hypothesis that external social conditions may regulate the molecular processes, which in turn activate the behavioral and biological alterations that increase the possibility of the onset of depression [21].

### 2.2.4. Disturbance in the neurotransmitters.

The theory of monoamine deficiency elucidates the basis of depression as the depletion of norepinephrine, serotonin and dopamine in the central nervous system. Among the most widely studied neurotransmitters in depression is serotonin. An abnormal reduction in

serotonin leads to the progression of the depressive symptoms [22]. There is also evidence of the abnormalities of the serotonin receptors in depression [23]. Moreover, in depressed people, a reduction in the metabolism of norepinephrine, an increase in the tyrosine hydrolase activity, and a decrease in the level of the transporters of norepinephrine in the locus coeruleus were reported [24]. Furthermore, it was found in the post-mortem analysis that in the brains of the depressed suicide victims there was an increased level of alpha-2 adrenergic receptor density and a decreased level of alpha-1 adrenergic receptor density [25]. The levels of *dopamine* in the cerebrospinal fluid are reduced in depression, [26]. Moreover, in acute depression there is a decrease in hippocampal total *gamma-aminobutyric acid (GABA)* concentrations in the prefrontal and occipital cortex [27].

### 2.2.5. Insomnia and depression.

Depression is very common in people with various sleep disorders. Insomnia is consistently identified as a risk factor for recurrent or a new-onset depression in people of every age group [28]. Recent studies demonstrated that depression can be reduced by both non-pharmacological and pharmacological interventions for insomnia [29]. Sleep disturbance leading to depression may occur due to the disturbance in the physiological / biological clock and the dysregulation of the circadian rhythm leading to disturbance in corticosteroids secretion that can be one of the causes of depression [30].

## 3. Vitamin D Deficiency and Depression

Vitamin D (vit D) is a fat soluble vitamin that works as a steroid hormone. The UVB-induced conversion of 7-dehydrocholesterol to vit D in skin is the prime source of vit D in human beings.

Vitamin D plays a critical role in bone development, intestine, cardiovascular system, immune system, muscles, pancreas, cell cycle control and brain [31].

Recent studies reported an association between this vitamin and depression, although the mechanism that governs this association is not fully understood. Moreover, it is still not clear whether depression causes a decrease in the level of vitamin D in serum or vice versa. The only available evidence is that the low serum vitamin D level escalates the risk of developing depression. One biologically plausible explanation of the association between vitamin D and depression is that the former is a neuroactive steroid which plays a role in the expression of neurotransmitters, neuroimmunomodulation, the regulation of neurotrophic factors and the production of antioxidants [32, 33].

The receptors of vitamin D are present throughout the central nervous system and the hippocampus [34]. The first evidence of the role of vitamin D in brain function came from the immunohistochemical studies. Multiple regions of the brain contain a wide distribution of vitamin D receptors and vitamin D activating enzyme 1-alpha-hydroxylase. They are particularly abundant in the amygdala, neurons, and glial cells of the hypothalamus of the brain [35]. The receptors of vitamin D are also present in the proliferating zones and the neuroepithelium of the brain; however, their expression is not limited to these regions. Studies reported low levels of circulating 25-hydroxyvitamin D (25(OH)D) to be associated with dementia and cognitive impairment in the older members of the population. In studies on animals, it was found that the supplementation of vitamin D plays a

protective role against Alzheimer's disease and aging. These experiments provided ample evidence of possible mechanisms through which vitamin D might play a role against neurodegeneration. On the other hand, no association was reported between the increase in the level of 25(OH)D and an improved cognitive result [36]. The role of vitamin D as a regulator of the expression of interleukins and neurotrophic factors has further increased the interest in investigating its possible role in the onset and progression of depression, although no general consensus has been achieved so far about the lower levels of 25(OH)D in the serum. Depressive symptoms triggered by the activation of P2X7R/NLRP3 due to the inadequacy of vitamin D demonstrate its possible neuroimmunological role via the regulation of expression and the activity of P2X7R. This prevents the excessive activation of the immune system due to long-term stress. [37]. Another evidence is changes in the neuronal activity during depression. These changes are linked with an increase in glutamate that drives the excitatory neurons and possibly declines the number and activity of GABAergic inhibitory neurons, thus causing an imbalance between excitatory and inhibitory neurons. This contributes to the beginning of the symptoms of depression. At cellular level, the concentration of intracellular  $Ca^{2+}$  increases within the inhibitory neurons possibly due to two processes. Firstly, it is driven by phosphoinositide signaling pathway activation. This releases calcium from the internal storage due to the generation of trisphosphate (InsP3). Secondly, an increase in influx through the NMDA receptors (NMDARs) increases the level of the intracellular  $Ca^{2+}$ . The upsurge in the level of  $Ca^{2+}$

contributes to depression. The phenotypic stability hypothesis states that vitamin D plays a role in depression by decreasing the neuronal level of  $Ca^{2+}$ . The role of vitamin D in moderating the signs of depression is due to its part in maintaining the expression of  $Ca^{2+}$  pumps and buffers that reduce the level of  $Ca^{2+}$  [38, 39]. Furthermore, Vitamin D has a role in controlling the synthesis of the neurotrophic agents such as the nerve growth factor (NGF) and glial cell-line-derived neurotrophic factor (GDNF), which imparts it a crucial role in the differentiation and maturation of neurons [40]. Vitamin D activates and deactivates enzymes in the brain and in the cerebrospinal fluid that are involved in the neurotransmitter synthesis and nerve growth [41, 42]. A study on obese subjects reported improvement in the depressive symptoms in subjects which received a high dose of vitamin D which indicates a possible relationship between depression and vitamin D [43].

#### 4. Conclusion

The lower level of vitamin D in serum presents an increased risk of depression. Many socio-demographic factors, genetics, dietary patterns, and sex should be accounted for to understand the role of vitamin D and the causes of its deficiency in order to improve and regulate depression. Moreover, extensive studies should be carried out at cellular and molecular levels to fully understand the various possible mechanisms of the action of vitamin D in the brain which may lead to the regulation of depressive symptoms.

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