Chapter

Association of Vitamin D Deficiency and Mood Disorders: A Systematic Review

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Abstract

The cells of our body comprise calcitriol (1,25(OH) vitamin D_2), the active form of vitamin D, an integral biological substance that has an impact on a large number of biological processes. While high prevalence of vitamin D deficiency is detected in population worldwide, the reports from sun-soaked countries like India are also alarming to note that the deficiency of vitamin D as high as 70 to 90% is observed leading to several chronic diseases in the majority of people. Deficiency of vitamin D is observed not only because of low levels of vitamin D in the diet, less exposure to sunlight, reduced cutaneous vitamin D synthesis, but also due to consumption of particular medicines, undue alcohol intake, and tobacco smoking. Vitamin D is known to affect estradiol, dopamine, and pro-inflammatory cytokine levels, besides being involved in the regulation of mechanisms pertaining to hormones like glucocorticoids. When vitamin D binds to vitamin D receptors (VDR) present in the central nervous system, it is noted to be responsible for the regulation of brain neuronal functions. Low 25-hydroxy vitamin D levels are found to have a higher incidence of various mood disorders. This review focusses on vitamin D receptors, VDR gene mutations, and pathophysiology causing vitamin D deficiency disorders.

Keywords: vitamin D, VDR receptors, mood disorders, deficiency, insufficiency, cognition

1. Introduction

Vitamin D is an integral biological substance used to maintain bone health primarily, but it also plays its importance in several other biochemical pathways within the human body. Vitamin D, at the end of its metabolizing physiology, gets converted into an active hormone metabolite of vitamin D, i.e., calcitriol $(1,25(OH)_2$ vitamin D), which binds to vitamin D receptors (VDR). Vitamin D enzymes present in the central nervous system are responsible for the regulation of cellular function in several tissues located in the body including brain neurons. Vitamin D comes in two main forms: the first form is vitamin D_2 also known as ergocalciferol which is obtained from sources like mushrooms grown in UV light, dietary supplements, and fortified food, and the second form of vitamin D is vitamin D_3 also known as cholecalciferol, obtained from oily fish and fish oil, liver, egg yolk, butter, and dietary supplements. Vitamin D_2 and D_3 are not equal when it comes to raising your vitamin D status. Both are effectively absorbed into the bloodstream. However, the liver metabolizes them differently. The liver metabolizes vitamin D_2 into 25-hydroxy

vitamin D_2 and vitamin D_3 into 25-hydroxy vitamin D_3. These two compounds are collectively known as calcifediol. The main circulating form of vitamin D is Calcifediol. The amount of Calcifediol can be determined by checking its blood levels in the body. However, vitamin D_2 seems to yield less calcifediol than an equal amount of vitamin D_3 [1, 2].

Vitamin D deficiency is prevalent worldwide. The knowledge of the causes of vitamin D deficiency and community affected by the same causes are prominent, and hence, differentiation in the therapy and supplementation of these populations is focused upon accordingly. Further, in India, the prevalence of vitamin D deficiency ranges from 40–90% in all age groups and high-risk groups alike, with the majority of study responses reporting 80–90% prevalence as reported by the National Center for Biotechnology Information (NCBI), India [3]. Vitamin D deficiency contributes to a high disturbance in the health/disease ratio and adds to the disease burden of the country [4, 5]. The daily requirement of the human body for vitamin D is not fulfilled by the dietary pattern of the Indian population, and hence, fortification of various foods with vitamin D is emphasized under the initiatives of various national programs [2].

Vitamin D deficiency can be defined as circulating 25(OH) vitamin D levels below 20 ng/ml, while vitamin D insufficiency is defined by circulating levels below 32 ng/ml [3]. Vitamin D receptors are located in the bone, skeletal muscle, immune cells, and several other body tissues (including brain, prostate, breast, and colon). Deficiency of vitamin D hormone at its receptor site or the enzyme metabolizing site causes disturbed cell signalling, further indicating the increased risk of diseases like autoimmune diseases, cancer, tuberculosis, cardiovascular diseases, bone diseases, neurodegenerative diseases, and mood disorders, specifically discussed in this review. Low 25-hydroxyvitamin D levels less than 20 ng/ml are found to have a higher incidence of mood disorders consisting of premenstrual syndrome (PMS), seasonal affective disorder (SAD), non-specified mood disorder, and major depressive disorder (MDD) [1].

The physiology of vitamin D in the human body involves both synthesizing and catabolizing pathways. Vitamin D is either absorbed by dietary intake or is synthesized in the presence of ultraviolet B (UVB) rays ranging from 290 to 310 nm. In the epidermal layer of the skin, 7-dehydrocholesterol gets converted into pre-vitamin D_3 in the presence of UVB rays, which further, under thermal reaction, forms vitamin D_3 (also known as cholecalciferol). Vitamin D-binding proteins bind to vitamin D_3, and by circulatory transport this protein-bound vitamin D_3 reaches the liver, where it is further metabolized into 25(OH) vitamin D (calcifediol) and an inert form of vitamin D. Tightly regulated by parathyroid hormone (PTH), 25(OH) vitamin D converts into 1,25-dihydroxy vitamin D (also known as calcitriol), which is an active hormonal form of vitamin D in the kidneys and other extrarenal tissues. This active metabolite binds to vitamin D receptors to regulate the several tissue and cellular functions. When vitamin D deficiency occurs due to inadequate intake of vitamin D through diet or by application of excessive sun-protective agents, it causes dysfunctional regulation of glucocorticoid signalling which is known to be implicated in major depressive disorders and various other mood disorders, together with other body functioning disorders. It is reported to have elevated levels of glucocorticoid (a type of cortisol) for the patients of MDD [1, 6].

This review discusses sources of vitamin D, its association with different types of mood disorders in a different population, and its disease processes, together with the possible downstream molecular and genetic pathways associated with vitamin D deficiency and mood disorders. Further, this review focusses on the vitamin D deficiency causing mood disorders to the childbearing mothers and premenstrual syndrome to the ladies on the onset of their menses.

2. Vitamin D status

Vitamin D status is determined by assessing serum levels of 25(OH) vitamin D after 3 months of a stable regimen of vitamin D intake. Serum 25(OH) vitamin D is used to measure vitamin D status because it is the major circulating form of vitamin D and the most stable form of vitamin D. The National Health and Nutrition Examination Survey (NHANES) III data 8, which used a conservative measure of vitamin D deficiency {25(OH) vitamin D} levels <15 ng/mL, has reported 42.4% of African American women and 4.2% of white women are deficient in vitamin D during their childbearing years [2, 8, 9].

Toxic states (hypervitaminosis D) may occur when 25(OH) vitamin D levels supersede 100 ng/ml; however, in a study involving individuals diagnosed with multiple sclerosis treated with high doses of vitamin D, there was no evidence of toxicity found in individuals with 25(OH) vitamin D levels above 200 ng/ml [1].

3. Dietary recommendations of vitamin D

The dietary recommendations are largely based on bone health and assuming a minimal sun exposure of an individual under study. While the safe upper limit is set at 4000 international unit/day (IU/d) for healthy adults, for pregnant women, doses are higher than 6000 IU/d. Based on limited data from randomized controlled trials, some authors suggest that pregnant women can be supplemented with 1000–2000 IU/d during the second and third trimesters, and a deficiency during pregnancy can be treated with daily doses of 4000 IU [5].

4. Synthesizing and metabolizing physiology of vitamin D

Vitamin D is a secosteroid hormone that is either absorbed by dietary intake or manufactured by the ultraviolet beam (UVB) rays ranging from 290 to 310 nm reaching the epidermis of the skin. In the presence of epidermal 7-dehydrocholesterol, the absorbed vitamin D gets converted into pre-vitamin D_3. Within the epidermis, a thermal reaction occurs to convert the pre-vitamin D_3 into vitamin D_3 also known as cholecalciferol [10, 11]. Vitamin D_3 further, in process, moves to bind to the vitamin D-binding plasma proteins. Vitamin D_3 is transported via vitamin D-binding proteins to the liver where it is metabolized into 25(OH) vitamin D (calcifediol) and an inert form of vitamin D. Calcifediol is tightly regulated by parathyroid hormone and converts it into 1,25-dihydroxy vitamin D also known as calcitriol [1]. Calcitriol is the active form of vitamin D, which binds to VDRs in the intestines, bones, and kidney and other extrarenal tissues to enhance the absorption of calcium from the intestines, promotes calcium deposition in bones, and decreases parathyroid hormone concentrations (PTH) [3, 6]. In the process, calcitriol binds to vitamin D receptors, the receptors from the nuclear receptor superfamily that regulates the cellular function in several tissues located in the body including brain neurons [1].

5. Challenges for estimation of serum vitamin D level

The estimation of calcitriol is very challenging as calcitriol ($1,25(OH)_2$ vitamin D) has very short $t_{1/2}$ and thus does not reflect long-term vitamin D status. Also, it is observed that the total 25(OH) vitamin D is the most reliable marker for vitamin D

status which measures both vitamin D-binding protein (DBP)-bound and free 25(OH) vitamin D. In the light of widespread variation in measured results and divergent results in response to vitamin D supplementation, there is a need for a distinct method for estimation of vitamin D levels. Further, free 25(OH) vitamin D levels may vary according to genotype and single nucleotide polymorphisms (SNPs) in the DBP gene for which the assays are still not well established [5].

6. Prevalence of vitamin D deficiency

Vitamin D receptors are traced throughout the brain explaining the role of vitamin D in psychosomatic disorders, and it was found to have an equivocal call for vitamin D deficiency and depression going hand in hand [12].

Vitamin D insufficiency/deficiency is a worldwide problem, affecting all ages and races. Optimal 25(OH) vitamin D concentrations for skeletal health are >30 ng/ml. Serum 25(OH) vitamin D concentrations are generally lower in blacks than in whites and people who avoid exposing them to the sun. The increased use of sunscreens is hypothesized to increase the prevalence of vitamin D deficiency. Older adults, as a result of hyperparathyroidism related to renal insufficiency, tend to require more vitamin D to achieve adequate levels of 25(OH) vitamin D. As a result of the change in the definition of adequate concentrations, the prevalence of vitamin D deficiency is higher than previously thought. The prevalence of vitamin D deficiency among older men and women living in the United States and Europe ranges from 40–100%. The National Health and Nutrition Examination Survey from 2000 to 2004 found that ~25% of men >50 years of age and 30–35% of women >50 years of age had 25(OH) vitamin D concentrations <0.001. Two studies performed in Colorado and Georgia found that despite reported consumption of more than the required daily intake of vitamin D (400–600 IU/d), the prevalence of vitamin D insufficiency (defined as <32 ng/mL and < 20 ng/ml, respectively) among community-dwelling older adults (mean age, 77.8 and 77.0 years, respectively) ranged from 36.7 to 74.0% [3].

7. Vitamin D receptor

7.1 VDR in the brain

Vitamin D receptors are present on the nervous system tissues and cells especially dopaminergic nerves. In the momentary phase of cerebral development, vitamin D may act like a neurosteroid hormone in the areas of neurotransmission, neuroprotection, and neuroimmunomodulation. Vitamin D receptors belong to a hybrid class of nuclear receptor superfamily, which gets activated by vitamin D, a neurosteroid hormone that plays its major role in the nervous system by following mechanisms of differentiating, regulating Ca^{2+} ions, homeostasis, modulation of neurotrophins, and release and activation of key brain hormones and enzymes for neurotransmitter metabolism. VDR is a large molecular weight protein molecule weighing 50–60 kilodaltons, which consists of several functional binding domains, specifically and typically for all steroid hormones responsible for ligand binding, DNA binding, heterodimerization, nuclear localization, and ligand activation of transcriptional factors [13].

VDR detection in the brain tissue has been studied by enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry to understand the localization of nuclear ligand binding sites for the transcription of phenotypic characters [14].

7.1.1 VDR gene location

Two important points of consideration for the production of the active form of vitamin D are 1,25(OH)2 vitamin D_3, a vitamin D receptor, and an enzyme 1 α-hydroxylase, which are found in the adult human brain. Identification of both the receptor and the enzyme were done in neuronal and glial cells in a regional and layer-specific pattern. The equivalent distribution of VDR regions and 1α-hydroxylase enzyme regions together with their frequent discrete distribution is found in layers and subregions of brain tissue [15].

7.1.2 Expression of VDR

Expression of VDR has been documented in tissues, including the brain, heart, skeletal muscle, breast, prostate, colon, activated macrophages, skin, and the areas prone to tumor expression with any devised mutation. The age factor is known to dominantly decrease the VDR expression. Many in vitro studies with human and animal cells have observed the expression of not only VDRs but also an enzyme, 1α-hydroxylase, which is expressed in most of the body tissues and cells, specifically in the kidneys. Therefore, it appears that these cells locally produce the active form of vitamin D by a regulated mechanism, in a paracrine fashion, to be used in various cellular and physiological functions. This structures the strong biologic basis for the association between serum vitamin D concentrations and extra-skeletal physiology [15].

7.1.3 VDR gene mutations

VDR gene mutations have been characterized by altered behavior of VDR null mutant mice. A study revealed anxiety-like behavior with decreased exploration when the VDR mutant mice were subjected to anxiety evaluation [16]. Another study focusing on the investigation of anxiety parameters in VDR mutant mice demonstrated unaltered spatial memory, olfaction, gustation, and hedonic responses [17].

VDR gene mutation is considered to influence the working of vitamin D hormone, which is essential for the growth and differentiation of a variety of organs, including the complete central nervous system. Many studies have suggested the crucial role of vitamin D in the brain, inducing many CNS genes. Inhibition of brain neurotransmission can be seen by VDR gene mutation causing modulation of neuroprotection, neurotrophins release, and activity of key neurotransmitter metabolism enzymes [16].

7.1.4 Regulation of normal brain neurotransmitters by normal VDR gene

The active form of vitamin D, i.e., calcitriol has a fast and strong ligand binding to their respective receptors located in the bone, brain, and breast tissues, as well as in immune cells [6]. The upregulation of transient receptor potential (TRP) vanilloid calcium-selective cation channels, such as TRPV5 and TRPV6, is done by positive induction of vitamin D. Vitamin D regulated channels may express the role of the hormone by potential modulation of sensory pathways representing several cellular sensors responding to temperature, touch, pain, osmolarity, taste, and other stimuli [17].

7.1.5 VDR immunoreactivity

The immunohistochemical study depicted the distribution of the VDR in multiple brain regions inclusive of neuronal and glial cells and other regions of the substantia nigra in the normal functioning human brain. Further, it also revealed

the presence of the VDR and 1α- hydroxylase in the human brain and confirmed the cell expression for either the receptor or the activating enzyme in neuronal or glial origin [14, 15].

8. Effect of vitamin D on mood and cognition

Vitamin D receptors and the 1α-hydroxylase enzyme have been isolated and found in the regions of the cerebral cortex and cerebellum, suggesting the conversion of calcifediol into an active form of vitamin D, i.e., calcitriol in the brain for a local cellular response [3, 18]. Several studies discuss the deficiency of vitamin D in the body at its targeted ligand binding sites due to less sunlight exposure or sun blockage, vitamin D receptor mutation causing phenotypic-conformational changes at the ligand binding site, and insufficient vitamin D-fortified diet, all causing major or minor mood disorders and illustrate the effectiveness of vitamin D or sunlight therapy (phototherapy), gene therapy, or supplemented vitamin D diet therapy for the treatment of depression and other mood disorders, demonstrating the associations between 25(OH) vitamin D concentrations and mood alone or mood and cognition in adults of all ages, including pregnant women, older adults, and targeted vitamin D-deficient population globally [3, 10].

9. Mood disorders

Vitamin D receptor mutant gene leads to the translation of mutant mRNA into defective vitamin D receptor proteins. Normal VDR is responsible for the regulation of glucocorticoid signalling, which, in this case, gets dysfunctional due to vitamin D deficiency. Dysfunctional glucocorticoid signalling is majorly implicated in several mood disorders like major depressive disorders, seasonal affective disorders, etc. Glucocorticoid, a type of cortisol, is seen to be increased in MDD and decreased in bone disorders. According to the recent diagnostic and statistical manual of mental disorders (DSM-IV), a major depressive disorder is diagnosed or said to be present when a person exhibits at least five of the following symptoms during 2 weeks, most of the day or nearly every day:

- Depressed mood
- Loss of interest or pleasure in daily activities
- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to concentrate or make decisions, problem with attention and cognition
- Recurrent suicidal thoughts with or without a plan [1]

Genes are encoding for vitamin D_3, 25-hydroxylase, and 1α-hydroxylase (CYP27B1), where CYP27B1 are the enzymes that metabolize vitamin D_3 into calciferol hormones, which is further involved in brain functions. These are expressed in neurons and glial cells presenting VDR. Calciferol hormone, being a neuroactive compound, regulates the behavioral functions such as anxiety, hyperactivity, and depression. Hypovitaminosis is a deficient condition that is found to be associated with an increased risk of multiple sclerosis, seasonal affective disorder, schizophrenia, Parkinson's disease, and Alzheimer's disease. Vitamin D deficiency could also be associated with autism, explained by a piece of indirectly related evidence. Furthermore, mood and cognitive performance appear to be dependent on plasma vitamin D level to some extent [19].

10. Types of vitamin D-deficient mood disorders

10.1 Seasonal affective disorder

Prevalence of seasonal affective disorder is seen when the vitamin D stored in the body are low with prominent seasonal changes. The disorder occurs during a particular time of a year where the sun exposure to the skin decreases leading to vitamin D deficiency, and the symptoms of the disorder can be resumed spontaneously on sun exposure. The individuals suffering from seasonal affective disorder have typically reported depression-like symptoms mostly in the winter months, where the levels of intensity of sunlight and photoperiod were predominately reduced [19–21]. Studies in the United Kingdom estimated the prevalence of SAD between 2.4 and 3.5%. The etiology of this disorder has not been fully elucidated, but the mechanisms leading to SAD are understood and linked to reduced sunlight exposure and daylight length. SAD is led via an eye-brain-endocrine system pathway or a skin-vitamin D causal pathway. In the mammalian population, the first stage of in vivo vitamin D synthesis necessitates the irradiation of skin by UVB light, dependently showing the lower vitamin D serum levels in the winter months than that in summer months. It has been also postulated that at cellular or subcellular levels, vitamin D can directly influence the endocrine system of our body via ligand binding on vitamin D receptors present in the entire central nervous system of a human body [21]. A prospective, randomized controlled trial was conducted in a group of 15 subjects with SAD to postulate the hypothesis of the association of vitamin D deficiency and seasonal affective disorder in which eight subjects received 100,000 IU of vitamin D and seven subjects received phototherapy. The Hamilton Depression Scale, Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Depression version (SIGH-SAD), and the SAD-8 depression scale were administered for the evaluation at two stages of treatment, i.e., first at onset of treatment and second after one month of the therapy. Also, intervention therapy was used to measure serum levels of 25-hydroxyvitamin D (25-OH D) planned in a gap of 1 week before and after the intervention. Improvement in all subjects was seen with the one's receiving vitamin D. Depression scale measure had no significant results for the phototherapy [1, 22]. Major improvement was seen in both the abovementioned groups, and this improvement in 25(OH)D was intertwiningly associated with the improvement in depression scale score. Hence, it is evident that vitamin D supplementation has an important role in the treatment of SAD [10, 13, 14].

In order to understand the seasonality of mood change, it is integral to understand the seasonal changes in photoperiod to hypothesize the most vitamin D-deficient mood disorders. Many biological techniques are utilized for detecting photoperiod.

For example, initiation of the behavioral changes such as migration patterns and breeding behavior is conserved in many species, primates, and humans which are evident with changes in season and intensity of sunrays. Further, the scientists pointed out that the regulation of circadian phase shift is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN has been shown to be involved in seasonal affective mood disorders. Further it was also presented that the SCN has an inhibitory action to the hypothalamic–pituitary–adrenal (HPA) axis and that this action can be altered by vitamin D dietary and supplementation restrictions [23].

10.2 Major depressive disorders

Major depressive disorder is a type of depressive disorder that is most likely to observe an association between vitamin D deficiency and anxio-depressive disorders. This association can be demonstrated with a parallel comparison between the motor and behavioral disorders observed in animal models of depression and VDR-KO mice [13]. Several theories are suggesting seasonal mood swings in humans. The binding of vitamin D on the ligand binding site of VDR present on the hypothalamic core (which plays a crucial role in mood regulation) can be witnessed to have a link between several seasonal changes in photoperiod and seasonal mood swings. Epidemiological data are coherent with such a cross-linking hypothesis. As an instance, the evidence is suggestive that the established low serum 25(OH) vitamin D_2 concentrations are closely related to the active experience of mood disorders in 80 subjects aging 65 years and older. Many studies have demonstrated that significant lower serum 25(OH) vitamin D_2 and 1,25$(OH)_2$ vitamin D_3 concentrations are observed in depressive sample subjects than healthy controlled subjects. Indirect confirmation was made by studying the association between depression and osteoporosis in around 4000 women aged 67 years [15]. Nevertheless, these results can also be mitigated and potentially related to functional impairment and physical inactivity, both of which reasons to increase with osteoporosis and have an independent correlative associated with depression [16].

Various clinical trials support the theory of the efficacy of vitamin D supplementation on mood disorders by varied sources like vitamin D-fortified diet, sunsoaking, etc. [17]. Improvement in depression scale experiments was noted, and the improvements were associated with vitamin D supplementation technique, while not much improvement was observed with the phototherapy technique. It is specifically prescribed to have at least 800 IU daily dose of vitamin D which plays a major decisive role in mood disorder case studies [4, 22, 24].

10.3 Premenstrual syndrome

Premenopausal women face one of the most common disorders known as premenstrual syndrome. Up to 20% of reproductive-aged women are affected in the range of moderate-to-severe premenstrual syndrome and is associated with significant levels of mood impairment. Irritability, mood swings, anxiety, depression, breast tenderness, bloating, and headaches are some of the most common symptoms included in PMS. Women are reported to have a depressed mood during the last week of the luteal phase which resides within for few days from the onset of menses [9]. Many studies have postulated that blood serum calcium levels and vitamin D levels are lower in women with PMS and that vitamin D supplementation and calcium supplementation may reduce the severity of the symptoms [25].

It is hypothesized that the dysregulation of calciotropic hormone is seen to be a major provocative factor in premenstrual syndrome. The severity of the symptoms of PMS is directly linked to calcium homeostasis, regulated directly by vitamin D

and parathyroid hormone as the key factors. However, low dietary vitamin D intake and inhibited induction of parathyroid hormone have been directly associated with the development of premenstrual symptoms [8].

10.4 Postpartum depression (PPD)

Vitamin D insufficiency is common in its most vulnerable pregnant population, and several studies have demonstrated the association of diminished levels of 25(OH) vitamin D with depressive symptoms [4]. Further, the diagnosis of low levels of 25(OH) vitamin D in maternal serum during pregnancy is associated with a higher incidental risk of postpartum depressive symptoms [26, 27]. Serum 25(OH) vitamin D levels for pregnant and postpartum women with major depressive episode, beginning within the first 4 weeks after childbirth, can be influenced by a multitude of factors like age, race/ethnicity, marital status, type of insurance, educational level, feeding type, and others. In addition, the season that accounts for the amount and strength of UVB exposure, i.e., photoperiod and vitamin D supplementation, also are found to be responsible for the episodes of major depression [28]. Vitamin D supplementation during pregnancy increases maternal serum 25(OH) vitamin D levels and thereby ensures higher availability for the offspring neuronal development. Vitamin D levels can also be inversely associated with infertility parameters, preeclampsia, blood glucose, bacterial vaginosis, primary caesarean section, and postpartum depression, but direct correlation is seen in pregnancy associated with breast cancer [28, 29].

The core symptoms of PPD are similar to that of any major depressive disorder like depressed mood or loss of interest in normal activities, sleep and appetite disturbances, loss of energy, feelings of guilt, and suicidal thoughts. Hence, the diagnosis of PPD becomes challenging as the sleep pattern changes and weight changes are also often observed in the normal postpartum period. It is further also exhibited that the lower maternal 1,25(OH)2 vitamin D levels have been found to be associated with higher levels of postpartum depressive symptoms as per the Edinburgh Postpartum Depression Scale scores. The promising results were observed by only one randomized clinical trial wherein the assessment was done by administration of high-dose vitamin D therapy in depressed subjects [6, 7].

Following birth in the first few days, the lower levels of 25(OH) vitamin D are reported for a greater risk of postnatal depressive symptoms and are also linked to serum vitamin D level in the second trimester of pregnancy. Further, the association of low 25(OH) vitamin D level was established with a continuous enhancing risk of reported level of symptoms that may indicate any one type of mood disturbance. Thus, it is confirmed that adequate intake of vitamin D is essential during pregnancy not only for the positive impact on the health and development of the offspring but also is a way to protect against postpartum mood disturbance in mothers [26]. Also, estrogen supplementation and vitamin D therapies have beneficiary effects on inflammatory response and related factors in women suffering from PPD [6, 29, 30].

When accounting the cortisol levels and hypothalamic–pituitary–adrenal axis reactivity in postpartum women, during the third trimester, maternal cortisol levels reach approximately three times that of nonpregnant levels. While the basal levels of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone, and cortisol are high, the HPA axis reactivity to stressful stimuli is dampened in late pregnancy. Furthermore, while the baseline cortisol levels return to normal within a couple of days after parturition, the hyporesponsiveness of HPA axis is found to be persistent in breastfeeding women [6].

The HPA axis hyperactivation or hypoactivation has always been associated with depressive states. It has also been hypothesized that depression during pregnancy

and postpartum depression may have different pathogenesis; the first is found to be dejected with hyperactivity in the HPA axis and the second being atypical. The activity of the HPA axis is usually reduced in seasonal affective disorder, atypical depression, and PPD, which could point to a similar pathologic mechanism in all the three conditions mentioned. Furthermore, the physiological excess production of CRH at the end of pregnancy leads to a transient downregulation of hypothalamic CRH postpartum, which could possibly lead to an elevated risk for depression. Indeed, the hypothesis of PPD being related to hypoactivation of the HPA axis has been substantiated by a number of studies where women with PPD display lower baseline or reduced HPA responsiveness than controls, although conflicting data are available. In addition, women with a history of PPD appear to have increased levels of corticotropin-releasing hormone which further stimulates the dependent cortisol response in the experimental conditions of pregnancy. PPD can also be predicted by increased stress-induced cortisol levels or CRH levels [6, 20].

Together with SAD, PPD has also been classified, under the depressive states characterized by hypoactivation of the HPA axis. Increased serum concentrations of biomarkers detecting the inflammatory response, for example, IL-6, a pro-inflammatory cytokine with a variety of endocrine and metabolic actions, have been observed in major depressive conditions. In this, IL-6 interacts with the HPA axis, and the interacted complex has significant higher serum levels in women with postpartum depressive symptomatology. Conclusively, vitamin D affects monoamine functional groups, the HPA axis, and immune responses to stress and symptom production [20, 38].

10.5 Aging depressive symptoms

Aging depressive symptoms are noticed for both hypervitaminosis D_3 and hypovitaminosis D_3, which leads to premature aging of fibroblast growth factor 23 (FGF-23) that is emerging as a significant mediator/hormone for early aging symptoms, and its FGF-23 effects are dominated by vitamin D-mediated excess of calcitriol. The early aging phenotypic features include thin skin, intestinal atrophy, spleen atrophy, muscle atrophy, weight loss, short life prognosis, osteoporosis, and atherosclerosis. There is a tight physiological regulation of 24-hydroxylase, the hormonal form of vitamin D_3, which can be modulated by physiological serum concentrations of calcidiol. This regulation of hormonal form of vitamin D_3 explains the development of aging depressive symptoms [31]. However, some intoxications occur during the early period of synthesis and distribution of vitamin D_3 with its substitution/fortification. After the Second World War, the children in many parts of Europe were administered with extremely high oral doses of vitamin D_3 and suffered from hypercalcemia, nephrocalcinosis, early aging, cardiovascular complications, and early death, supporting the possibility of hypothesizing that the hypervitaminosis D_3 can accelerate aging symptoms [19, 24, 31].

Calciferol hormone insufficiency may accelerate the risk of diseases of CNS. A recent study postulated that the hypovitaminosis D_3, also famously known as vitamin D deficiency, may cause premature or immature aging of cognitive functions. Thus, both a lack and an excess of calciferol hormones enhance aging in major dependency [32]. Initial events affect the genome, causing telomere shortening or accumulation of DNA damages, which are modulated by the tumor suppressor protein, p53. Hormonal forms of vitamin D_3 appear to control the basic mechanisms of aging and related diseases [19].

The hypothesis of the role of vitamin D in aging is considered based on three axial parameters, namely, calciferol hormone serum concentrations, risk of disease,

and onset of aging. The former two parameters are seen based on lower and higher values, and the latter parameter is seen as the typical or premature onset of aging. It is observed that both low and high action of calciferol hormones trigger premature aging, including diseases of CNS. Hence, an optimal serum concentration appears to delay aging [19].

10.6 Suicidal attempts due to vitamin D deficiency

Significant lower levels of vitamin D are seen in patients with suicidal tendencies than both non-suicidal depressive patients and healthy control individuals. Deficiency of vitamin D was found in 58% of cases of all the reported cases of suicides, compared to around 30% cases found for the healthy controlled cases and the non-suicidal depressed patient cases [33–35].

Accumulating studies indicate that a dysregulated immune system could be a contributing factor to depression and possibly specifically to suicidal tendency. Direct evidence of causality comes both from animal models, where induction of peripheral inflammation is known to lead to depressive changes, and from the so-called cytokine-induced depression in humans, where treatment with interferons (IFN) of patients with hepatitis increases the risk for development of both depression and suicidal tendency [32]. Thus, an indirect proportional relationship between serum vitamin D concentration and inflammatory cytokines is seen to be established, i.e., the lower the vitamin, the higher are the levels of the inflammatory cytokines IL-6 and IL-1β in the blood. The future prospective must be seen to compare vitamin D levels between other groups of psychiatric patients and groups of patients with personality disorders [7, 34, 36].

10.7 Schizophrenia

A study conducted in the year 2006 on the psychiatric population to understand the association between lower plasma levels of 25(OH) vitamin D_3 and mood disorders revealed that all 82 subjects were suffering from psychiatric disorders. Further, 53 patients were suffering from mood disorders, and the remaining 29 patients were diagnosed with schizophrenia. All these patients were found to have low vitamin D_3 plasma concentration which confirms the significant association of low vitamin D_3 plasma concentration with mood disorders and related disease symptoms. Additionally, significant hypovitaminosis D was also witnessed in mood disorders like major depression, bipolar disorder, and dysthymia than with schizophrenia [37]. Also, according to one of the neurodevelopmental hypothesis of schizophrenia, it was revealed that the prenatal vitamin D deficiency in a mother could be a high-risk factor for schizophrenia in an offspring [24].

10.8 Attention deficit hyperactivity disorder (ADHD)

Attention deficit hyperactivity disorder is an early-onset, chronic, a neurodevelopmental disease characterized by attention deficit, hyperactivity, and impulsivity mostly in children, affecting nearly 2–18% of children worldwide, and is found to be one of the most common psychiatric disorders in childhood stage [32]. Learning like basic skills can be affected in childhood and can also cause various psychological and social interaction problems in children and the adult population. The neurotransmitters like dopamine (DA) and noradrenaline (NA) play a crucial role in maintaining attention, concentration, motivation, awareness, and cognition. With the major role of vitamin D in cerebral function, it might have a direct role

in the etiopathogenesis of ADHD in children and young adolescence. Further, vitamin D is also responsible for the regulatory synthesis of neurotrophic factors such as neurotrophin (NT), NT 3 and NT 4, nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF), known to be significantly involved in cell differentiation and survival. Thus, ADHD is etiopathologically connected to vitamin D deficiency. In initial years of growth and development of life, vitamin D deficiency or extensive insufficiency can be harmful to neuronal development and function, resulting in stimulation of neurogenesis [7, 10].

11. Conclusion

To summarize, vitamin D deficiency is associated with several types of mood disorders involving various molecular and genetic mechanisms related to vitamin D receptors and VDR gene. The VDR gene mutation alters vitamin D binding capacity to vitamin D receptor, preventing vitamin D activation into calcitriol which regulates synthesis of neurotrophic factors. Failing to maintain these neurotrophic factors in the presence of vitamin D deficiency leads to cerebral dysfunction and thereby contributes to mood disorder symptoms. Further, vitamin D deficiency is also associated with cognitive reasoning and mind disturbance that trigger off mood disorders like major depressive disorders, seasonal affective disorder, suicidal tendency, postpartum depression to the childbearing mothers, premenstrual syndrome to the ladies on the onset of their menses, ADHD, schizophrenia, and aging depressive symptoms. Futures studies and clinical trials can also be structured to establish a better understanding of the effects of the vitamin D deficiency on several mood disorders, behavioral disorders, and cognition.

Conflict of interest

None.

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