

## Vitamin-D induced neurological disorders: A review

G. Ramya Balaprabha \*, Jeevaniya Anil, G. Surya kiran Reddy, Aryamal Pillai and T. Rama rao

*Department of Pharm. D, CMRCP, Hyderabad, India.*

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### Abstract

Vitamin D inadequacy represents a pervasive global health concern, impacting an estimated 1 billion individuals. Beyond its well-established role in calcium regulation and skeletal health, contemporary investigations reveal that vitamin D serves as a crucial neuro-steroid hormone, exhibiting diverse protective and regulatory functions within the brain. Neurons and glial cells express vitamin D receptors, with particularly elevated levels found in key regions such as the hippocampus, hypothalamus, thalamus, subcortical grey nuclei, and substantia nigra. Insufficient levels of vitamin D have been associated with compromised functionality in various cerebral processes. The deficiency in serum 25-hydroxyvitamin D concentrations may be reversible, providing a potential avenue for intervention. Given the limited availability of efficacious therapeutic alternatives, beyond disease-modifying strategies, comprehensive exploration of various risk factors is imperative. Addressing these factors in the realm of neurology may contribute to ameliorating brain disorders. Associations between genetic and environmental factors and prolonged vitamin D insufficiency as a predisposing element for diverse neurological conditions necessitate thorough examination. This underscores the importance of scrutinizing the role and justification of vitamin D-based therapeutic interventions. The straightforward and cost-effective nature of such interventions may offer potential benefits in both primary and secondary prevention of a spectrum of neuropsychiatric illnesses.

**Keywords:** Vitamin D; Neurological disorders; Calcium regulation; Gene-environmental influence

### 1. Introduction

Vitamin D, sometimes referred to as "calciferol," is a fat-soluble vitamin that may be obtained as a dietary supplement, added to some meals, and found naturally in select foods. Additionally, it helps the intestines absorb more calcium, magnesium, and phosphorus. Vitamin D Receptors have been found in neurons and glial cells, with the hippocampus, hypothalamus, thalamus, subcortical grey nuclei, and substantia nigra exhibiting the greatest expression. The two main kinds of vitamin D are vitamin D<sub>2</sub> (ergocalciferol) supplements and fortified foods, whereas vitamin D<sub>3</sub> (cholecalciferol) is produced in the skin after exposure to sunshine or UV radiation, or from vitamin D<sub>3</sub> supplements or fortified foods [1]. Normal neurodevelopment depends on vitamin D, and deficiencies are associated with several diseases [2]. Vitamin D levels in the normal range are measured in nanograms per milliliter (ng/mL). 30ng/ml-40ng/ml is considered appropriate and healthy, 20ng/ml-30ng/ml is considered inadequate, less than 20ng/ml is considered deficient, and greater than 80 ng/ml is considered excessive is associated with negative side effects. Low blood calcium levels (hypocalcemia), low blood phosphate levels (hypophosphatemia), rickets (childhood bone softening), and osteomalacia (adult bone softening) can all be caused by vitamin D deficiency [3].

Neurological disorders are medical conditions that affect both the brain and the nerves. This substance is found throughout the human body, including the spinal cord. A wide range of symptoms can be produced by anatomical, metabolic, or electrical abnormalities in the brain, spinal cord, or other body parts, possibly different nerves [4]. Neurological difficulties include epilepsy, learning disorders, neuromuscular issues, autism, attention deficit disorder,

\* Corresponding author: G. Ramya Balaprabha

brain tumors, and cerebral palsy. Certain neurological illnesses are congenital, which means they appear before birth. Other diseases can be caused by tumors, degeneration, traumas, infections, or structural anomalies [5]. Vitamin D can be created by the skin via photosynthesis or consumed. UVB rays hydroxylate pre-vitamin D twice, the first in the liver and the second in the kidney. Vitamin D exists in a variety of forms depending on the degree of hydroxylation: the active form is 1,25-dihydroxy vitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub>D<sub>3</sub>), which is produced by the alpha-hydroxylation of 25-OHD<sub>2</sub>. By primarily attaching to the vitamin-D receptor, 1,25-(OH)<sub>2</sub> D<sub>3</sub> influences target tissue expression. Vitamin D targets have been discovered in non-bone tissues, particularly brain tissue, in rats and humans, with Vitamin D receptor densities comparable in both species [6].

Vitamin D is a neuroprotectant as well as a growth regulator for the brain. It contributes to the regulation of neurotrophin, neural differentiation, and maturation by controlling the synthesis of growing factors (such as neural growth factor [NGF] and glial cell line-derived growth factor [GDNF]), septohippocampal pathway trafficking, and the synthesis of various neuromodulators (such as acetylcholine [Ach], dopamine [DA], and gamma-aminobutyric [GABA] [7].

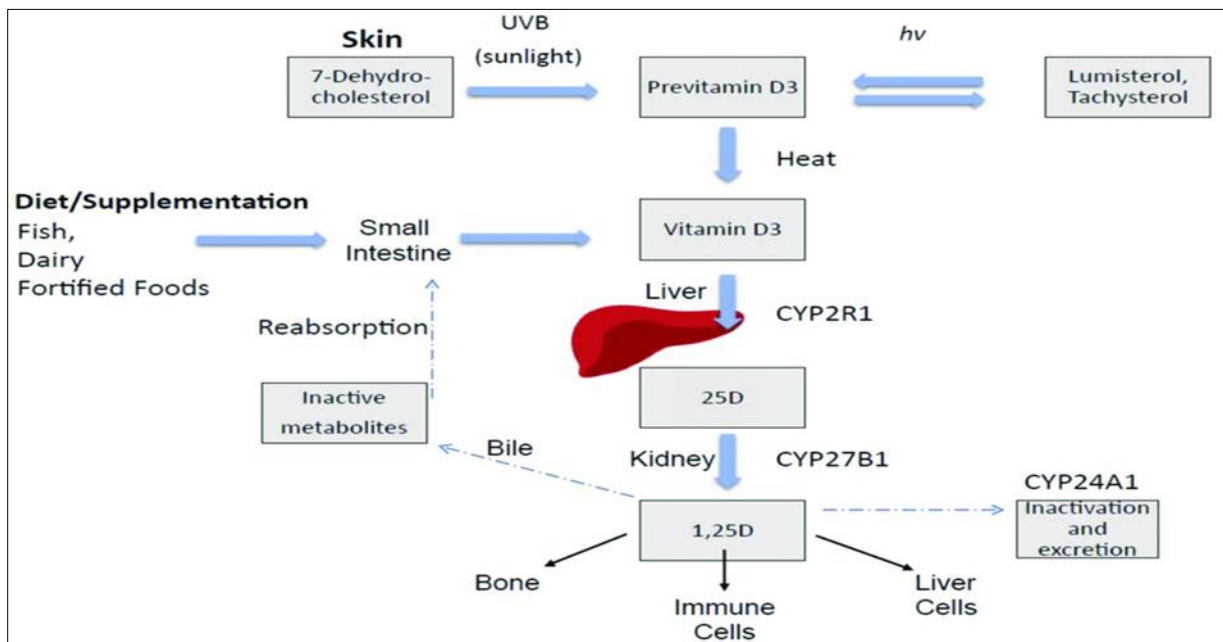


Figure 1 Vitamin D synthesis and metabolism.<sup>[8]</sup>

## 2. Co-Relation Between Vit-D and Neurological Disorders

### 2.1. Role of Vitamin D in Neurological Disorders

The intricate nervous system, a sophisticated network of cells and organs, governs physiological functions within the body. Comprising the brain, spinal cord, and peripheral nerves, this intricate system oversees all cognitive processes and actions. The brain serves as the command center, dictating thoughts and actions, while the spinal cord facilitates the transmission of information from the brain to the body. Peripheral nerves act as conduits, relaying information from the central nervous system throughout the rest of the body [9].

Integral to the optimal functioning of the nervous system, Vitamin D plays a crucial role in the development and maintenance of nerve cells. By modulating calcium levels within the brain, Vitamin D ensures the continual growth and support of nerve cells.

A deficiency in Vitamin D has been associated with various neurological disorders, encompassing Alzheimer's disease, dementia, Parkinson's disease, and multiple sclerosis. Moreover, inadequate levels of Vitamin D have been correlated with conditions such as depression, anxiety, and other mental health disorders [10].

### 2.1.1. In Depression

Vitamin D-responsive elements have been discovered in the promoter regions of two genes associated with depression: serotonin receptors and tryptophan hydroxylase. Vitamin D is also known to protect against the serotonin-depleting effects of neurotoxic methamphetamine doses. When compared to the general population, those with moderate and severe depression had significantly lower mean levels of 25-hydroxyvitamin D. Lower blood 25OHD<sub>3</sub> levels and greater serum parathyroid hormone levels were shown to be significantly associated with the severity of symptoms [11]. Vitamin D is thought to play a key role in depression development by altering intracellular calcium levels and cellular signalling [12]. Several organs, including the brain, produce active forms of vitamin D, as do vitamin D receptors (VDRs); moreover, vitamin D binding proteins (DBPs) have been found in the CNS, notably in areas associated with mood and sadness [13].

Given the relevance of the hippocampus in the causes of depression, the discovery of Vitamin D receptors inside it has encouraged numerous researchers to study how vitamin D impacts hippocampal shape and function [14]. Several studies using in vitro hippocampus cell culture and in vivo trials on adult mouse brains have shown that vitamin D deficiency can alter the structure or function of hippocampal development [15]. Females were found to be low in vitamin D than males. The association between vitamin D and depression was studied, and it was shown that persons with low vitamin D levels are more prone to suffer from depression [16].

A variety of mechanisms are involved in the aberrant increase in neuronal Ca<sub>2</sub><sup>+</sup>, which appears to be the cause of depression [17]. A rise in glutamate, which raises Ca<sub>2</sub><sup>+</sup> by acting on both ionotropic and metabotropic receptors, appears to be a key feature of depression. For example, the NMDA receptor (NMDAR) is an ionotropic channel that increases the entry of extracellular Ca<sub>2</sub><sup>+</sup> in response to glutamate. Ketamine, an antidepressant, works by inhibiting NMDARs and decreasing the input of exogenous Ca<sub>2</sub><sup>+</sup> [18]. One of the impacts of ketamine acting to reduce intracellular Ca<sub>2</sub><sup>+</sup> levels is that it stimulates protein synthesis, which is essential to re-establish synaptic connections destroyed during depression [19].

### 2.1.2. In Anxiety

Vitamin D activity should be assessed in anxiety due to increased transcription of the vitamin D receptor and the presence of the 1-hydroxylase enzyme. There is an association between vitamin D and anxiety. It is suggested that dopamine, serotonin, and norepinephrine deficits are also involved in the pathogenesis, but this is frequently associated with lower inhibitory signalling by GABA or hyperexcitability caused by increased excitatory glutaminergic neurotransmission [20]. Females show a somewhat higher relationship between anxiety and vitamin D deficiency than males. Increased 25(OH)D levels have been associated to a decreased incidence of anxiety [21]. By binding to VDR and the vitamin D activating enzyme 1α-hydroxylase, which are broadly distributed in neuronal and glial cells in the human brain, vitamin D works as a neurosteroid hormone across the blood-brain barrier [22].

Anxiety, depression, and other mental health issues can coexist [23]. Vitamin D activity should be investigated due to increased expression of the vitamin D receptor and the presence of the 1-hydroxylase enzyme. Vitamin D insufficiency has been linked to hypothalamic-pituitary axis dysfunction [24]. This research supports the relationship between vitamin D and anxiety. Anxious people have decreased calcidiol levels. Calcidiol is formed as a by-product of vitamin D metabolism. Inadequate vitamin D levels have been related to an increased risk of depression, diabetes, and cancer after diagnosis. Anxiety and vitamin D insufficiency has long been associated in ancient writings. According to several findings, limited sun exposure leads to poor mental health [25].

### 2.1.3. In Dementia

Low vitamin D levels have been related to lower brain sizes and an increased risk of dementia and stroke. The lowest vitamin D concentrations (25 nmol/L) had the greatest impact on dementia risk. There are multiple proposed pathways that link low vitamin D levels to the risk of dementia. Vitamin D receptors are distributed throughout the brain, including memory centres, and the active form of vitamin D, 1-hydroxylase, is produced in a variety of cerebral sites. The active form of vitamin D, 1,25-D<sub>3</sub> (1,25-D<sub>3</sub>), regulates neurotrophin expression, including nerve growth factor, neurotrophin 3, and glial-derived neurotrophic factor, as well as neural cell survival, development, and function [26]. The most substantial links between vitamin D insufficiency and dementia and stroke were seen in those with levels less than 25 nanomoles per litre, or nmol/L. Low vitamin D levels were linked to dementia but not to the risk of stroke in subsequent investigations that looked into probable explanations. Low vitamin D levels of 25 nmol/L were projected to be 54% more likely to cause dementia than usual vitamin D levels of 50 nmol/L [27].

#### 2.1.4. In Cerebral Palsy

Cerebral palsy (CP) is a group of unique neurologic children's developmental illnesses characterized by a combination of physical symptoms such as aberrant posture, difficulty balancing, and unusual movement. This clinical disease is the result of brain damage or malfunction [28]. Vitamin D deficiency is frequent in children with Cerebral Palsy due to a multitude of factors such as insufficient sunlight exposure, non-ambulatory nature, anticonvulsant use, and feeding issues [29]. The prevalence rates for vitamin D deficiency and insufficiency in children with cerebral palsy are subject to varied degrees of ambiguity [30].

#### 2.1.5. In Alzheimer's Disease

Alzheimer's disease (AD) is a neurological illness that causes behavioural abnormalities as well as progressive, irreversible cognitive decline. Vitamin D increases macrophage activity, which reduces the cytotoxicity and cell death caused by amyloid in the brain's main cortical neurons. It is involved in the activation of induced nitric oxide synthase (iNOS), which aids in the regulation of inflammation caused by Alzheimer's disease. According to epidemiological studies, vitamin D insufficiency and the neurodegeneration associated with Alzheimer's disease are significantly connected. Alzheimer's patients are more vulnerable to neurodegenerative illnesses due to the combined effects of vitamin D deficiency and ageing. Vitamin D deficiency affects up to 70% to 90% of Alzheimer's sufferers. Despite the fact that low vitamin D levels are a substantial but non-specific risk factor for Alzheimer's disease, vitamin D therapy may be the most effective strategy to prevent long-term brain damage [31].

Vitamin D may give advantages to reduce the chance of or postpone the onset of, Alzheimer's disease at pre-clinical and mild cognitive impairment ages when noticeable changes in glucose intake and A build-up are already apparent. On average, those with Alzheimer's disease had decreased levels of vitamin D. Low vitamin D levels significantly raise the risk of developing Alzheimer's disease later in life. In one randomized controlled trial, high-dose vitamin D supplementation was not shown to be better to low-dose vitamin D supplementation for the identification or treatment of impairment [32]. Many genes in the MHC region promote sensitivity to Alzheimer's disease [33]. According to the current study, serum vitamin D deficiency (25 nmol/L) was not statistically significant and was only marginally (by 29%) connected to the risk of acquiring Alzheimer's disease in individuals with serum vitamin D deficiency (25-50 nmol/L). Every 1 nmol/L reduction in blood vitamin D levels was associated with a 6% higher risk of Alzheimer's disease [34].

#### 2.1.6. In Parkinson's Disease

The motor symptomatologic trinity of tremor, stiffness, and bradykinesia seen in Parkinson's Disease (PD), the second-most prevalent neurodegenerative disease, is often asymmetric at first. Additional motor elements of the clinical presentation include postural instability, camptocormia, freezing of the gait (FOG), and Pisa syndrome. Non-motor symptoms (NMSs) of Parkinson's disease include autonomic dysfunction, orthostatic hypotension, sleep problems, olfactory dysfunction, sialorrhea, dysphagia, exhaustion, pain, and cognitive and neuropsychiatric issues. In addition to promoting brain development and growth, vitamin D is required for the formation of many neurological illnesses, including Parkinson's disease [35].

Vitamin D deficiency causes dopaminergic neurons to die. Vitamin D receptors and an enzyme essential for the production of 1,25-hydroxyvitamin D, the active form of vitamin D, have been discovered in high quantities in the substantia nigra, the brain area most typically damaged by Parkinson disease [36]. Because the substantia nigra has high quantities of both the vitamin-D receptor and the enzyme that converts vitamin D into its active form, 1-hydroxylase, low vitamin D levels may result in cell death or dysfunction [37]. Thus, chronic vitamin D deprivation may have a role in the death of dopaminergic neurons in the substantia nigra and the development of Parkinson's disease [38]. Vitamin D deficiency is common in Parkinson's disease patients, and the severity of the deficiency is associated to the severity and prognosis of the disease [39]. Vitamin D is beneficial for patients with Parkinson's disease, as evidenced by one patient who had vitamin D therapy and was able to lower their levodopa dosage. Genetic study has enabled the identification of proteins that may link vitamin D to Parkinson's disease pathogenesis [40].

#### 2.1.7. In Epilepsy

Rickets is the most common sign of vitamin D deficiency in children, although it can also produce hypocalcaemic seizures in severe cases. A deficiency of vitamin D impairs the absorption of calcium and phosphorus from the diet. This increases the production of parathyroid hormone, which aids in the maintenance of blood calcium levels by releasing calcium from the skeleton. As a result, blood calcium levels in children with vitamin D insufficiency are frequently maintained; nevertheless, if the skeleton's calcium stores are completely depleted, the new born will suffer hypocalcaemia [41]. Addressing vitamin D insufficiency has resulted in fewer seizures in epileptic patients [42]. There is

some evidence that, in addition to perhaps lowering seizures (SUDEP), vitamin D may contribute to sudden unexpected death in epilepsy [43]. The precise mechanism through which vitamin D aids in the treatment of epilepsy remains unknown. The brain has several vitamin D receptors as well as the enzyme that produces 1,25(OH)<sub>2</sub>D, the active form of vitamin D [44]. Both calcaemic and non-calcaemic activities of vitamin D are considered to impact its effects on the central nervous system [45]. Furthermore, the latter entails alterations in gene expression caused by 1,25(OH)<sub>2</sub>D binding to the nuclear vitamin D receptor [46].

#### 2.1.8. In Multiple Sclerosis

Multiple sclerosis (MS) is a central nervous system inflammatory, demyelinating, and neurodegenerative disease. Multiple sclerosis is thought to be caused by a combination of genetic and environmental factors, although the precise cause is uncertain [47]. The active form of vitamin D increases innate immune responses to some bacteria by inducing monocyte proliferation and macrophage synthesis of interleukin-1 (IL-1) and cathelicidin (an antibacterial peptide). 1,25(OH)<sub>2</sub>VD inhibits the production of immunoglobulin as well as the growth of plasma cells [48]. 1,25(OH)<sub>2</sub>D<sub>3</sub> increases glucocorticoid receptor protein expression, which inhibits methylprednisolone-induced apoptosis in human and murine CD<sub>3</sub> + T cells [49]. Because there is no evidence to support the efficacy of vitamin D in treating clinical symptoms and controlling disease activity, its benefits are largely demonstrated in decreasing immunological markers and improving mental health in patients [50].

#### 2.1.9. In Amyotrophic Lateral Sclerosis

ALS, sometimes known as "Lou Gehrig's disease," is a fatal neurodegenerative illness affecting the motor cortex, brain stem, and spinal cord. It paralyzes people by damaging upper and lower motor neurons. Excess glutamate, the major excitatory neurotransmitter in the brain, is a key component of amyotrophic lateral sclerosis [51]. The nuclear vitamin D receptor is found in human muscle tissue and regulates a large number of genes (up to 5% of the human genome) [52]. Excess glutamate, the brain's principal excitatory neurotransmitter, is a pathogenic feature of amyotrophic lateral sclerosis [53]. Motor neurons are sensitive to high calcium concentrations due to a lack of intracellular calcium-buffering proteins [54].

#### 2.1.10. In Stroke

The central nervous system (CNS) is especially sensitive to low blood sugar and oxygen levels, as well as an ischemic stroke caused by a fast reduction in blood flow to a portion of the brain caused by thrombosis, embolism, or systemic hypoperfusion [55]. Low serum 25(OH)D levels are linked to stroke. Patients undergoing coronary angiography who have low vitamin D levels are at an increased risk of stroke, and vitamin D supplementation may minimize this risk [56]. Individuals with ischemic stroke who were vitamin D deficient had restored vitamin D levels and a significant improvement in their post-stroke prognosis when treated with supplemental vitamin D [57].

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### 3. Conclusion

On the contrary, vitamin D deficiency appears to have a less compelling influence on the onset, progression, and clinical burden of amyotrophic lateral sclerosis. Most research to date have not taken into consideration reverse causality, i.e., low vitamin D levels may be caused by reduced movement or sun avoidance. As a result, randomised clinical trials on vitamin D treatment in people at risk of neurodegenerative diseases are needed to improve knowledge and accuracy about how effectively vitamin D congeners work, how well they are delivered, and how well they are monitored biochemically and clinically. More research is needed in this area since a correct endocrine approach would suggest employing gradually increasing doses of vitamin D congeners connected to optimum medicine delivery through the brain-blood barrier to reduce the risk of falls in vulnerable groups. This is because vitamin D pills are widely available and reasonably priced.

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### Compliance with ethical standards

#### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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