

# Association of Hypovitaminosis D and Hypocalcemia with Neuropsychiatric Disorders

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## ABSTRACT

Vitamin D3 (cholecalciferol) is an essential vitamin for calcium and bone homeostasis. Several neuronal cells, muscles cells and different regions in CNS (Central Nervous System) express Vitamin D receptors. CNS is recognized as target organ for vitamin D3. Several clinical and experimental data show the regulation of physiological brain function by vitamin D which includes neuroprotection, anti-leptic effects, immunomodulation, regulation of behavior and motor function. Vitamin D3 metabolite 1,25 Dihydroxy Vitamin D3 modulates the activity of brain genes and enzymes involved in neurotransmitters metabolism. Similarly neuronal cells have highly developed calcium signaling system which is responsible for number of neuronal functions such as control of brain rhythms, information processing and the changes in synaptic plasticity that underpin learning and memory. Calcium signaling is a key component pathway for the regulation of neuronal excitability and neural brain rhythms for cognition. Dysregulation in Vitamin D and calcium signaling pathway may be responsible for neuronal disorders in human such as Dementia, Alzheimer, Parkinson, multiple sclerosis, epilepsy, bipolar and schizophrenia. In this review our efforts are to incorporate clinical based epidemiological studies with potential calcium and vitamin D mediated physiological mechanism in neuropsychiatric diseases. The key idea of this evaluation is to provide an update summary and function of calcium signaling and vitamin D in the growth of human brain cells. During this assessment we have pinpointed the research areas where future research should be focused for the betterment of human health and cure of neurological diseases.

**Key words:** Vitamin D, neuropsychiatric diseases, calcium, epidemiology, neurotransmitters

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## INTRODUCTION

Vitamin D, also known as sunshine vitamin is a steroid hormone that plays an important role in performing crucial body functions including bone development, muscles contraction, boosting of immune system, prevention of autoimmune diseases and calcium and phosphorus homeostasis. In humans, Vitamin D is found in two forms: Vitamin D2 also known as ergocalciferol is acquired from a variety of food sources which include

fish, yogurt and milk whereas vitamin D3 also known as cholecalciferol which is synthesized in the body by exposure to the sunlight<sup>1</sup>. It is believed that approximately 90 % of the Vitamin D in our body is obtained from sunlight through cutaneous route<sup>2</sup>. Absorption of vitamin D from sunlight is directly linked with the availability of sunlight. Escalating distance from the equator gradually increases the risk of vitamin D deficiency due to the lower availability of sunlight in those parts<sup>3</sup>. On the other hand, very high exposure to the sunlight causes high melanin formation resulting in darker skin tone. This high level of melanin impairs the absorption of vitamin D and causes hypovitaminosis D condition in human<sup>4</sup>.

It has been estimated that about one billion people around the world are suffering from vitamin D deficiency (VDD). According to a survey done in USA, Australia and Europe, the estimated prevalence of VDD is about 35 %<sup>5</sup>. This situation is rather worse and alarming in the Asian pacific region including Pakistan. Recently published reports indicate a high VDD prevalence in Pakistan. A study conducted in an ambulatory care

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setting of Karachi reported very high vitamin D deficiency (92 %) among their selected population<sup>6</sup>. In 2009, Masood *et al.*, studied the seasonal variation in Vitamin D serum level and reported 75.5% VDD during peak summer season in the residents of Faisalabad<sup>7</sup>. Another study conducted in Islamabad in 2012 Khan *et al.*, reported an increasing trend of VDD in females (56.2%) compared to males (15.3%)<sup>8</sup>. Hossain *et al.*, (2011) has also reported a high prevalence of vitamin D deficiency in the Pakistani parturient and their newborns<sup>9</sup>. More recently Hossain *et al.*, 2014 conducted a study at DUHS<sup>10</sup> and reported the results of an open label randomized controlled trial of antenatal vitamin D supplementation in Pakistani women.

Hypovitaminosis D specifically the deficiency of 25-hydroxy-vitamin D has been found to be associated with certain chronic conditions, like cancer, cardiovascular diseases, type 2 diabetes, hypertension, endothelial dysfunction, obesity, chronic kidney disease and dyslipidemia<sup>11</sup>. Furthermore, decreased level of Vitamin D has significant consequences on human psychology and its deficiency impairs neuronal connectivity. Experimental data have proved that Hypovitaminosis D is strongly associated with a number of including Alzheimer's disease, epilepsy, dementia, Schizophrenia, Parkinson's disease and multiple sclerosis. According to the institute of Medicine guidelines, the daily intake of Vitamin D should be 200 IU for Children, 400 IU for adult (<50 years) and 600 IU for elderly adults (<70 years)<sup>12</sup>. Decreased intake of vitamin D mounts the risk of major depression<sup>13</sup>, premenstrual mood symptoms in women, mood disorders, and cognitive impairment in older adults<sup>14</sup>. An increased in intake of vitamin D helps to prevent and reduces the risk of major brain disorders.

Despite the high association of Vitamin D in the pathogenesis of different ailments, the exact mechanism by which hypovitaminosis D may impact on these disorders remains inconclusive. Several mechanisms have been proposed, one mechanism is during the neuronal (programmed neuronal cell death). Vitamin D deficiency causes apoptosis through decreasing the amount of cytochrome C expression and declining the neuron cell cycle. Protein is involved to support the activation of pro-apoptotic factors<sup>15</sup>. While in a second mechanism a variety of different neurotrophic factors are implicated and this mechanism is completed through the involvement of factors such as BDNF(s) (brain-derived neurotrophic factors), GDNF (glial cell line-derived neurotrophic factors) and NGF (nerve growth factors). Neurotrophic factors are protein in nature. According to the data from existing literature survey that vitamin D involvement in association with

neurotrophic growth factors play a role in the growth and survival of mounting neurons and it is also involved in the protection of adult neurons<sup>16</sup>. Additional studies evaluated that vitamin D is not only involved in the neuronal growth signal process it also activate those that play role in the activation and regulation of human immune system. Another imperative role of vitamin D is release of neurotransmitters from neuronal cells such as serotonin and dopamine. Vitamin D deficiency disturbs the dopamine and serotonin level which may have an effect on brain development and moreover modulate the brain functions<sup>17</sup>.

Recently study evidenced that DVD (developmental vitamin D deficient) rats have altered brain physiology such as they have decreased neuronal apoptosis and decreased expression of neurotrophic factors while increased mitosis. These results imply that Vitamin D has potential effect in the development of neurons and in their survival as well. Currently scientists are focusing their research to find out whether vitamin D is an essential contributing factor to perform normal brain function. Vitamin D<sub>3</sub>; 1, 25-dihydroxyvitamin, 24, 25-dihydroxyvitamin and 25-hydroxyvitamin are the most commonly found active metabolites of Vitamin D in our body. These metabolites are highly expressed in different regions of brain which includes cerebral spinal fluid, Substantia nigra and the hypothalamus. Receptors of these Vitamin D metabolites are also present in various brain parts like cerebellum, substantia nigra, lateral geniculate nuclei, cingulate gyrus, prefrontal cortex, basal forebrain, and caudate/ putamen<sup>18</sup>. These receptors are steroid in nature and play fundamental role in neuronal signaling and earlier studies have reported the expression of these receptors in human brain<sup>19</sup>. Use of radio labeled complementary deoxyribonucleic acid probes in the patient of Alzheimer's or Huntington's disease postmortem brain confirmed the expression of vitamin D receptor expression. Gene polymorphisms of vitamin D receptor are linked with cognitive decline, Alzheimer's disease, multiple sclerosis and Parkinson's disease<sup>20</sup>.

Calcium is an important component for overall health. According to NIH the recommended dose as a supplement for calcium not more than 600 mg should be taken because the percentage of calcium absorbed decreases as the amount of calcium in the supplement increases. Approximately 99 % calcium is stored in bones, teeth to provide support to our body<sup>21</sup>. Remaining 1% of the calcium is used in muscles contraction, nervous system (especially) and heart. If the calcium status is low in the body, parathyroid gland releases parathyroid hormone which in due course sends signal to the bones to release more calcium into the blood

stream. The function of vitamin D is best described as it facilitates calcium absorption and regulates calcium homeostasis<sup>22</sup>. PTH (parathyroid hormone) also helps in activation of vitamin D which in turn increases intestinal calcium absorption.

According to the recent study, GAWAS has revealed mutations (SNPs) in two important genes (CACNA1C and CACNB2) which are strongly involved in the balance of calcium in brain cells. Mutations in these genes are implicated in several neuropsychiatric disorders, and could provide a potential target for new treatments<sup>23</sup>.

### Alzheimer and Dementia

Alzheimer's disease is a neurodegenerative disorder, which is a severe form of dementia and it is more frequent among elderly people. Dementia has been well defined as a disease of the brain in which there is disruption of various higher cortical functions, including language, memory, learning, thinking and judgment. Alzheimer's disease also can be characterized by multiple cognitive impairments including memory, impairment and progression of physical deterioration<sup>24</sup>. Memory is the most important function of the brain and is essential for survival, through which organisms are capable of keeping records and use these records to adapt their responses. Due to hyper phosphorylation of tau protein and amyloid presence in the form of senile plaques and occurrence of neurofibrillary tangles are the main neuro-pathological features of Alzheimer's. The hallmark is degeneration of neurons and brain atrophy, also cerebral cortex and hippocampus shrinkage and enlargement of ventricles<sup>25</sup>.

In several recent studies, lower risks of Alzheimer's disease have been associated with higher level of vitamin D<sup>26</sup>. Vitamin D helps in neuroprotection by modulating nerve growth production and decrease L-type calcium channel expression<sup>27</sup>. Its metabolites become involved in neuroprotection, vasoprotection and amyloid phagocytosis mechanisms (28). Vitamin D is inversely associated with vascular calcification, a risk factor for dementia Estimate in 2005 showed that dementia occurrence was 24.3 million globally and this number increased to double after every 20 years<sup>29</sup>. Vascular Dementia is also a common type of dementia after Alzheimer. Alzheimer's patients with lower Vitamin D level showed lower cognition by Mini Mental State Examination score (MMSE)<sup>30</sup>. Although relationship between cognition and Vitamin D concentrations is not clear as much but supplementation might have a protective effect for dementia<sup>31</sup>.

Vitamin D is well known and it is essential for the intestinal calcium absorption. Calcium also takes part

together with vitamin D in homeostasis, optimal skeletal development, and together it shows the prevention of rickets and osteoporosis<sup>32</sup>. According to Barbara, Vitamin D shows the neuroprotection of hippocampal cells. This neuroprotective effect occurs through regulating calcium ion channels. Through these calcium ion channels it activates PKC and map PK pathways<sup>33</sup>. Associations between dietary calcium and vitamin D also have been seen in a population study and hypo function of both of these can cause brain lesions in a number of reasons. These lesions cause cognitive impairment and depression, metabolic syndrome, increase obesity rates<sup>34</sup>. In this population study supplementation of vitamin D and calcium prevent osteoporosis and other diseases related to vitamin D and calcium<sup>35</sup>.

### Parkinson's disease

Parkinson's disease is an incurable, late-onset chronic neurological disorder characterized by tremor, slowness of movement, muscles rigidity, loss of automatic movements and postural reflexes, speech impairment and shuffling gait. Aggregative (Severe) depression, anxiety, and sleep disturbances may also appear prior to the onset of the classical symptoms of Parkinson's disease. The principal causes of Parkinson's disease which affects about 5 million people worldwide are yet not well understood, however a number of factors are more frequently found associated with the disease. These risk factors include advancing of age, gender, family inheritance, exposure to the toxins, insufficiency of vitamin D, and/or imbalances of calcium. Increasing number of published epidemiological data and animal studies strongly support the notion that Vitamin D may be involved in the pathogenesis of Parkinson disease<sup>36-40</sup>.

The results of these studies suggest that vitamin D may help to prevent or delay the inception of motor symptom and provide protection against Parkinson disease. The exact mechanism of how vitamin D decreases the risk of Parkinson disease is yet to be identified. In brain, vitamin D receptors mainly localize in the dopamine-releasing substantia nigra pars compacta (SNc)<sup>41</sup>. Dopamine is crucial for the movement and balance. Continuous vitamin D inadequacy results in the selective death of dopaminergic neurons which lead to the development of various non-motor and motor signs of the Parkinson's disease.

Calcium is an important element for normal brain functions. It acts as a second messenger and is a crucial part of the electrical signals within the nervous system. Disturbance of calcium homeostasis is supposed to be another key factor allied with the pathogenesis of Parkinson's disease<sup>42</sup>. Dopamine-releasing neurons of the SNc depend on L-type Ca<sup>2+</sup> channels (comparing

to the other neuronal cells that use sodium pumps) to mediate pace making activity and use calcium for the conductance of the depolarizing signal<sup>43</sup>. The dependence of dopamine releasing neuron on the metabolically expensive calcium signaling, leads to an early and more swiftly aging of these neurons comparing to normal aging-related cell death of other neurons. During Parkinson's disease the ability of neurons to maintain a sufficient energy level can be compromised, there after affecting  $Ca^{2+}$  homeostasis<sup>44,45</sup>.

### Multiple Sclerosis

Multiple sclerosis (MS) is the inflammation of central nervous system mediated by body's own immune system. In MS, nerve axons get destructed and the protective myelin coating of the brain and spinal cord get damaged. This damage or demyelination delays / halts the nerve impulses transmission between brain and different parts of the body thereby affect muscles control, vision, balance, and sensation.

Multiple sclerosis is most likely to develop in the individuals having family history of MS, who belong to specific ethnic group or who are exposed to particular environmental factors. Genetic factors have very little influence in the development of MS<sup>46</sup>. However, environmental factors comparatively play a large contributory role in MS in genetically susceptible persons<sup>47</sup>. MS affects approximately 2 million individuals worldwide<sup>48</sup> with a very high frequency of young adults. The incidence of MS rises with an increasing distance from the cordon. Mounting distance from the equator linked with the decrease sunlight exposure which is the main inducer of vitamin D synthesis. The increasing risk of MS with increasing latitude is reported to be directly associated with the deficiency of vitamin D<sup>49</sup>. As people with MS have an extremely active immune system, existing thought on how Vitamin D helps to prevent MS is to regulate the immune system by suppressing its activity<sup>50</sup>. Recent studies showed that is a strong immune modulator that is crucial for the immune function and development<sup>51,52</sup>. This active form of Vitamin D plays a major defensive role against autoimmunity by reducing the expression of major histocompatibility complex (MHC) class II and costimulatory receptors on antigen presenting cells<sup>53</sup>. In this connection, vitamin D deficiency may be implicated with the imbalance or impairment of immunological functions and subsequently with the development of MS. Studies on experimental autoimmune encephalomyelitis (EAE), an animal model of MS evidently support this hypothesis whereby vitamin D supplements have been shown to slow the progression of this neurological disorder<sup>54,55</sup>. These findings suggest that the supplemental intake of may help to improve or even cure MS as proved from animal experimental models of MS.

Calcium is the universal intracellular messenger that is vital for the functioning of crucial body's processes including immune and nervous systems. The foremost functions of calcium are in the development of nervous system and cell signaling. Axonal damage and demyelination of the in brain and spinal cord are the major correlates of multiple sclerosis though the mechanism of this degeneration remains questionable. A number of current studies have evidently support the involvement of calcium ions in the development of axonal disturbance<sup>56</sup>. In accordance with these assumptions, scientists have revealed that the blockage of calcium channels can protect a sub population of myelinated axons degeneration in animal model<sup>57</sup>. These findings highlighted the prospective use of calcium channels blockers as potential drugs to halt MS progression.

### Epilepsy

Epilepsy is the most common neurological condition affecting people of all ages, races and social classes. Over 50 million people throughout the world are epileptic of whom up to 75% live in resource-poor countries with little or no access to medical services and treatment<sup>58,59</sup>. Repeated seizures are the most common characteristics of epilepsy that indicate the instability in brain activities where neurons fire abnormally. Vitamin D supplementation is reported to decrease the frequency of seizures in epileptic individuals. Vitamin D regulates several factors. It exclusively down regulates a proconvulsant cytokine IL a and upregulates anticonvulsant neurotrophic factors such as GDNF and TN3. Hypovitaminosis D condition in epileptic child disturbs heproconvulsant and anticonvulsant homeostasis that subsequently decreases the threshold values for convulsive activity<sup>60</sup>. Vitamin D is play role in the process of proper breakdown and use of calcium and promotes the expression of calcium binding protein which has anti-epileptic properties<sup>61</sup>.

Vitamin D deficiency causes hypocalcemia in human body. Calcium has important function in muscle movement and nervous system, hypocalcemia can cause muscle aches, spasms, stiffening of the muscles, and tingling sensations in the face, mouth, lips, fingers and toes. Low calcium level causes several types of seizures which include: tonic-clonic seizures (shaking and loss of consciousness), focalmuscle seizures (irregular muscles contraction) and absence seizures (staring off into space). Certain anti-seizure medications can contribute to further lowering calcium levels, especially when taken daily for a long time period. These medications also impose harmful effects by eliminating calcium deposits from the bones.

## Schizophrenia

Schizophrenia is multifactorial brain disease which affects both men and women with equal frequency. Schizophrenia is distinguished by distortion of thoughts, perception, discernment and hallucinations. The prevalence of schizophrenia in Pakistan is about 1.5 %. So far the main cause of Schizophrenia is unknown. A number of theories exist regarding the onset of Schizophrenia which include disturbance in neurotransmitters level, environmental factors, hereditary factors and other brain development abnormalities and the combination of these factors lead to schizophrenia. It has been conjectured that babies born in the winter season are at higher risk for developing this mental illness in their early adulthood. An environmental affront was associated with decreased grey matter and increased cerebrospinal fluid (CSF) in patients with schizophrenia and their relatives but not in genetically low-risk individuals<sup>62</sup>. The relationship between vitamin D and sunlight exposure has been postulated by examination of different population across the world. In winter months due to short period of sunlight exposure the brain development of child is compromised<sup>63,64</sup>.

Numbers of studies have shown that birth in spring and winter season have been associated with significantly high risk of developing schizophrenia at the adult ages<sup>65</sup> and people who are born and live at higher latitude are on risk<sup>66</sup>. The incidence and prevalence of Schizophrenia is significantly higher at such sites<sup>67</sup>. This high prevalence of schizophrenia may be due to hypovitaminosis that is more common in children and adults living at high latitude and during winter and spring season<sup>68</sup>. Maternal starvation or viral infection may lead to increased risk of schizophrenia development in the offspring<sup>69</sup>. Other prenatal factors include maternal Rubella and respiratory infections, low socioeconomic class, maternal deprivation resulting from war or famine, urban birth, obstetric complications, and birth in late winter/early spring<sup>70</sup>. It has been proven that Vitamin D supplementation is associated with decreased risk for viral infections<sup>71</sup>.

Animal and human studies strongly support this hypothesis that continual vitamin D deficiency is harmful to the brain development and adult neuronal functions. Vitamin D deficiency has been associated with an increased risk of schizophrenia. The findings suggest that vitamin D affects the brain independent of hormonal pathways which regulate serum level of calcium<sup>72</sup>.

Vitamin D is believed to be involved in the development of the brain during the gestational period. It has been

suggested that higher circulating levels of vitamin D improve cognitive function and studies shown positive associations between serum levels of 25-hydroxyvitamin D [25(OH)D] and cognitive function<sup>73</sup>. Vitamin D deficiency reduce the level of neurotrophic factors or nerve growth factor such as NGF and GDNF<sup>74</sup>. These nerve factors are involved in enhancement of neurotransmitters and also in the survival of dopaminergic neurons.

Calcium on the other hand is crucial for various cellular functions including muscle contraction, neuronal synapses release synaptic vesicle, synaptic plasticity etc., usually calcium influx cause the activation of NMDA receptor, therefore, calcium deficiency leads to hypofunction of NMDA receptors which has an important consequence of developing schizophrenia.

## Conclusion and Future Direction

In this review we have highlighted the fundamental role of Vitamin D and calcium signaling in the growth, development and functioning of brain and neuropsychiatric ailments and some suggestions for the future research and clinical interventions. It is ironic that Vitamin D which is so abundant in nature, environmentally stable, easily available and cheap yet its deficiency is rampant not only in low socio economic strata but highly educated and affluent communities and nations.

Keeping in view the role of vitamin D in spectrum of neuropsychiatric conditions blood and tissue vitamins and nutritional status assessment should be included as routine tests for neuropsychiatric patients. Vitamin D and calcium supplements both dietary and therapeutic are an urgent public health priority especially during pregnancy and early postnatal period in both mother and child since during brain development and up to couple of weeks after birth as they are playing vital role in prevention of mental disorders in child on one hand and preventing postpartum psychiatric challenges in the mother on the other. Additionally for all ages vitamin D supplementation should be promoted to prevent and manage not only neuropsychological consequences but bone, joint, teeth and several other known and hitherto unknown problems.

Some simple measures such as exposure of body parts like arm, face and legs in sunlight for 5 to 30 minutes between 10 am to 3 pm at least twice a week can help prevent vitamin D3 deficiency and also help in recovery of affected patients<sup>75</sup>. People can also intake vitamin D from natural dietary resources such as cod liver oil, egg yolk, mackerel, milk, orange juice, butter, yogurts, cheese and cereals. In severe or acute cases therapeutic vitamin D may also be required.

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