Role of Vitamin D in Alzheimer's Disease: A review

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❖ **Abstract** :

Vitamin D also known as sunshine Vitamin , has long been known to be related with strong bone health and proper bone metabolism. Deficiency of Vitamin D is usually translated into osteoporosis, and other bone disorders like rickets or osteomalacia. But newer studies have revealed its significant role in the reversal of different kinds of diseases such as Type 2 diabetes, Cardio vascular diseases, Dementia, Breast Cancer, Colorectal and Prostrate Cancer, Depression, Penile erectile dysfunction etc. Other noticeable signs of vitamin D deficiency are muscle pain, depressed mood, recurrent fatigue and tiredness, slow healing of wounds, hair loss and many more. Many of these diseases are linked with the major physiological functions of Vitamin D. Nowadays researchers are more concerned about this vitamin for its involvement in brain function. Deficiency of this vitamin shows some linkage particularly in the progression of dementia, specially Alzheimer's disease . Alzheimer's Disease affects mainly the aged population and its clinical treatment is not yet fully established. The present article aims at exploration of the role of this vitamin in this deadly disease.

Vitamin D or Sunshine Vitamin , discovered 100 years ago by Mc Collumn et al (1) is a fat soluble vitamin with a steroid structure . It is considered as a prohormone hormone which has a well-established role in maintaining bone health by regulating calcium metabolism (2). It exists in two isoforms, known as vitamin D2 and D3. Around 90% of Vitamin D is synthesised in the skin by the action of ultraviolet radiation (from sunlight exposure) on the cholesterol precursor, 7-dehydrocholestorol (2,3). Other sources include diet, including fortified foods, and supplementation (4). The molecule is initially biologically inert and requires two separate hydroxylation steps in order to be converted into its active form. At first it is converted to 25-hydroxyvitamin D (25(OH)D) in the liver and then to the active hormonal form, 1,25-dihydroxyvitamin D in the kidney (2). This hormone reacts with a single nuclear type receptor (VDR) in the target cell to facilitate the activation or suppression of target genes and the proteins produced in response to the hormone then carry out different functions of vitamin D, such as calcium absorption , phosphate absorption from intestine, calcium metabolism in the bone and calcium reabsorption from kidney and many other functions (48). Classically, this vitamin has a recognized role in the regulation of bone health physiology and calcium-phosphorus homeostasis by exerting action at the level of the skeletal bone, intestine and kidney. But for the last two decades there is consistent evidence in favour of the non –calcemic effects of vitamin D metabolites in vitro and in vivo. (6.). Emerging evidence suggests that vitamin D is involved in a wide variety of functions unrelated to bone health, such as immune function and vascular processes (7). Longitudinal studies have found that low vitamin D concentrations are also associated with an increased risk of colorectal cancer (8), Type 2 diabetes (9, 43) and cardiovascular disease (10,44). Other functions are regula-

tion of parathyroid growth and parathyroid hormone production; a role in the islet cells of the pancreas .(11). It is also used to prevent a variety of diseases including several degenerative diseases. (12). In fact, vitamin D and cognition has been considered as a popular association for the last 50 years , which can be proved by publication of a remarkable body of literature. (50). Our brain has the ability of synthesizing, catabolising and receiving Vitamin D which in turn can regulate many cellular processes in neuron and microglia. (5) It also helps in synaptic plasticity, neurotransmission in dopaminergic neural circuits, exerts anti inflammatory activities, neuroprotective activities within brain by reducing synthesis of pro inflammatory cytokines and the oxidative stress load.(51)

This Vitamin also stimulates our brain to release "happy hormones" like dopamine. These hormones are the ones that help us feel a sense of well-being and happiness and thus indirectly Vitamin D plays an important role in mental health and mood.(58)Some researchers refer to vitamin D as the "forgotten neurosteroid" (45). There is also increasing interest in the potential role of low vitamin D concentrations in the pathogenesis of cognitive decline, dementia and Alzheimer's disease (AD) (13, 14,15.). Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by irreversible cognitive deficits and behavioural alterations, impairment of memory and loss of spatial memory. (16) Eventually it leads to complete incapacity and death within three to nine years since diagnosis. (17) . AD is a multifactorial disease which include gender, family history, genetics, and head trauma, low educational attainment and environmental factors. (18). ButAging is a strong risk factor for AD (19). Elderly adults are particularly at risk of vitamin D deficiency for a variety of reasons, for example ageing reduces skin thickness resulting in a decrease in cutaneous concentrations of vitamin D3 precursor 7-dehydrocholesterol. Other reasons include a lack of adequate exposure to sunlight, decreased intake of vitamin D from diet, impaired intestinal absorption and impaired hydroxylation in the liver and kidney (20).

As Vitamin D has been found to be involved in neurotrophy, neurotransmission, neuroprotection, and neuroplasticity, it has been suggested that Vitamin D deficiency may play a key role in the progression of dementia and Alzheimer's disease.(35)

The objective of the present review article is to assess justification of the relation believed to exist between Vitamin D and the course of Alzheimer's disease.

- ❖ Literature review :

A cross-sectional analysis on elderly and young people (30–60 years old) with low level of vitamin D and decline in cognitive ability using Pearson's correlations showed significant result. (39). Epidemiological studies also have outlined a strong correlation between deficiency of vitamin D and neuro-degeneration associated with AD. Many of the A D patients (70-90%) were found to be vitamin D deficient, and these patients are the most vulnerable group to develop neurodegenerative disorder due to additive effect of Vitamin D deficiency along with aging factor (31, 32)

The central nervous system has proved to be a major target for vitamin D activity (5). The main vitamin D metabolites are present in the human cerebrospinal fluid (CSF), which circulates in different areas surrounding the brain. It is true that CSF concentrations are highly

correlated with concentrations in blood plasma (22). Both the 1,25-dihydroxyvitamin D3 receptor and 1α-hydroxylase, the enzyme responsible for synthesizing the bioactive form of vitamin D, are widely distributed throughout the human brain. Additionally, the Vitamin D receptor and enzyme are densely located in areas associated with memory and higher order cognition, such as the CA1 and CA2 regions in the hippocampus as well as the dentate gyrus, cingulate gyrus and prefrontal cortex (23). Vitamin D has been implicated in neuroprotective functions and appears to play an important role in brain development in rat models., such as inducing nerve growth factors in embryonic hippocampal neurons (24.) or rats born to vitamin D3 deficient mothers demonstrated a pronounced reduction in nerve growth factor in addition to decreased glial-derived neurotrophic factor compared to control rats (25.) Furthermore, Vitamin D had a drastic inhibitory effect on the expression of the inducible form of nitric oxide synthase in activated microglia and astrocytes in rats, an enzyme involved in the production of nitric oxide which is implicated in the brain's immune responses (26).

But Vitamin D itself depends on the brain tissue for its own activation . Enzymes involved in the synthesis and elimination of 1,25-(OH)2D3 are expressed in brain regions such as the thalamus, hippocampus, and basal ganglia. This suggests vitamin D has both autocrine and paracrine pathways in the central nervous system (37,38).

In patients with Alzheimer's Disease (AD), the main hallmarks are amyloid-β (Aβ)-rich plaques, neurofibrillary tangles (NFTs), synapse loss, and atrophy in brain areas with memory and executive functions (27).Many researchers have tried to explore the relevant preventive interventions to delay the development of the disease and several relevant risk factors (45, 53). In addition to other potentially modifiable risk factors for AD, such as being overweight, smoking, diabetes mellitus, hypertension, hypercholesterolemia, and cardiovascular diseases, Alzheimer's disease a potential prognostic role of vitamin D deficiency has also been proposed recently (36.49). A recent meta-analysis of 18,974 adults reported that severe vitamin D deficiency (< 10 ng/ml) increased the risk of dementia by 54% (40).

Although vitamin D status is a crucial but non-specific risk factor for AD (14) Cui et al. Opined that there may be specific "critical windows" through which vitamin D deficiency might result in the most deleterious ailment in brain. Recent reports have shown during these time-frames, Vitamin D supplementation could be the most beneficial factor to act as panacea or to prevent long-term damage to the brain (34). Earlier , in a number of occasions, Vitamin D has found to exert prospective action to combat the pathological problems associated with AD.

1. In vitro, vitamin D stimulates macrophages which increase the clearance of Aβ plaques (28)
2. It reduces amyloid-induced cytotoxicity and apoptosis in primary cortical neurons.], and influences Aβ stimulation of induced nitric oxide synthase (NOS), which contributes to modulate the inflammatory process related to AD (29).
3. Genome-wide association studies have focused on the role of VDR polymorphism in late onset AD (LOAD) susceptibility (30).

4. A potential therapeutic window during which vitamin D might provide benefits to reduce the risk, or delay the onset, of AD could occur during the pre-clinical and mild cognitive impairment ages, when measurable changes in glucose utilization and Aβ accumulation already occur. (35).

5. Vitamin D has been found to modulate the voltage-gated calcium channel targeted by Aβ peptides, indicating its role in repair of neuronal calcium homeostasis altered by Aβ peptides (35)

6. Vitamin D can prevent glutamate neurotoxicity by upregulating VDR expression and exerting antioxidant effects (41)

7. Studies have shown that gene polymorphisms of vitamin D are associated with AD susceptibility (42**)**

8. Animal studies have shown that Vitamin D can promote the clearance of Aβ and vitamin D deficiency leads to an increase in Aβ in the brain (40). In human studies, it has been shown that vitamin D causes an increase in plasma Aβ, especially in the elderly, suggesting a decrease in brain Aβ (42)

9. A good number of studies in the recent past , have shown deficiency in Vitamin D status is associated with dementia and AD in a varieties of population (52, 53, 54)

However, there is also other side of the coin , which explain negative correlation between Vitamin D status and Cognitive decline in human**.** A review work almost one decade ago failed to find a significant correlation between cognitive decline and plasma 25-(OH)D concentration (47). Another prospective cohort study for 20 years of follow up period among 13,044 participants in the Middle East reported that lower concentrations of vitamin D measured during middle age were not significantly associated with faster cognitive decline [46]. More and more studies nowadays are coming out with the no correlation results between these two parameters.(55, 56). Supplementation with Vitamin D has not proved to prevent onset of dementia or AD (57,58) However, there has been no systematic evaluation of whether vitamin D deficiency (< 20 ng/ml) is associated with risk of development of dementia and AD. Such information would be significant for preventing the development of dementia.

❖ **Conclusion** :

A good number of publications in the Scientific world exists in support of the role of Vitamin D in Alzheimer's Disease. There is also much certainty that Vitamin D takes part in normal brain function, and low Vitamin D levels can occur among demented patients. But this event is to be reproduced both clinically and in laboratory based experiments without fail. Still now there is much conflict and inconsistencies in the experimental findings involving this Vitamin in the interventional studies. Hence, much more experimental path is yet to traverse. Prevention of the onset of AD by modifying/ supplementing Vitamin D, demands much more trial studies on heterogeneous human age group before stating the final verdict.

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