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Low levels of vitamin D linked to poor cognitive function in older adults

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ABSTRACT:

The objective of this study was to review the association of vitamin D with age-related cognitive impairment. Vitamin D is actually a neuroactive steroid produced endogenously that acts on brain development, leading to alterations in brain neurochemistry and adult brain function which directly or indirectly regulates thousands of genes acting mainly via the vitamin D receptor. Vitamin D receptors are widespread in brain tissue. Vitamin D's biologically active form [$1,25(OH)_2D$] has shown neuroprotective effects on integrity of neurons by detoxification routes, anti-inflammatory effects and neurotropic synthesis, also associated with reduced β-amyloid plaques, a hallmark of Alzheimer's disease. In older adults, the integrity of the skin decreases with aging. Skin thinning and transdermal cholesterol decreases the efficiency of UVB vitamin D production by up to 50% compared to younger adults. Lower levels of vitamin D were repeatedly found to be associated with worse memory performance, executive dysfunction and overall impaired cognitive functioning in older adults. The risk of cognitive impairment was up to 4 times greater in the severely deficient elders ([25(OH)D] <25nmol/L) in comparison with individuals with adequate levels (>75nmol/L). Even if vitamin D levels of patients with severe vitamin D deficiency were increased to an adequate level, the cognitive performance of patients did not reach to the cognitive performance of patients whose vitamin D levels were adequate from the beginning.

KEY WORDS: Vitamin D deficiency, Cognitive function , Older adults, Dementia, 25-hydroxyvitamin D.

INTRODUCTION:

Vitamin D is a fat-soluble vitamin that plays an essential role in calcium homeostasis and bone metabolism. It exerts immunomodulatory, anti-inflammatory, anti-fibrotic and antioxidant actions. Regardless, the association of vitamin D with age-related cognitive impairment has been reviewed. Vitamin D, biologically active 1,25-Hydroxyvitamin D ($1,25(OH)_2D$) is an endogenously produced

neuroactive steroid that acts on brain development, resulting in changes in brain neurochemistry and brain function in adults. This vitamin has direct antioxidant effects and also regulates the production of several neurotrophic factors that promote the survival, development, and function of neurons. It exerts protective and regulatory roles in the central nervous system by releasing neurotrophic factors such as neurotransmitter 3, nerve growth factors, and glial-derived neurotropic factor, which directly or indirectly regulate thousands of genes that act mainly via the vitamin D receptor (VDR).

EPIDEMIOLOGY:

Vitamin D deficiency is a global public health issue. About 1 billion people worldwide have vitamin D deficiency. Countries lying below 35° north latitude-low mortality rate, above 35° north latitude-do not encounter adequate sunlight during winter and suffer vitamin D deficiency. It may be related to populations who have higher skin melanin content and who use extensive skin coverage, particularly in Middle Eastern countries.

VITAMIN D PHYSIOLOGY :

Vitamin D is a precursor of the active form 1,25-dihydroxyvitamin D (calcitriol) and is present in two forms; vitamin D3 (cholecalciferol) which is synthesised in the skin by exposure to ultraviolet-B (UVB) radiation and vitamin D2 (ergocalciferol) which is produced via UV-B radiation on plant sources such as mushrooms and yeast. Natural dietary sources of vitamin D3 are few and include fish liver oils, oily fish, egg yolks and some fortified foods (e.g. some dairy and breakfast cereals) and supplements. Irrespective of how it is acquired, vitamin D2 and D3 are hydroxylated in the liver to 25-hydroxyvitamin D (25(OH)D), the prominent circulating form used to determine vitamin D status in human subjects. Further hydroxylation in kidney, by action of the enzyme 25vitamin D3-1α-hydroxylase (CYP27B1), to the biologically active metabolite, 1,25-dihydroxyvitamin D3. Due to the ability to be synthesised endogenously, vitamin D is widely accepted not as a classical vitamin but as a steroid hormone. Furthermore, its synthesis in the human brain has led to it being commonly referred to as a neurosteroid.

The effects of age on intestinal absorption and renal function may hinder vitamin D metabolism and availability. It has been hypothesised that the metabolism of vitamin D may be reduced due to a decline of intestinal VDR distribution in older adults.

COGNITIVE FUNCTION:

The term cognitive function refers to a variety of brain functions and processes that involve receiving external information, processing it internally, and responding with the behaviour.

It can be thought of as a hierarchy, going from the overall (global) cognitive function to the domain specific. The most common measure of cognitive outcome in vitamin D studies is the global tests, i.e. the Mini Mental State Examination (MMSE) and, therefore, most correlations were seen with

a global measure. Domain-specific functions include memory, executive functioning, attention, perceptual functions, psychomotor abilities and language skills.

In a recent study, it was found that higher concentrations of vitamin D across the brain were associated with up to a 33% lower chance of developing dementia and cognitive decline. Dementia is a syndrome, usually progressive and chronic in nature, in which there is a decline in cognitive function beyond what would be expected of normal aging. Due to the degenerative nature of the disease, sufferers lose their ability to perform routine tasks, and experience a poor quality of life.

MECHANISM :

Exact mechanisms are unclear, but the results from previous studies suggests that low vitamin D levels are involved in the pathophysiology of neuropsychological deficits and accelerated brain aging and impaired memory functioning. Vitamin D protects against cognitive dysfunction through its effect on neuroprotection, neurotransmission, synaptic plasticity, immune modulation, neuronal calcium regulation and enhanced nerve conduction, with secondary protective effects on vascular systems and modulation of vascular risk factors. Vitamin D has neuroprotective effect on integrity of neurons by detoxification pathways, anti-inflammatory effects by inhibiting TNF-α and IL-6 production and neurotropin synthesis. It is known to affect the expression of three of the four neurotropins; nerve growth factor, glial-derived nerve factor and neurotropin 3. Vitamin D is involved in cell signalling pathways that may be part of neurodegeneration. It is a transcriptional regulator for a large number of genes. To initiate its actions, $1,25(OH)_2D3$ binds the vitamin D receptor (VDR). VDR is a nuclear receptor with pluripotent effects. There may be a number of possible molecular mechanisms for its diverse actions in the developing and adult brain. Vitamin D receptor (VDR) is expressed on multiple tissue sites including brain, cardiovascular and musculoskeletal systems where it acts on several gene target products. Vitamin D receptors are widespread in both neurons and glial cells mainly in human cortex and hippocampus, key areas of cognition. Vitamin D metabolites naturally pass through blood brain barrier, giving them access to neuronal and glial cells. The action of 1,25-dihydroxyvitamin D_3 upon binding to the VDR has been linked with a diverse range of biological systems such as immune modulation, cell growth and cell differentiation all of which impact brain function via interaction with target genes. $1,25 (OH)_2D3$ strongly stimulates phagocytic clearance of amyloid beta (Aβ) plaques, a hallmark pathological lesion in Alzheimer's disease(AD) which triggers neurodegeneration in primary cortical neurons. $1,25 (OH)_2D3$ treatment protects against apoptosis in the macrophages of patients with AD and glucocorticoid-induced apoptosis in hippocampal cells.

VITAMIN D DEFICIENCY :

With age, the integrity of the skin decreases. Skin thinning and transdermal cholesterol decreases the efficiency of UVB vitamin D production, by up to 50% in older adults compared to younger adults.

During the winter months and for those at risk of deficiency, vitamin D supplementation should be considered. Evidence suggests that intake of vitamin D supplements is usually low in the general population, including the elderly. For the most part, dietary sources are limited and are not consumed in sufficient quantities by the elderly in general except for those who reside in countries where there is dietary fortification with vitamin D.

The UK Scientific Advisory Committee on Nutrition recommends an intake of 10µg/d (400 IU/d) vitamin D for older adults, a target hard to achieve by dietary contribution alone unless oily fish is eaten daily.

Behavioural and social changes seen with age limit cutaneous vitamin D production. Spending less time outdoors due to ill health or limited mobility (institutional or home), use of medications (loop diuretics, statins, glucocorticoids), changes in body composition (fat gain and muscle decrease), avoidance of sunlight (risk of skin cancer), decreased skin exposure (Clothing, cold temperatures) and sunscreen use are all important barriers that contribute to insufficient UVB vitamin D production in the elderly.

Vitamin D deficiency is a world wide pandemic and is seen commonly in older adults and has been associated with reduced neurocognitive functioning and neurodegenerative processes. The risk of cognitive impairment was up to 4 times greater in the severely deficient elders ([25(OH)D] <25nmol/L) in comparison with individuals with adequate levels (>75nmol/L). Lower vitamin D levels were repeatedly found to be associated with worse memory performance, executive dysfunction and overall impaired cognitive functioning in older adults. Vitamin D deficiency has been linked with neuropsychiatric disorders, including schizophrenia, Parkinson's disease, Alzheimer's disease, depression and cognitive decline. It can result from several causes such as

1.Decreased dietary intake of vitamin D or decreased absorption of vitamin D.

2.Inadequate sun light exposure.

3.Decreased endogenous synthesis of vitamin D due to defect in 1-alpha 25-hydroxylation.

4.Increased hepatic catabolism which activate degradation of vitamin D.

5.End organ resistance to vitamin D.

6. Use of Antiepileptic medications can decrease the levels of vitamin D.

MANAGEMENT OF VITAMIN D DEFICIENCY :

25 hydroxy-vitamin D [25 (OH) D] levels are used to assess the vitamin D status in humans. The severity of vitamin D deficiency is divided into 3 groups. Vitamin D-level status was accepted as <10 ng/mL severe deficiency, 10 to 20 ng/mL deficiency, and ≥20 ng/mL sufficient in the baseline. Oral cholecalciferol was routinely replaced to patients with vitamin D deficiency. Initial supplementation for 8 weeks with Cholecalciferol was administered with 50,000 IU once weekly, followed by 5000 IU cholecalciferol per week for severe vitamin D deficiency. After 6 months, these 3 groups were divided into 2 groups according to the levels of vitamin D of ≥20 ng/mL and

<20 ng/mL. Once the level of 25-hydroxyvitamin D in the blood exceeds 20 ng/mL, a daily maintenance dose of 600 to 1,000 IU is required.

Adults less than 65 years of age who do not have year-round effective sun exposure shall consume 600 to 800 international units of vitamin D3 daily to prevent deficiency. Older adults 65 years of age or more shall consume 800 to 1000 international units of vitamin D3 daily to prevent deficiency.

CONCLUSION:

It has been concluded that a healthy level of vitamin D is associated with better cognitive function and a lower risk of developing dementia in older adults. Even if vitamin D levels of patients with severe vitamin D deficiency were increased to an adequate level, the cognitive performance of patients did not reach to the cognitive performance of patients whose vitamin D levels were adequate from beginning. For this reason, patients should be screened and treated for vitamin D deficiency as a component of successful aging from middle ages.

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