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Vitamin D and Cognition: Are There Any Cautions Against Intervention Trials for Older Adults?

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Editorial

Vitamin D has long been known as the sunshine vitamin, as it is synthesized in the skin from 7-dehydrocholesterol in the presence of sunlight. It is known for its role in strengthening bones through metabolic processing of calcium. The main circulating metabolite form of vitamin D is 25-hydroxyvitamin D (25(OH)D); this is processed mainly via the liver and kidneys to the active form, $1,25(OH)_2D$, which is water soluble. Extra-renal cells can also produce $1,25(OH)_2D$. Blood levels are controlled by the parathyroid hormone, growth factors, cytokines and calcium [1]. Deficiencies of vitamin D are linked to conditions such as rickets in children and osteoporosis, falls and fractures in older adults, as well as some psychiatric conditions such as depression and seasonal affective disorder (SAD) [2].

Surveys suggest that up to a third of the populations in the Western World may be D vitamin deficient, depending on the lower limit for normal serum levels [3]. Levels vary seasonally, although exposure to sunshine is not absolutely necessary, if dietary sources and supplements are sufficient. Sources of vitamin D3include oily fish, eggs, fish oils such as cod liver oil and liver. Vegan sources include lichen for vitamin D3, cholecalciferol, and mushrooms and alfalfa for D2, ergocalciferol. Vitamin D3 supplementation has been shown to be more efficacious than D2 in increasing levels of serum 25(OH)D, possibly due to more rapid clearance of vitamin D(2), or other mechanisms [4]. Fortification of milk, milk products, and flour may also supplement intake in certain countries. Older adults are more prone to deficiency due to thinning of the skin and decreasing amounts of dehydrocholesterol, accompanied by less absorption of sunlight and conversion to the active form. Low dietary intake and poorer absorption by the gut, limited sunlight exposure and limited physical activity may also contribute to deficiency.

Health claims for vitamin D supplements include maintenance of a normal immune system and inflammatory responses, reduction in falls, fractures and osteoporosis. However, recent research has shown links between vitamin D3deficiency (25(OH)D) and increases in the incidence of hypertension, hyperlipidaemia, diabetes, myocardial infarction and stroke [3]. These conditions are associated with increased risk of neurodegenerative diseases such as vascular dementia, Alzheimer's disease (AD) and Parkinson's disease. Cross-sectional and longitudinal observational studies used for a meta-analysis [5] showed associations of low 25(OH)D with cognitive impairment and decline in older adults. Generally, deficiency or low 25(OH)D was equated to serum levels below 20ng/ml, while normal levels ranged between 20–50 ng/ml. Meta-analyses have confirmed significantly lower levels of vitamin D in Alzheimer's disease patients and in those with mild cognitive impairment (MCI) compared to normal controls [6].

A meta-analysis reviewed by van der Schaft et al. [7] suggested a more than doubled risk of cognitive impairment in patients with vitamin D deficiency among 7,688 participants. 67% (4/6) of the prospective studies showed a higher risk of cognitive decline after a follow-up period of 4–7 years in participants with lower 25(OH)D levels at baseline compared with participants with higher 25(OH)D levels. Depending on the cognitive status of those included in these studies, reverse causation limits the interpretability of the findings, as cognitive impairment may be the cause of poor nutritional status.

Reduced risk of AD has been associated with higher vitamin D levels [5]. Additionally, reduced risk of cognitive impairment, higher concentrations of CSF Aβ1–42 and greater brain volumes (e.g. white matter and structures belonging to medial temporal lobe) were found in patients attending a memory clinic who had higher serum 25(OH)D [8].

A biological rationale for the effect of vitamin D on cognitive performance is plausible. Vitamin D receptors have been located in many brain regions (including the hippocampus) [9] associated with cognitive functions that decline with the development of dementia. Vitamin D correlates negatively with cerebral ventricle size, suggesting that it contributes to brain atrophy [10]. It has been suggested that the anti-ischaemic, anti-inflammatory and anti-oxidant roles of vitamin D are neuroprotective and vasoprotective [8,11]. In addition, various functions of vitamin D in neurotransmitter metabolism, particularly in the dopaminergic system, have been proposed [9]. Overexpression of the vitamin D receptor in the brain, or vitamin D treatment, and may suppress amyloid precursor protein transcription [12].

Most intervention trials with vitamin D supplements have shown improvements in bone health and reduction in falls [4]. However, clinical trials for cognitive benefit are few. One showed no benefit for cognitive performance after 4 weeks of supplementation [13]. Another showed a benefit for executive function in older adults who were prescribed vitamin D for any reason compared to patients who were not [14]. A small 6-month controlled trial reported that a combination of memantine+vitamin D was superior to memantine alone and vitamin D alone in preventing cognitive decline among AD participants [15].

There is little evidence from existing trials that vitamin D above current reference intakes is harmful. In most trials, reports of hypercalcemia and hypercalciuria were not associated with clinically relevant events [4]. The Women's Health Initiative study did report a small increase in kidney stones in postmenopausal women on high levels of calcium supplements (1000mg) and normal D3 intake. The increase in renal stones corresponded to 5.7 events per 10,000 person-years of exposure.

Side effects of high vitamin D levels are mostly associated with effects of increased calcium and include vascular calcification and kidney stones. Vitamin D overdose causes hypercalcaemia, and may contribute to renal failure in extreme cases [16].

Thus, the evidence is not convincing enough to recommend regular high dosing with vitamin D for older adults. However, more clinical trials are needed as there appears to be sufficient epidemiological evidence to recommend treatment of vitamin D deficiency to benefit cognitive function, perhaps in a window of time for older adults with or without cognitive impairment. Vitamin D supplements combined with other memory enhancers may be more effective than vitamins alone for those with dementia.

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