VITAMIN D AND AGING: AN INTERPLAY OF MULTIPLE MECHANISMS

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Abstract
Vitamin D has anti-inflammatory and pro-autophagy actions and influences the genetic and epigenetic landscape to promote healthy aging. A deficiency of this vitamin leads to accelerated aging. The deficiency of vitamin D causes sarcopenia, osteoporosis, frailty and a high risk of fractures and consequently high morbidity. To complicate matters, in the elderly, various factors like reduced dietary intake, reduced mobility and sun exposure, decreased production and activation of vitamin D, reduction in the population of vitamin D receptors and diminished responsiveness of tissues to vitamin D cause reduced vitamin D levels and function. The above factors indicate that a special considered approach be adopted for the prevention and treatment of vitamin D deficiency in the elderly.

Keywords: old age, elderly, cholecalciferol, calcitriol, vitamin D level

Introduction
Vitamin D is a fat-soluble vitamin that exists in the body in two forms – D3 or cholecalciferol and D2 or ergocalciferol. Vitamin D and age have a complex interplay and relationship. On one hand, with increasing age, there is a decline in skin production and then activation of this vitamin in the kidney, on the other hand, a deficiency of this vitamin accelerates aging. Increasing age requires higher vitamin D supplementation, which if not provided, leads to a greater rate of sarcopenia, frailty, fractures and related morbidity. A randomized clinical trial found that the supplementation of 2000 IU (compared to 800 IU daily) of vitamin D3 daily for 24 months significantly reduced systolic blood pressure variability [1]. A study on patients with Parkinson’s disease did not find a 16-week, 10,000 IU daily supplementation of vitamin D3 to improve balance. But a post hoc analysis of the study findings revealed that there may be a potential for improvement in the younger (52-66 versus 67-86 years) patients [2]. Studies have found that lower serum concentrations of vitamin D are associated with higher odds of type 2 diabetes and its supplementation reduces the progression of prediabetes to diabetes and increases reversal to normoglycemia [3,4]. Large studies have found an inverse relationship between serum vitamin D levels and interleukin-6 and C-reactive protein levels in older individuals, emphasizing the protective role of vitamin D in age-related inflammation [5,6]. A Cochrane database review of 56 randomised trials most involving women over 70 years of age found that vitamin D3 supplementation decreased mortality in elderly people living independently as well as in institutional care [7]. Thus, vitamin D deficiency is both a cause and a consequence of aging. It is important to understand and acknowledge the intricacies in this relationship to be able to address the various issues related to vitamin D and aging.
While there is literature where the effect of vitamin D deficiency on aging has been reviewed, there is a lack of systematic discussion of the effect of vitamin D deficiency and age on each other [8].

**Metabolism of Vitamin D**

Previtamin D is formed in the skin when sunlight acts on 7-Dehydrocholesterol. This previtamin gets converted to vitamin D which can also come from the diet in the form of vitamin D2 or D3. In the liver vitamin D gets converted to 25-hydroxyvitamin D (25OHD), which is the main circulating form of vitamin D. 25OHD is then converted to the biologically active form 1,25-dihydroxyvitamin D (1,25(OH)2D) in the kidneys. Vitamin D binding proteins carry the hydroxy forms of the vitamin in the circulation [9].

**Literature Search Strategy**

A literature search was performed on Cochrane library, Directory of Open Access Journals, Web of Science, Scopus, and MEDLINE/Pubmed databases using the terms ‘Vitamin D’, ‘cholecalciferol’, ‘age’, ‘aging’ and ‘ageing’. After screening the titles and abstracts, a full-text review of selected articles was conducted and the articles referenced in these manuscripts were also screened. Articles discussing vitamin D and age or aging were referred to for this narrative review [10].

**Vitamin D levels and age**

Vitamin D levels and function decline with age due to a combination of factors (Figure 1). Reduction in production of vitamin D, declining renal function, reduced sensitivity of the bowel to 1,25(OH)2D and fewer cellular receptors are some of the factors responsible. A Turkish study found the highest levels of vitamin D in the age group less than 10 years and deficiency was most prevalent in the 20-30 years age group [11]. But it was a retrospective study, fraught with limitations, and it did not take into account vitamin D supplementation, which is likely to be higher in the older age groups [12].

The deposits of dehydrocholesterol in the epidermis reduce with age. There is also a reduction in response to the ultraviolet rays of the sunlight. These factors combined lead to a reduction of over 50 per cent in the skin production of vitamin D [13]. Advancing age is often accompanied by a decline in dietary intake including that of vitamin D. Reduced mobility also contributes to inadequate sun exposure. A decline in renal function with age leads to decreased activity of 1α hydroxylase, which is responsible for the activation of 25OHD to 1,25(OH)2D [14].

There is a reduction in the absorption of calcium from the intestine. While a part of it occurs independent of the action of 1,25(OH)2D, it is also due to the reduced responsiveness of the intestinal lining to the actions of 1,25(OH)2D [15]. Calcitriol can have a first-pass effect on this transport and set the calcium transport right, but the problem is often not acknowledged or addressed [16]. Studies have shown reduced concentrations of vitamin D receptors in the intestine in older individuals with normal serum concentrations of 1,25(OH)2D [17]. Similarly, there is a decline in the population of vitamin D receptors in the muscles, which contributes to sarcopenia in the elderly. A study in the USA showed a higher total oral intake of vitamin D in the older age group, of which most came through multivitamin supplements [18]. But this did not translate into higher serum levels, highlighting the various other age-related impediments discussed above.

**Vitamin D deficiency and accelerated aging**

Vitamin D is a promoter of autophagy, a process that clears dysfunctional proteins and cell organelles, and facilitates healthy aging. Vitamin D counters inflammation and reduces oxidative stress, both of which cause accelerated aging [19]. An increase in neural calcium levels has been related to aging in the brain and cognitive decline. Vitamin D checks and downregulates calcium levels restoring cognitive function and delaying aging [19]. Low levels of vitamin D are associated with Alzheimer’s, Parkinson’s disease, multiple sclerosis, cardiovascular and other age-related diseases. Vitamin D levels also influence genes and epigenetics. Methylation of deoxyribonucleic acid (DNA) and histones influences the expression of genes that regulate aging and these epigenetic changes are linked to oxidative stress, which is downregulated by vitamin D [19,20]. Aging is marked by alterations in the DNA and telomere shortening, which can again be reduced by vitamin D [21]. Thus, it is evident that vitamin D can influence multiple factors responsible for aging and delay it.

**Vitamin D deficiency-related morbidity in the aged**

Adequate vitamin D intake and maintained levels prevent osteoporosis and are associated with lower rates of fractures. Vitamin D at a dose of 300-
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800 IU (most commonly 800 IU) per day in various studies was associated with an up to 30 per cent reduction in the risk of hip fractures [22]. Studies have also shown a higher risk of hip fractures in those with a serum level of 25OHD lower than 20 ng/mL [23]. Although marred by their limitations, small studies have shown the role of vitamin D and calcitriol supplementation in the prevention of falls in the elderly [24].

Implications for practice

Levels of 25OHD lower than 20 ng/mL or 30 ng/mL have been used to define insufficiency by various academic bodies and societies. A daily intake of 600-800 IU of vitamin D is required to reach a level of 20 ng/mL [23]. While the estimated average requirement of vitamin D remains the same across all age groups at 400 IU per day, the recommended dietary allowance is 800 IU per day over 70 years of age, compared to 600 IU in the other age groups [23]. More than 20,000 IU of vitamin per day over the long term can be toxic. Thus, in general care, it is advisable to consider 4000 IU per day as the tolerable upper limit. It is to be noted here that the recommended doses are much lower than this limit [22,25].

COVID-19, Vitamin D and age

Studies have found lower levels of vitamin D to be linked to a higher risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as well as severe coronavirus disease 2019 (COVID-19) and increased risk of hospitalization [26,27,28]. Interventional studies have also found vitamin D supplementation to be associated with faster recovery and reduced risk of worsening in those with COVID-19 [29,30]. Angiotensin-converting enzyme 2 (ACE2) is the main receptor for the entry of the virus into the host cells. Vitamin D deficiency causes upregulation of the renin-angiotensin system and can thus potentially worsen COVID-19 through its effect on ACE2. ACE2 dysregulation and immune senescence, both of which are worsened by vitamin D deficiency have been implicated as causes of higher mortality due to COVID-19 in the elderly [31].

Take home message

To conclude, vitamin D deficiency is associated with accelerated aging and higher comorbidities and morbidity related to aging. To further complicate matters, various factors lead to reduced intake, production, activation and action of vitamin D in the elderly. Maintenance of vitamin D levels through ensuring adequate dietary intake, supplementation of vitamin D and encouraging outdoor activity is important in this age group.
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MG and AKK performed the literature search. MG drafted the manuscript. MG and AKK revised and approved the final manuscript and take full responsibility for the integrity and originality of all aspects of the work.

CONFLICTS OF INTEREST
The authors declare that there are no potential conflicts of interest.

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