International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

Review Article

Vitamin D and Frailty in Older Adults: A Review

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ARTICLE INFO

Keywords:
Frailty
Vitamin D deficiency
Adults
Aging
Vitamin D

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Received: January 10, 2021
Revised: March 30, 2021
Accepted: April 15, 2021

ABSTRACT

Elderly population is growing rapidly in all parts of the world; therefore, the health related outcomes of aging are important to be studied. Frailty is a major health condition associated with aging that increases the risk of adverse outcomes including falls, disability, and mortality. Nutritional inadequacies such as vitamin D deficiency have been implicated as important factor in increasing the risk of this chronic condition. Deficient vitamin D status has been reported to be common in frail older adults, and it was suggested to be one of the risk factors that might cause muscle weakness, decline in functional capabilities and leads to strength loss. Effects of vitamin D deficiency on frailty might happen through multiple dysregulated pathways including DNA synthesis, protein biosynthesis, mitochondrial function, and cell regulation processes. Results of studies on the effects of vitamin D supplementation on frailty are still inconclusive, and there are not sufficient evidences on vitamin D supplementation in frail patients. So this study has investigated vitamin D and frailty in aging adults.

Please cite this article as: Shamshirgardi E, Shahsavani Z, Akbarzadeh M. Vitamin D and Frailty in Older Adults: A Review. Int J Nutr Sci. 2021;6(2):70-73. doi: 10.30476/IJNS.2021.88716.1102.

Introduction

The population aged 65 years and older is expected to grow very rapidly around the world in the coming decades (1). According to the World Health Organization (WHO) report, the universal population of people aged 60 years and older was 600 million in 2000 and is expected to increase about 2 billion by 2050 (2). With improving life expectancy and declining birth rates, the aging population in the Eastern Mediterranean region (EMR) such as Iran, is growing rapidly (1). Iranian elderly population is predicted to have 31% rises by 2050 (3). In old age, an increase in chronic diseases and a decrease in physical and cognitive functions predispose older people to disability or dependence. In general, with aging, health problems develop and we become f railer (4).

Frailty

Frailty is a main health condition associated with aging (5), which is diagnosed by multisystem loss of physiological reserve, systemic decompensation in response to stressors, and increased risk of adverse consequences such as falls, disability, and mortality. Frailty represents the shift between healthy aging and disability, and is an aim for increasing healthy life years (6). Internationally, the prevalence of frailty among adults aged 65 years is reported to be 4-59%, depending on the instrument of frailty and the population studied (6). In Iran, The frailty prevalence in older adults admitted to public hospitals affiliated to Tehran University of Medical Sciences was 39% and the prevalence of frailty in the rural elderly population of Shabestar, East Azarbayjan was almost 50% that is a warning rate (7).

Comprehensive geriatric assessment (CGA) is

the gold standard for diagnosing frailty. The frailty phenotype, the Frailty Index (FI), and the FRAIL (fatigue, resistance, ambulation, illnesses, and loss of weight) scale are also widely accepted screening tools for frailty at the population level (6). If there are three or more of the following five criteria, a person is known with frailty syndrome including weight loss, exhaustion, weakness, slowness, and inactivity (8). Frailty affects several functional areas including nutrition, strength, mobility, physical activity, cognition, and social engagement. Inadequate dietary intake increases the risk of chronic diseases and frailty. The importance of adequate nutrition to delay frailty and sarcopenia (a major component of frailty) among the elderly has been well established (6).

This relationship is bidirectional; however, older adults with frailty often experience accelerated aging including loss of appetite and/or malabsorption of macro- and micronutrients. This causes chronic deficiencies resulting in further and often irreversible physiological and functional decline (6). Insufficient micronutrients might affect frailty through multiple dysregulated pathways including DNA synthesis, protein biosynthesis, mitochondrial function, and cell regulation processes. This results in an oxidative cellular environment that increase inflammation and stress responses, leading to cellular dysfunction and aging. Over time, cellular dysregulation eventually appears as functional disorders at the organ and system level (6). One of the main characteristics of frailty is its profound effect on muscle strength and reduced functional abilities. The cause of muscle weakness is multifactorial, and insufficient vitamin D status is suggested as one of the risk factors (9).

Vitamin D and Frailty

Besides several roles of vitamin D on chronic conditions such as diabetes (10), cardiovascular diseases (11), deficient vitamin D status [serum 25(OH)D<50 nmol/L] have been reported in frail older adults, with a prevalence reported up to 62%. Low serum 25(OH)D concentrations have been linked to muscle dysfunction and an increased risk of frailty (9). In a study on older population, it was reported that participants with vitamin D deficiency (25(OH)D<50 nmol/L) were ~2 times more likely to score frail, compared to those with adequate serum 25(OH)D concentrations (9).

Also, in the Longitudinal Aging Study Amsterdam (LASA), participants with serum 25(OH)D level between 25 and 50 nmol/L and those with serum 25(OH)D<25 nmol/L were respectively 1.7 and 2.6 times more likely to be frail, compared to the reference group with 25(OH)D>50 nmol/L (9). Also, in the NHANES III, elderly people with vitamin D deficiency (<37 nmol/L) were 3.7 times more likely to score frail on the Fried criteria compared to the reference group (≥75 nmol/L) (9).

Mechanism Linking Vitamin D to Frailty

With aging, blood 25(OH)D concentrations decline due to decreased kidney function, diminished sun exposure, intrinsic skin response to ultraviolet radiation and inadequate diet. Vitamin D deficiency leads to the development of osteoporosis and sarcopenia in the elderly people, which increases the risk of fractures, falls, morbidity and mortality (12). Low serum 25(OH)D level is associated with decreased calcium absorption and increased parathyroid hormone which contributes to higher risks for fractures. In addition, low 25(OH)D level, along with a decrease in the vitamin D receptors that occur with growing age, may lead to decreased protein synthesis and have effects on the immune system and wider organ tissue system. This in turn leads to poor musculoskeletal, cardiovascular, and immune function, which are considered as frailty features (6).

A muscle biopsy study reported type II muscle fibers atrophy in people with severe vitamin D deficiency (12). During sudden movement, the fast and strong type II muscle fibers are the first to play a role in balance and help preventing falls. 1,25-Dihydroxyvitamin D (1,25 (OH) 2D) can bind to the nuclear vitamin D receptor (VDR) on muscle fibers and thereby increasing *de novo* protein synthesis, which regulates muscle strength (12). With growing age, the number of VDR in several organs involved in calcium metabolism decreases. Also secondary to decreased renal function, the activity of 1 alpha-hydroxylase is diminished, leading to reduced vitamin D activation. With low level of 25(OH)D, active metabolite 1,25(OH)2D levels and calcium absorption are reduced (12).

This decreased serum calcium contributes to an increased parathyroid hormone levels to stimulate 1,25(OH)2D production, resulting in an increased risk of bone turnover and bone loss. As a result, decreased muscle strength and function due to vitamin D inadequacy could explain slowness, low physical activity and weakness (12). Another pathway through which low 25(OH)D level might be effective on frailty is related to its hypothesized anti-inflammatory properties. Several studies have shown an increased inflammatory state among frail elderly people characterized by high serum levels of inflammatory mediators, such as cytokines and acute phase proteins (12).

This supports the presence of a dysregulated immune function frailty. According to previous

studies, vitamin D might play an important role in regulation of the inflammatory responses (12, 13). Vitamin D deficient people are at higher risk for infection and autoimmune diseases (12). Active vitamin D metabolites can reduce inflammatory markers via the nuclear VDR expressed in antigen-presenting cells, and vitamin D deficiency may lead to an increase in pro-inflammatory cytokines that affect muscle strength and performance (12).

The association between vitamin D and muscle function can also be explained through regulation of calcium and phosphate levels, required for muscle contraction, or through activating vitamin D receptor (VDR) in muscle cells. In addition, VDR has been observed in neurons and glial cells in several areas of the brain, suggesting a role for vitamin D in the neuromuscular system. Therefore, vitamin D deficiency might be related to an increased postural sway and more risk of falling (9).

Vitamin D Supplementation in Frailty

Considering the role of vitamin D on frailty, several clinical trials assessed the effects of vitamin D supplementation on frailty in older population. The results of the supplementation studies are inconclusive. Supplementation of vitamin D was shown to have positive effects on muscle strength and physical frailty in adults over 65 years old and people with vitamin D deficiency (14). But there are studies that did not observe any effect of vitamin D supplementation on physical performance (8). Therefore, there are insufficient evidences to recommend vitamin D supplementation beyond regular doses. Furthermore, a recently published international guideline on the management of sarcopenia focused on protein supplementation or a protein-rich diet for the treatment of sarcopenia, and does not recommend vitamin D supplementation (15).

Conclusion

In the population of older adults, vitamin D deficiency has been associated with an impaired muscle function and an increased risk of being frail through various mechanisms. But the results of supplementation studies are conflicting. Future clinical trials are required to investigate the effects of vitamin D supplementation on the severity and prognosis of frailty.

Acknowledgement

No fund was received for this review.

Conflict of Interest

None declared.

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