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Research paper

Vitamin D in sarcopenia: Understanding its role in pathogenesis, prevention and treatment

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ABSTRACT

Vitamin D has a well-known critical role in calcium and bone homeostasis. In recent years, there has been an increased interest in the potential regulatory role of vitamin D on metabolic pathways implicated in muscle functions. Evidence coming from epidemiologic studies has demonstrated that poor vitamin D status is associated with worse muscle functions. However, whether vitamin D deficiency and supplementation has a role on sarcopenia is not fully known. This review will focus on current knowledge and emerging data regarding the role of vitamin D in muscle functions and sarcopenia.

1. Introduction

Sarcopenia, which is defined as age-related reduction in skeletal muscle mass and strength [1–3], is very common in geriatric population reaching up to 30% in the community [4], even up to 68% in long-term care facilities [5]. Sarcopenia is a multifactorial geriatric syndrome. Low level of physical activity and malnutrition contribute to the process of sarcopenia. Hormonal changes such as reduced serum testosterone and growth hormone, resistance of aging muscle to anabolic hormones, decrease in protein synthesis disproportionate to protein degradation, reduced muscle restorative capacity, oxidative stress, mitochondrial dysfunction, alterations in neuromuscular junction, reduction in the number of motor neuron units, and chronic inflammation are major accused factors associated with sarcopenia [6–10].

Mounting evidence emerging from clinical and experimental studies suggests a role for vitamin D in sarcopenia. Vitamin D has a widespread role in many organ systems, even considered as a hormone rather than a vitamin. Low vitamin D levels are linked to major health problems, such as cardiovascular disease, cancer, immune disorders, obesity, metabolic syndrome, diabetes, osteoporosis, fractures, and increased risk of falls [11]. These widespread effects of vitamin D are partly due to broad expression of vitamin D receptors (VDR) in many cell types. Although not consistent, immunohistochemical studies revealed presentation of vitamin D receptor in human skeletal muscle [12–15]. VDR knockout mice was shown to display muscle atrophy and growth retardation despite calcium and phosphorus replation [16]. VDR activation regulates the expression of genes involved in skeletal muscle cell development, differentiation, proliferation and functions [17,18]. In this review, we will discuss the effects of vitamin D on muscle functions and potential roles of vitamin D in prevention and treatment of sarcopenia.

2. Overview of vitamin D deficiency

2.1. Epidemiology

Hypovitaminosus D is highly prevalent among older adults. Especially in postmenopausal women, deficiency is observed up to 90% in Asia, and 92% in Europe [19,20]. In the United States population, according to The National Health and Nutrition Examination Survey 2005 to 2006 data, the overall prevalence of vitamin D deficiency was 41.6% for adults, with the highest rate in blacks (82.1%), followed by Hispanics (69.2%). The prevalence for over 65 years of age was 41.1% [21].

Abbreviations: IGF-1, insulin like growth factor-1; VDR, vitamin D receptor; PTH, parathyroid hormone; 25OHD, 25-hydroxyvitamin D3; GLUT4, glucose transporter type-4; RCTs, randomized controlled studies; ng/mL, nanogram/milliliter; nmol/L, nanomole/liter; IU, international unit; IU/d, international unit per day.

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Factors such as inadequate dietary intake, lack of sun exposure, use of sunscreens, clothing, chronic renal disease, malabsorption (such as celiac disease, Crohn disease, pancreatic insufficiency) may contribute to vitamin D deficiency. The older adults, especially institutionalized subjects, might be confined to indoors for prolonged periods of times, thus unable to benefit from daylight. In addition, the skin of elderly individuals have reduced ability for efficient vitamin D production [22].

2.2. Metabolism

Vitamin D is mainly synthesized in the skin. Less than 10% comes from dietary sources. In the skin, previtamin D3 is converted from 7-dehydrocholesterol during exposure to the ultraviolet-B wavelengths in sunlight. Previtamin D3 undergoes a temperature-dependent isomerization to form vitamin D3. Vitamin D3 binds to the vitamin D-binding protein, and is transported to the liver. Vitamin D3 is converted enzymatically to 25-hydroxyvitamin D3 (25OHD) by the enzyme 25-hydroxylase in the liver and then to 1,25-dihydroxyvitamin D3 (the biologically active form), in the kidney by the enzyme 1-alpha-hydroxylase. Although, this enzyme is expressed in many tissues including skin, intestine, macrophages, and bone; the kidney is the primarily responsible organ for circulating levels of 1,25-dihydroxyvitamin D3.

2.3. Optimal serum levels of vitamin D

The major circulating form of vitamin D and the indicator for vitamin D status is 25OHD. Generally, vitamin D insufficiency is defined as serum 25OHD levels of less than 30 ng/mL (to convert to nmol/L, multiply by 2.496). Vitamin D deficiency is defined as serum 25OHD levels of less than 20 ng/mL (50 nmol/L) [23,24]. In randomized clinical trials that demonstrated decreased risk of falls, fractures and preservation of bone mineral density, with higher vitamin D levels to achieve these positive results, the average concentrations of 25OHD were greater than 26 ng/mL (65 nmol/L). Based on these studies, recommended target level for 25OHD concentration is 30 ng/mL for fracture prevention and preservation of bone mineral density as a physiologically conservative estimate [25–27]. The Institute of Medicine recommends vitamin D repletion to reach a level of 20 ng/mL or greater [28]. However, Endocrine Society, American Geriatrics Society, National Osteoporosis Foundation, International Osteoporosis Foundation, suggest a minimum level of 30 ng/mL in older adults to prevent falls and fractures [24,29–32].

3. Vitamin D in sarcopenia

3.1. Role of vitamin D in muscle health

The beneficial effects of vitamin D supplementation on bone health has been well established. However, the role of vitamin D on sarcopenia is a relatively newer concept and has fewer clear evidences. Vitamin D deficiency causes osteomalacia in adults, a disorder characterized by decreased mineralization of newly formed osteoid at sites of bone turnover and presents with bone tenderness, diffuse body pain and muscle weakness. Metabolic abnormalities such as hypocalcemia due to reduced calcium absorption and hypophosphatemia due to increased urinary excretion may accompany osteomalacia. Vitamin D supplementation in osteomalacia improves muscle weakness and pain dramatically. In case of vitamin D deficiency weight-bearing lower-extremity muscles are predominantly affected. Vitamin D deficiency induced proximal myopathy can be reversed with vitamin D supplementation [33,34]. In vitamin D deficiency induced proximal myopathy, predominant loss of type II muscle fibers is demonstrated in biopsies, which is also a similar histopathological finding in sarcopenia [35]. In a randomized controlled study among older females with stroke, daily supplementation of vitamin D (1000 IU) for 2 years increased type II muscle fiber diameter [36]. In the prevention of falls, fast reaction to balance losses is very important. Type II muscle fibers, which are declined in sarcopenia has a critical role in this fast reaction. Vitamin D is considered to reduce the risk of falls by combined effects on bone and muscle.

3.2. Cellular mechanisms of vitamin D–muscle interactions

The underlying biologic mechanisms that explain the role of vitamin D on musculoskeletal function are not fully clarified. Vitamin D may affect gene transcription and protein synthesis, directly by binding nuclear VDR. Myostatin, a muscle derived hormone, has negative effects on muscle mass. Vitamin D has a substantial inhibitory effect on myostatin gene expression, in this way, positively effects muscle cell proliferation [37]. Vitamin D also has a role in recovery after muscle injury [38]. Serum 25-hydroxyvitamin D3 (25OHD) levels decreases following muscle injury due to use, and baseline vitamin D levels correlate with faster recovery of strength after muscle injury [39]. Increased expression of VDR was demonstrated in the nuclei of regenerating muscle cells [40]. Vitamin D may effect muscle directly by binding nuclear VDR or indirectly by regulating calcium and phosphate mineral metabolism [41–43]. Both the calcium influx to muscle cell from the extracellular compartment and the rapid mobilization of calcium from the sarcoplasmic reticulum into the cytosol relies on vitamin D. Vitamin D also regulates muscle cell inorganic phosphate uptake for production of energy rich phosphate compounds required for muscle contraction [44]. Intracellular calcium elevation induces muscle contraction, impairment of intracellular calcium mobilization decreases the muscle tension. Furthermore, calcium itself, increases exercise induced GLUT4 expression, translocation to the muscle cell membrane, and glucose uptake to muscle cell [45,46]. Vitamin D treatment was shown to reverse the free fatty acid induced insulin resistance in the muscle [47]. In a recent meta-analysis, vitamin D was found to reduce fasting plasma glucose and HbA1c levels significantly [48]. Insulin resistance is an accused factor in sarcopenia. Adipose infiltration is another implicated factor in muscle aging. A study of older patients receiving magnetic resonance imaging of shoulder, revealed a correlation between higher fatty infiltration of rotator cuff muscles and lower serum levels of 25OHD [49]. Another study also reported an inverse correlation between serum vitamin D levels and intramyocellular lipid accumulation [50]. Owing to the positive effects on muscle tissue, vitamin D supplementation could lead to protection from sarcopenia and may be beneficial for treatment of already developed sarcopenia in older adults. In the following, several available studies focusing on this topic are summarized.

3.3. Observational trial data

Data coming from cross-sectional observational studies suggest an association between poor vitamin D status and muscle health. In a randomized population survey among hospitalized older patients and randomly selected ambulatory older participants, higher 25OHD concentrations were correlated with better muscle strength, improved musculoskeletal function, and fewer falls in both groups [51]. However the hospitalized subjects in this study were more disabled and had worse nutritional status, so reduced muscle strength along with reduced vitamin D levels could be caused by malnutrition. In a study, enrolling 986 ambulatory older women, participants with vitamin D deficiency (levels either