Vitamin D deficiency, muscle function, and falls in elderly people¹,²

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ABSTRACT An inadequate serum vitamin D status is commonly seen in elderly people as the result of various risk factors interacting in this population. Apart from the well-known effects on bone metabolism, this condition is also associated with muscle weakness, predominantly of the proximal muscle groups. Muscle weakness below a certain threshold affects functional ability and mobility, which puts an elderly person at increased risk of falling and fractures. Therefore, we wanted to determine the rationale behind vitamin D supplementation in elderly people to preserve and possibly improve muscle strength and subsequently functional ability. From experimental studies it was found that vitamin D metabolites directly influence muscle cell maturation and functioning through a vitamin D receptor. Vitamin D supplementation in vitamin D–deficient, elderly people improved muscle strength, walking distance, and functional ability and resulted in a reduction in falls and nonvertebral fractures. In healthy elderly people, muscle strength declined with age and was not prevented by vitamin D supplementation. In contrast, severe comorbidity might affect muscle strength in such a way that restoration of a good vitamin D status has a limited effect on functional ability. Additional research is needed to further clarify to what extent vitamin D supplementation can preserve muscle strength and prevent falls and fractures in elderly people.


KEY WORDS Vitamin D deficiency, muscle function, muscle strength, injurious falls, elderly, review

INTRODUCTION Aging, even in healthy elderly people, is accompanied by a reduction in muscle mass and muscle strength (1–3). The gradual loss of muscle strength (below a certain threshold) results in functional impairment (4, 5), the need for assistance in the performance of daily activities (6, 7), and an increased risk of falling and nonvertebral fractures (8). Therefore, the preservation of muscle strength in the elderly is of major importance. Vitamin D deficiency is associated with muscle weakness (9) and is common in elderly people (10). Older people are prone to develop vitamin D deficiency because of various risk factors: decreased dietary intake, diminished sunlight exposure, reduced skin thickness, impaired intestinal absorption, and impaired hydroxylation in the liver and kidneys (11–13). Of 824 elderly people aged >70 y from 11 European countries, 36% of men and 47% of women had wintertime serum 25-hydroxyvitamin D₃ [25(OH)D₃] concentrations <30 nmol/L (14).

Muscle weakness due to vitamin D deficiency is predominantly of the proximal muscle groups and is manifested by a feeling of heaviness in the legs, tiring easily, and difficulty in mounting stairs and rising from a chair; the deficiency is reversible with supplementation (15–18). Muscle atrophy—particularly of type II fibers—has been described histopathologically (17, 19, 20). In this review we focused on the relation between vitamin D deficiency, muscle function, and falls in elderly people to determine whether vitamin D supplementation can improve muscle strength and functional ability in this population.

VITAMIN D METABOLISM In the skin, under influence of ultraviolet radiation, 7-dehydrocholesterol is photoconverted to previtamin D₃, which is converted to vitamin D₃ (cholecalciferol). In the serum, bound to a vitamin D binding protein (DBP), vitamin D₃ is transported to the liver, where it is hydroxylated to 25(OH)D₃. In the kidneys, 25(OH)D₃ is further metabolized to 1α,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], the biologically active form of vitamin D (21). Its production and subsequent degradation is under tight metabolic control by various feedback systems, which are presented in Figure 1 (22–28).

In addition to being photoconverted in the skin, vitamin D can be obtained from the diet through ingestion of vitamin D–containing products (eg, fatty fish), from vitamin D–fortified milk or margarine, and from the use of multivitamins. The vitamin D ingested via this route is metabolized in the same manner as is endogenously produced vitamin D.

Because 1,25(OH)₂D₃ exerts its influence on distant target tissue, mediated by a vitamin D receptor (VDR), it is considered to be a hormone rather than a vitamin (29). The serum concentration of 25(OH)D₃ is 1000 times that of serum 1,25(OH)₂D₃, and this excess concentration constitutes a storage facility similar to that of other steroid hormones. Although it is generally agreed that vitamin D status is most accurately reflected by serum 25(OH)D₃ concentrations, evidence regarding adequate serum

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concentrations is inconclusive. An elevated serum parathyroid hormone concentration is a common indicator of vitamin D deficiency. However, varying concentrations of 25(OH)D3 have been proposed as the minimum required to prevent secondary hyperparathyroidism: from 20–40 to 122 nmol/L (30–34). Alternatively, a gradual scale was proposed in which hypovitaminosis D is defined as a 25(OH)D3 concentration <100 nmol/L (40 ng/mL), vitamin D insufficiency as a 25(OH)D3 concentration <50 nmol/L (20 ng/mL), and vitamin D deficiency as a 25(OH)D3 concentration <25 nmol/L (10 ng/mL) (35).

Physical inactivity increases bone turnover and serum calcium concentrations, which prevents an elevation in serum parathyroid hormone, even in the presence of vitamin D deficiency (36). Thus, caution should be exercised when an elevated serum parathyroid hormone is used as an indicator of vitamin D deficiency. In addition, caution is needed in comparisons of results from studies that used different assay techniques to determine serum 25(OH)D3 (37).

Apart from the classic target organs for maintaining body calcium homeostasis (intestine, kidney, bone, and parathyroid gland), other target sites for vitamin D metabolites have been identified (ie, skin, muscle, pancreas, immune system, hematopoietic system, and reproductive organs), and new actions have been discovered (21).

**MUSCLE AS A TARGET SITE FOR VITAMIN D METABOLITES**

Birge and Haddad (38), in the mid-1970s, were the first to show that 25(OH)D3 directly influences muscle phosphate metabolism in the diaphragms of vitamin D–deficient rats. Since then, several studies have shown that vitamin D metabolites affect muscle cell metabolism through various pathways. It is beyond the scope of this article to present these mechanisms in detail, which are thoroughly described elsewhere (39, 40). Vitamin D metabolites have been found to affect muscle metabolism in 3 ways: 1) by mediating gene transcription, 2) through rapid pathways not involving DNA synthesis, and 3) by the allelic variant of the VDR.

Both in animal models (41) and in humans (42, 43), a VDR has been found in skeletal muscle cells that specifically binds 1,25(OH)2D3. After transportation to the nucleus, this ligand–receptor interaction is modulated by various transcription factors and biochemical processes, resulting in a final transcription complex (21). In cultured myoblasts, this genomic pathway was found to influence muscle cell calcium uptake, phosphate transport across the muscle cell membrane, and phospholipid metabolism and to mediate cell proliferation and subsequently differentiation into mature muscle fibers (40, 43–46).

Vitamin D supplementation induces rapid changes in calcium metabolism of the muscle cell that cannot be explained by a slow genetic pathway. Evidence indicates that 1,25(OH)2D3, possibly through a vitamin D membrane receptor (47, 48), acts directly on the muscle cell membrane. On 1,25(OH)2D3 binding, several interacting second-messenger pathways were activated in the muscle cell, resulting in enhanced calcium uptake (within minutes), both through voltage-dependent calcium channels (49, 50) and calcium release–activated calcium channels (51).

Finally, muscle strength appears to be influenced by the genotype of the VDR in the muscle cell. With the use of specific restriction endonucleases, several VDR polymorphisms have been determined. In nonobese, elderly women, a 23% difference in quadriceps strength and a 7% difference in grip strength between the 2 homozygote types of a restriction site were found (52).

**VITAMIN D AND MUSCLE FUNCTION**

In the past decade, various cases of both young (15, 17, 19) and elderly (16, 53) adults have been described in which prolonged vitamin D deficiency was associated with severe muscle weakness, often leading to marked disability (15, 16) that improved within several weeks of vitamin D supplementation. However, few studies have been conducted in which muscle strength was objectively quantified in relation to vitamin D status in elderly people.

In an elderly population (65–95 y of age), of whom 12% of women and 18% of men had a serum 25(OH)D3 concentration <30 nmol/L, a significant correlation was found between vitamin D metabolites and leg extension power (54). This finding agrees with that of the study by Mowé et al (55), in which the association between serum vitamin D metabolites and muscle function was examined. In 349 elderly people (≥70 y of age), of whom 246 were hospitalized, serum 25(OH)D3 concentrations were significantly lower in those with less handgrip strength, unable to climb stairs, without any outdoor activity, and who had fallen in the previous month (55). In addition, a low serum 25(OH)D3 concentration (<40 nmol/L) was associated with reduced handgrip strength and walking distance in 63 community-dwelling elderly (82.5 ± 5.4 y of age) (56). However, a causal relation cannot be
Vitamin D deficiency has been reported to affect predominantly the weight-bearing antagonist muscles of the lower limb, which are necessary for postural balance and walking (67), and a significant correlation between serum 25(OH)D, concentration and the occurrence of falls in elderly people has been reported (55, 68). Furthermore, supplementation for 8 wk with vitamin D and calcium in 148 elderly women with a serum 25(OH)D2 concentration <50 nmol/L resulted in a decrease (9%; \( P < 0.05 \)) in body sway and fewer falls per subject over 1 y of follow-up compared with calcium monotherapy (0.24 compared with 0.45; \( P < 0.05 \)) (69). In contrast, supplementation in an elderly Dutch population (\( \geq 70 \) y of age) with 10 \( \mu g \) (400 IU) vitamin D/d for 2 y did not result in significantly fewer falls than in a placebo group (65). In conclusion, vitamin D deficiency is a condition that may cause muscle weakness in elderly persons. Although only a few intervention studies with vitamin D have been conducted in elderly people, the available evidence indicates that vitamin D supplementation preserves muscle strength and functional ability in high-risk groups, eg, frail, mostly homebound elderly people. Additional research, preferably by means of controlled randomized trials, is needed to confirm these findings.

**DISCUSSION**

The aims of this review were to clarify the effect of an inadequate vitamin D status on muscle function in elderly people and to determine the rationale behind vitamin D supplementation for the preservation of muscle strength and functional ability. A comparison of results from various studies is somewhat hampered by differences in subject demographics, study design, and outcome variables. Nevertheless, evidence indicates that muscle function in elderly people is affected by an inadequate vitamin D status (54–56). Supplementation in this population improved muscle strength, walking distance, functional ability (57–59), and body sway (70). These findings and the observed improvements in bone density after vitamin D supplementation (67, 72) provide an explanation for the association between vitamin D supplementation and fewer falls and nonvertebral fractures in elderly people (69, 71).

However, vitamin D deficiency is merely one condition that affects muscle function in elderly people (73, 74), which is illustrated by the fact that even in healthy, vitamin D–replete, elderly people, muscle strength declined with age (61), which was not prevented by vitamin D supplementation (62, 75). Moreover, severe comorbidity (and subsequent immobility) may cause muscle weakness and functional impairment, which cannot be improved by treating a coexisting vitamin D deficiency (60).

Experimental studies showed that muscle tissue is a direct target site for vitamin D metabolites and offer biochemical evidence for the association between vitamin D deficiency and muscle weakness (38). Although 1,25(OH)D3 is considered to be the active metabolite affecting target sites, including muscle (41), clinical studies reported a relation between serum 25(OH)D, and muscle strength (55, 68) and functional ability (59). Two mechanisms might explain these findings. First, the serum 25(OH)D, concentration is 1000 times that of serum 1,25(OH)D3, which might result in competitive binding of the 2 vitamin D metabolites on the VDR (76). Another possible explanation is that peripheral tissues, previously recognized as target sites for vitamin D metabolites, were found to express the mitochondrial enzyme calcidiol 1-monooxygenase, or \( \alpha \)-hydroxylase (77). Activation of 25(OH)D3 locally in target tissues may be involved in regionally controlled cell function (78).

In conclusion, vitamin D deficiency is a condition that may cause muscle weakness in elderly persons. Although only a few intervention studies with vitamin D have been conducted in elderly people, the available evidence indicates that vitamin D supplementation preserves muscle strength and functional ability in high-risk groups, eg, frail, mostly homebound elderly people. Additional research, preferably by means of controlled randomized trials, is needed to confirm these findings.
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