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Vitamin D and Its Role in Skeletal Muscle

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Abstract

Purpose of review—Vitamin D is best known for its role in regulating calcium homeostasis and in strengthening bone. However, it has become increasingly clear that it also has important beneficial effects beyond the skeleton, including muscle. This review summarizes current knowledge about the role of vitamin D in skeletal muscle tissue and physical performance.

Recent findings—Molecular mechanisms of vitamin D action in muscle tissue include genomic and non-genomic effects via a receptor present in muscle cells. Knockout mouse models of the vitamin D receptor provide insight into understanding the direct effects of vitamin D on muscle tissue. Vitamin D status is positively associated with physical performance and inversely associated with risk of falling. Vitamin D supplementation has been shown to improve tests of muscle performance, reduce falls, and possibly impact on muscle fiber composition and morphology in vitamin D deficient older adults.

Summary—Further studies are needed to fully characterize the underlying mechanisms of vitamin D action in human muscle tissue, to understand how these actions translate into changes in muscle cell morphology and improvements in physical performance, and to define the 25-hydroxyvitamin D level at which to achieve these beneficial effects in muscle.

Keywords

Vitamin D; Skeletal muscle; Vitamin D receptor; Physical performance

Introduction

Vitamin D is involved in the regulation of calcium homeostasis and bone metabolism by exerting its actions on target tissues including the intestine, the kidney, and bone (Figure 1) [1]. Increasing evidence indicates that vitamin D plays an essential role in many other tissues including skeletal muscle. Early clinical descriptions of a myopathy associated with severe vitamin D deficiency recognized a potential association between vitamin D and muscle [2]. The myopathy has been characterized by proximal muscle weakness, muscle wasting, and a waddling gait [3]. In early studies, symptoms were found to be responsive to treatment with vitamin D suggesting that vitamin D played an etiological role; however, the underlying mechanisms remained undefined [4,5]. In the last several decades, a growing number of clinical studies of the muscular effects of vitamin D supplementation and research on the vitamin D receptor in muscle cells have helped to improve our understanding of the role and actions of vitamin D in muscle tissue and on physical performance. This review summarizes the potential underlying mechanisms of vitamin D activity in muscle tissue and the clinical evidence of an association between vitamin D status and muscle strength and performance.

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Molecular Mechanisms of Vitamin D Activity

In its biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], exerts its actions by binding to a vitamin D receptor (VDR). Investigators have identified the VDR in both animal and human muscle tissues [6-9]. There are a well-described 1,25$(OH)_2$D nuclear receptor and a less clearly defined cell membrane receptor which mediates the rapid nongenomic actions [10].

At the genomic level, 1,25$(OH)_2$D binds to its nuclear receptor which results in changes in the gene transcription of mRNA and subsequent de novo protein synthesis [11]. The activation of VDR induces the heterodimerization between the active VDR and an orphan steroid receptor known as retinoic receptor (RXR) [11]. The formation of this heterodimer facilitates the interaction between the receptor's zinc finger region with DNA activating the protein transcription process [12]. The genomic pathway influences muscle calcium transport [13-20] and phospholipid metabolism [16,21,22].

1,25$(OH)_2$D also has rapid non-transcriptional effects that cannot be explained by a slow genetic pathway. There is evidence supporting the presence of a cell surface receptor which mediates 1,25$(OH)_2$D's rapid effects [23]. The characterization of this receptor remains somewhat controversial [16]. Thus far, it has been proposed that the initiation of the fast 1,25$(OH)_2$D signal may involve binding to a novel membrane receptor [24] and/or the VDR itself which is translocated from the nucleus to the cell surface [25]. At the nongenomic level, 1,25$(OH)_2$D activates several interacting second-messenger pathways that transmit the signal to the cytoplasm. These rapid effects also have been found to influence calcium transport and regulate intracellular calcium [26-33].

Other data indicate that 1,25$(OH)_2$D promotes the fast activation of mitogen-activated protein kinase (MAPK) signaling pathways [34,35], which result in initiation of myogenesis, cell proliferation, differentiation, or apoptosis. In mammalian cells, the MAPK family has four different subgroups: extracellular signal-regulated kinases (ERKs 1/2), c-Jun N-terminal kinases (JNK), ERK5, and p38 MAPK [35]. When activated, these MAPKs regulate cell processes through phosphorylation of other kinases, proteins, and transcription factors. 1,25$(OH)_2$D activates the ERK pathway through phosphorylation by several kinases, such as c-Src, Raf-1, Ras, and MAPKK [36,37]. Through these mechanisms, 1,25$(OH)_2$D stimulates muscle cell proliferation and growth [36,38]. A recent in vivo study in rats suggested that vitamin D_3 given over 8 weeks reduced exercise-induced apoptosis in gastrocnemius muscle [39].

VDR Knockout Mouse Model

VDR null mutant mice are characterized by growth retardation, osteomalacia, muscle impairment, and systemic metabolic changes such as secondary hyperparathyroidism and hypocalcemia [40]. VDR null mutant mice have muscle fiber diameters that are 20% smaller and more variable in size than those of wild type mice at 3 weeks of age (prior to weaning) [41]. By 8 weeks of age, these muscle fiber changes are more prominent in the VDR null mutant mice compared to the wild type suggesting either that these abnormalities progress over time or that as these mice age the metabolic alterations that occur contribute to the morphological changes [41]. The muscle fiber abnormalities are noted diffusely without any preference for type I or II fibers, differing from the human hypovitaminosis D myopathy with a predominance of type II fiber loss. At 3 weeks of age, VDR null mutant mice also demonstrate abnormally high expression of myogenic differentiation factors compared to wild type mice [41], thus suggesting alterations in muscle cell differentiation pathways resulting in abnormal muscle fiber development and maturation.

Other features of the VDR knockout phenotype include poor swimming ability (a well-known method to assess motor/balance functions in rodents) [42,43]. Initially this finding was attributed to muscular/motor impairments; however, a recent study by Minasyan et al. considers whether impaired vestibular function in the VDR null mutant mice may be a key factor [43]. Via immunohistochemical analysis, Minasyan et al. identified VDR-positive nuclei in epithelium of different structures in the vestibular system in wild-type mice and a significantly reduced expression of VDR in these structures in the VDR null mutant mice [43]. To further support the presence of a vestibular deficit in the VDR knockout, the VDR mutant mice had significantly greater abnormalities in postural control on balance tests such as the accelerating rotarod and tilting platform, compared to wild type mice [43]. These findings suggest another mechanism, loss of vestibular function, in the pathway to poor muscle performance and falls seen in humans with low 25(OH)D levels as discussed later in this review.

Effect of Vitamin D Status on Muscle Histology

Biopsies of skeletal muscle in adults with vitamin D deficiency have shown predominantly type II muscle fiber atrophy [3]. Type II muscle fibers are fast-twitch and are the first to be recruited to prevent a fall. Muscle tissue sections of vitamin D deficient individuals reveal enlarged interfibrillar spaces and infiltration of fat, fibrosis and glycogen granules [44]. Vitamin D supplementation may have an impact on muscle fiber composition. In a small uncontrolled study, Sorenson et al. [45] reported an increase in relative fiber composition and in fiber area of type IIa muscle fibers in muscle biopsies from elderly women after treatment with 1-α-hydroxyvitamin D and calcium for 3-6 months. A randomized, controlled study found that treatment of 48 elderly stroke survivors with 1000 IU of vitamin D_2 daily significantly increased mean type II muscle fiber diameter and percentage of type II fibers over a 2 year period [46]. There was also a correlation between serum 25(OH)D level and type II muscle fiber diameter both at baseline and after two years of follow-up. It remains unclear, however, if the increase in type II muscle fiber number is caused by new formation of type II fibers or a transition of already existing fibers from type I to type II.

Effects of Vitamin D on Physical Performance

Multiple cross-sectional studies in community-dwelling older adults have found a direct association between vitamin D status and parameters of physical performance, especially when 25(OH)D levels are <75 nmol/l [47-52]. A recent cross-sectional analysis of the Longitudinal Study of Aging Amsterdam (LASA) reported a 25(OH)D threshold of 60 nmol/l for improvement in physical performance [51]. Whereas in an analysis of the NHANES III survey, elderly individuals with higher serum 25(OH)D levels up to 94 nmol/l showed better lower extremity muscle performance than subjects with lower levels [47], particularly in the subset with 25(OH)D levels <60 nmol/l.

In a prospective analysis of the LASA, older adults with lower serum 25(OH)D (<50 nmol/l) were found to be at increased risk of a decline in physical performance over three years compared to those with higher levels (≥75 nmol/l) [49,53]. In a prospective analysis of the Rancho Bernardo Study cohort, a population with higher baseline 25(OH)D levels, older women with 25(OH)D levels ≤80 nmol/l performed more poorly on lower extremity muscle performance tests compared to women with the highest 25(OH)D levels ≥115 nmol/l over a 2.5-year period [54]. Interestingly, the association was not seen in men [54]. A longitudinal survey of community-dwelling Japanese older women with impairments in physical function reported that higher baseline 25(OH)D levels (defined as >67.5 nmol) were associated with improvements in physical fitness after 3 months of an exercise program [55]. An

observational study in older Italians, on the other hand, found a relationship between vitamin D status and measures of frailty in older men, but not women [50].

Two recent studies in adolescent girls [56,57] suggest that the effect of vitamin D on muscle performance may not be unique to older individuals. Ward et al. reported a direct relationship between 25(OH)D levels and muscle power, force, velocity, and jump height in 99 post-menarchal 12-14 year-old girls in the United Kingdom [57]. Of note, most of the girls had low 25(OH)D levels with a mean of 21.3 nmol/l and the analyses were not adjusted for physical activity [57]. The study by Foo et al. also found a similar positive relationship between 25(OH)D levels and handgrip strength after adjusting for physical activity in 301 adolescent girls with a mean age of 15 and serum 25(OH)D levels of 34 nmol/l [56]. Other studies combining younger and older women did not find a correlation between vitamin D status and handgrip strength [58] or other tests of physical performance [59].

Randomized clinical trials have examined the effect of vitamin D supplementation on tests of physical performance [46,60-62]. Specifically, vitamin D with calcium, compared to calcium alone, improved body sway by 9% in ambulatory elderly women with serum 25(OH)D levels <50 nmol/L within 8 weeks [60] and improved lower extremity muscle performance in institutionalized elders with serum 25(OH)D levels <50 nmol/L by 4-11% within 12 weeks [61]. Similarly, in a recent longer-term study among healthy older men and women with serum 25(OH)D levels <75 nmol/L, vitamin D_3 800 IU and calcium 1000 mg daily, compared to calcium alone, significantly improved tests of physical performance over a 12-20-month period [62]. A randomized trial in 179 pre-menarchal girls, age 10-17, who received either oral vitamin D_3 1,400 IU/week, vitamin D_3 14,000 IU/week or placebo for 1 year, reported an increase in whole body lean mass (a surrogate marker of muscle mass) in supplemented girls [63].

Vitamin D and Falls

Given the relationship between 25(OH)D level and physical performance, one would expect a similar link when examining fall risk. In the LASA cohort, low 25(OH)D levels (<25 nmol/L) were associated with an increased risk of repeated falling over the subsequent year, particularly in persons under 75 years of age [64]. A similar association has been replicated in varied older populations [52,65-67]. In a randomized, controlled trial, Bischoff et al. showed that treatment with vitamin D_3 and calcium (800 IU and 1200 mg per day) for 3 months reduced the risk of falls by 49% compared to calcium alone [61]. Similarly in an Australian study, treatment with vitamin D_2 (initially 10,000 IU per week then 1000 IU per day) and calcium (600 mg per day) for 2 years reduced the risk of falls in the compliant group by 30% compared to calcium alone [68]. A recent large clinical trial in 242 healthy older seniors with 25(OH)D levels <75 nmol/l demonstrated that long-term supplementation with vitamin D_3 and calcium (800 IU and 1000 mg per day), versus calcium alone, resulted in a 39% decrease in the number of subjects with first fall over a 20-month period [62]. In a meta-analysis of five randomized controlled trials, including over 1200 ambulatory and institutionalized subjects, vitamin D supplementation of 700 IU or greater lowered the risk of falling by 22% [69].

Other experimental studies using vitamin D in various doses did not observe significant effects on falls, but falls were not the primary outcomes in these studies, adherence to treatment was poor, and 25(OH)D levels achieved were suboptimal [70,71]. These two very large negative studies were pooled along with twelve other studies in a recent narrative review [72] and a recent Cochrane review [73], both examining the effect of vitamin D on falls. As a result, effects of vitamin D supplementation had a minimal to no benefit on falls [72,73].

VDR Polymorphisms and Muscle

Subtle variations in DNA sequence of the VDR gene, also known as VDR polymorphisms, are associated with a series of biological characteristics including muscle strength. For example, *FokI* is a polymorphism involving a T/C transition in exon 2 of the VDR gene [74]. Individuals with the C allele ("F") have a shorter VDR than do those with the T ("f") allele. The shorter VDR is associated with enhanced VDR transactivation capacity as a transcription factor [75], which would suggest a possible improvement in muscle strength in light of the clinical data reporting a positive association between vitamin D status and muscle strength. On the contrary, the C allele is associated with reduced fat-free mass and quadriceps strength in healthy elderly men [76] and elderly individuals with COPD [74].

BsmI, a restriction fragment length polymorphism at the 3′ end of the VDR gene, has also been associated with muscle performance. The 3′ end is known to play an important role in regulating gene expression. Young healthy women with the bb allele, which may be associated with higher VDR activity in combination with the C allele of *FokI*, were found to have lower fat-free mass and hamstring (but not quadriceps) strength compared to those with the BB allele [77]. In non-obese older women aged 70 and older, those with the bb genotype were found to have a 7% higher grip strength and a 23% higher quadriceps strength than those with BB genotype [78]. Why the allele associated with higher VDR activity would be found to have reduced muscle strength remains unclear.

Conclusion

Vitamin D and its receptor are important for normal skeletal muscle development and in optimizing muscle strength and performance. Supplementation with various forms of vitamin D in older adults has mostly shown reduction in falls risk and improvements in tests of muscle performance. Despite these promising data, further research is needed to fully characterize the underlying mechanisms of vitamin D action on human muscle tissue, to understand how these actions translate into changes in muscle cell morphology and improvements in physical performance, and to define the 25-hydroxyvitamin D level at which to achieve these beneficial effects in muscle.

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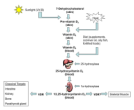

Figure 1.

Synthesis of vitamin D_3 occurs in the skin where 7-dehydrocholesterol is converted to pre-vitamin D_3 in response to sunlight (ultraviolet B radiation) exposure. Vitamin D_3 is produced from the isomerization of pre-vitamin D_3 in the skin or intestinal absorption of natural and fortified foods and supplements. Vitamin D_3 (bound to vitamin D-binding protein) circulates in the bloodstream, and is transported to the liver where it is hydroxylated by liver 25-hydroxylases. The resultant 25-hydroxyvitamin D_3 is hydroxylated to the active secosteroid 1α,25$(OH)_2D_3$ in the kidney by 1α-hydroxylase. 1α,25$(OH)_2D_3$ acts on various target tissues via its receptor (VDR). 1α, 25$(OH)_2D_3$ appears to affect other nonclassical target tissues such as skeletal muscle possibly via the VDR.