Rev Endocr Metab Disord
DOI 10.1007/s11154-011-9200-6

Relevance of vitamin D in muscle health

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Abstract This review will summarize the impact of vitamin D deficiency on muscle health. Mechanistic evidence regarding the presence of the specific vitamin D receptor in muscle tissue and muscle biopsy abnormalities observed with deficiency will be reviewed, as well as molecular and non-molecular effects of vitamin D in muscle tissue. At the clinical level, the evidence from randomized controlled trials of vitamin D supplementation on functional improvement and fall reduction will be summarized. Further, the manuscript will discuss whether vitamin D effects on fall prevention modulate in part its benefit on fracture prevention and why fall prevention is essential in fracture prevention at higher age. Finally, trial and epidemiological data will be reviewed to assess desirable serum 25-hydroxyvitamin D levels for optimal muscle health.

Keywords Vitamin D · Falls · Muscle strength · Bone density · Fractures

1 Introduction

Four lines of evidence support a role of vitamin D in muscle health. *First*, proximal muscle weakness is a prominent feature of the clinical syndrome of vitamin D deficiency [1]. Clinical findings in vitamin D deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as waddling way of walking [2]. *Second*, the vitamin D receptor (VDR) is expressed in human muscle tissue [3, 4], and VDR activation may promote *de novo* protein synthesis in muscle [5, 6]. Mice lacking the VDR show a skeletal muscle phenotype with smaller and variable muscle fibers and persistence of immature muscle gene expression during adult life [7, 8]. These abnormalities persist after correction of systemic calcium metabolism by a rescue diet [8]. *Third*, several observational studies suggest a positive association between 25-hydroxyvitamin D (25(OH)D) and muscle strength or lower extremity function in older persons [9, 10]. *Fourth*, vitamin D supplementation increases muscle strength and balance [11, 12], and reduces the risk of falling in community-dwelling individuals [12–14], as well as in institutionalized individuals [11, 15] in several double-blind randomized-controlled trials (RCTs) summarized in a 2009 meta-analysis discussed below [16].

1.1 VDR in skeletal muscle tissue

The presence of the VDR in skeletal muscle tissue has been questioned recently by Wang and DeLuca suggesting that the VDR is undetectable in muscle tissue [17]. Wang and DeLuca's findings are in contrast with many earlier studies [3, 18–21], including the most recent one by Ceglia and collagues using a new multi-step immunofluorescent technique to detect the VDR in muscle biopsy tissue from older female subjects [4]. Ceglia and collagues used 3 commercially available anti-bodies to the VDR, including the D-6 Santa Cruz monoclonal antibody used by Wang and DeLuca, and detected the VDR in muscle with each of the three anti-bodies [4].

The presence of a nuclear VDR in muscle tissue suggests that the effect of vitamin D on muscle is most likely direct via

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Published online: 22 October 2011

a genomic transcriptional effect. Mechanistically, it has been suggested that 1,25-dihydroxyvitamin D binds to the nuclear VDR in muscle resulting in *de novo* protein synthesis [5, 6]. At a clinical level, this is supported by findings of two small trials in older adults (see paragraph below), which documented an increase in type II muscle fibers after treatment with 1-alpha-calcidiol [22] or vitamin D2 [23].

In addition to the relatively slow genomic effect of vitamin D on muscle mediated by its nuclear receptor, a non-genomic rapid effect of vitamin D on muscle tissue has been suggested. The non-genomic effect has been found to support calcium transport into the muscle cell relevant to muscle contraction [24, 25]. This effect may be mediated by a VDR located in the cell-membrane of muscle fibers as recently suggested by findings from Ceglia and colleagues. Their data support the presence of a VDR in muscle cell nuclei and suggest a peripheral VDR staining pattern unrelated to the nuclei [4].

One study quantified VDR expression in human skeletal muscle tissue biopsies from 32 orthopedic surgery patients by immunohistological staining of the VDR using a monoclonal rat antibody to the VDR (Clone no. 9A7) [3]. In the multivariate analysis, older age was a significant predictor of decreased VDR expression (number of VDR positive nuclei) after controlling for biopsy location (gluteus medius or the transversospinalis muscle), and 25-hydroxyvitamin D status. An age-related decline in VDR expression is supported by studies in rats where VDR expression declined with advancing age in both intestine [26, 27] and bone [26]. Whether vitamin D supplementation increases VDR expression in muscle is not known to date.

1.2 Vitamin D receptor knockout mouse model

Mice lacking the VDR have key abnormalities that may serve as a model of what severe vitamin D deficiency may cause in humans [28]. Further, the ability to maintain calcium homeostasis in these mice by a recue diet allows insight in actions of the VDR that are critical for normal development independent of its role in calcium homeostasis [29, 30]. Based on these studies an important function of the VDR has been identified in several target tissues, including muscle [28]. Compared to their wild type litter mates, mice lacking the VDR have variable muscle fibers that are 20% smaller in diameter at 3 weeks of age (prior to weaning), and this difference is even more pronounced at 8 weeks of age [8]. Notably, these abnormalities in VDR knock-out mice persist after correction of systemic calcium metabolism by a rescue diet [8] and therefore support a role of the VDR in muscle development and maturation that is based on a direct effect of vitamin D on muscle unrelated to calcium metabolism.

1.3 Vitamin D deficiency and type II muscle atrophy in humans

Muscle biopsy studies in humans suggest a potentially selective effect of vitamin D on type II muscle fibers. *First*, patients with osteomalacic myopathy reveal type II muscle atrophy in muscle histology investigations [31]. *Second*, in two smaller clinical trials treatment with 1-alpha-calcidiol [22] or vitamin D2 [23] increased type II muscle fibers in older adults. Sorenson and colleagues performed one small uncontrolled study with muscle biopsies taken at baseline and after 3 month of treatment with 0.5 micrograms of 1-alpha-calcidiol per day in 11 postmenopausal women with osteoporosis [5]. The authors documented a relative change in fiber composition with an increase in the diameter and number of type II muscle fibers after a 3 month of treatment [5]. In the second randomized controlled study among 48 senior stroke survivors by Sato and colleagues, similar findings were observed after 2-years of treatment with 1000 IU ergocalciferol per day [23].

Type II muscle atrophy in profound vitamin D deficiency, and the observed increase of type II fast-twitch muscle fibers with vitamin D treatment from the two small trials fit well with the findings that high dose vitamin D supplementation (700 to 1000 IU per day) reduced the risk of falling by 34% in a meta-analysis of 8 double-blind randomized controlled trials [32] (see section on fall prevention below). Type II muscle fibers are fast-twitch fibers and therefore are the first to be recruited when fast reaction is needed, such as in the prevention of a fall. Notably, ageing itself has been associated with a decrease in type II fast-twitch relative to type I slow-twitch muscle fibers [33]. Given the high prevalence of vitamin D deficiency in senior adults, it is possible that the age related decline in type II muscle fibers is in part explained by vitamin D deficiency, which may be accompanied by a decrease in muscular VDR expression with age [3].

1.4 Is there 1-alpha hydroxylase activity in muscle?

The 1α-hydroxylase enzyme (CYP27B1) performs the conversion of 25(OH)D into 1,25(OH)2D. Its classic location is the kidney, however more recently the enzyme has been observed in many human cells and tissues [34] including vascular smooth muscle cells [35]. Whether 1α-hydroxylase activity is present also in skeletal muscle is undefined to date.

Children with 1α-hydroxylase deficiency due to mutations in the enzyme (vitamin D dependent rickets type 1/pseudovitamin D deficiency rickets) present with a clinical picture of joint pain and deformity, hypotonia, growth failure and muscle weakness [36]. Notably, muscle weakness in these children is rapidly reversible with physiologic doses of calcitriol or 1α-hydroxyvitamin D [37]. In support of a concept that the 1α-hydroxylase activity is present in muscle tissue, myopathy in patients with "regular" vitamin D deficiency rickets or osteomalacia is reversible with cholecalciferol or ergocalciferol supplementation [2, 38].

1.5 Vitamin D and function and strength

Most observational studies show a positive association between higher 25(OH)D status and better lower extremity function in older adults. Higher 25(OH)D levels were associated with a lower risk of functional decline [39, 40], a lower risk of future falls and a lower risk of nursing care admission [41], including two population-based studies from the US [10] and Europe [39].

Consistently, in several trials of older individuals at risk for vitamin D deficiency, vitamin D supplementation improved strength, function, and balance [11, 12, 14]. Most importantly, these benefits translated in a reduction in falls in some of the same trials [11, 12, 14]. In three recent double-blind RCTs supplementation with 800 IU vitamin D3 resulted in a 4–11% gain in lower extremity strength or function [11, 12], and an up to 28% improvement in body sway [12, 14] in older adults age 65+ within 2 to 12 month of treatment. Extending to trials among individuals with a lower risk of vitamin D deficiency and including open design trials, a recent meta-analysis by Stockton identified 17 RCTs that tested any form of vitamin D treatment and documented a muscle strength related endpoint. The authors suggested that based on their pooled findings, vitamin D may not improve grip strength, but a benefit of vitamin D treatment on lower extremity strength could not be excluded (p=0.07) among individuals with 25(OH)D starting levels of >25 nmol/l and the authors report a significant benefit among two studies with participants that started with 25(OH)D levels <25 nmol/l [42].

1.6 Vitamin D benefits on fracture prevention may be in part explained by muscle benefit

The beneficial effect of vitamin D on calcium absorption and bone mineral density may not be the only explanation for its protective effect against fractures [43]. In fact, vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur [44]. Further, supported by the presence of the VDR in human muscle tissue [3] and an early (within 2 to 5 months) [11, 15] and sustained [13, 45–47] effect of vitamin D on falls [16], the observed fracture reduction with vitamin D may be modulated in part by its benefit on muscle. Moreover, the early effect of vitamin D supplementation on fall prevention [16] may explain a fracture reduction that was apparent within 6 months of treatment in the Boston STOP-IT [48] and the Decalyos I studies [49].

A dual-benefit vitamin D on bone and muscle is especially attractive among seniors who have a high incidence of non-skeletal risk factors for fracture [50]. Mechanistically, fractures at later age are closely linked to muscle weakness [51] and falling [52, 53]. Over 90% of fractures occur after a fall and fall rates increase with age [54] and poor muscle strength or function [54]. While the circumstances [50] and the direction [55] of a fall determine the type of fracture, bone density and factors that attenuate a fall, such as better strength or better padding, critically determine whether a fracture will take place when the faller lands on a certain bone [56]. Additionally, fear of falling may adversely affect bone density through self-restriction of physical activity [57, 58]. After their first fall, about 30% of persons develop fear of falling [57], resulting in decreased mobility and quality of life [57]. Notably, anti-resorptive therapy alone is not adequate treatment in elders with muscle weakness and other risk factors for falls [59].

1.7 Anti-fall efficacy of vitamin D

Several recent peer-reviewed meta-analyses of randomized, controlled trials have addressed the effect of vitamin D on fall risk reduction [16, 60–67], all of them suggesting a benefit. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed as a recommendation among the senior population. This suggestion is in line with the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force [66], the 2010 American Geriatric Society/British Geriatric Society Clinical Practice Guideline [68], the 2010 assessment by the IOF [69], and the 2011 recommendations on vitamin D by the Endocrine Society [70], all 4 of which identified vitamin D as an effective intervention to prevent falling in older adults.

Challenging for their assessment is that falls tend to be forgotten if not associated with significant injury [71], requiring short periods of follow-up and well defined ascertainment strategies. Thus, one recent meta-analysis assessed the efficacy of vitamin D supplementation based on double-blind RCTs that also used a high quality fall assessment [16, 32]. Notably, restricting the evidence to double-blind RCTs with a high-quality fall assessment, fall prevention was observed only in trials with a treatment dose of 700 to 1000 IU vitamin D per day [32]. Any lower dose of vitamin D supplementation did not reduce fall risk (see Fig. 1).

The recent 2010 Institute of Medicine (IOM) Report claimed that the peer-reviewed meta-analysis illustrated in Fig. 1 may have been flawed regarding the choice of 8 trials and the method chosen to explain heterogeneity. In a rebuttal [32], the authors confirmed their selection of trials

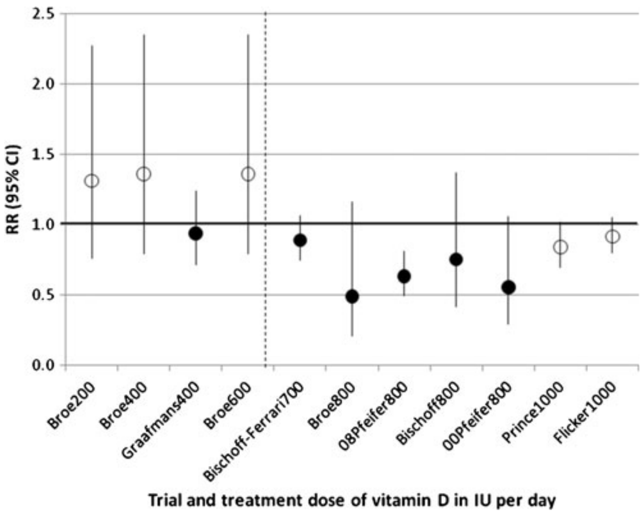

Fig. 1 Fall prevention by dose of vitamin D. Circles show the relative risk of falling in 8 double-blind RCTs testing vitamin D supplementation with or without calcium supplementation against calcium or placebo. Markers filled indicate trials with oral vitamin D3 (cholecalciferol) and markers unfilled indicate trials with oral vitamin D2 (ergocalciferol) [16, 32]. By visual inspection, fall reduction only occurs in trials that tested a vitamin D dose of at least 700 IU per day. Including all trials (regardless of dose level), there was a significant reduction in the odds of falling: OR=0.73 [.62, .87]; p=.0004. When the model is expanded to capture the impact of both high dose and low dose treatment, high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling (OR=0.66 [.53, .82] p=.0002), while low dose vitamin D did not (OR=1.14 [.69, 1.87]; p=.61)

and re-analyzed their data to account for the stochastic dependencies (correlations) between the corresponding risk ratios in the multiple dosing trial by Broe et al. as suggested by the IOM. In the re-analysis, when treatment was the only predictor (regardless of dose level), there was a significant reduction in the odds of falling based on the primary analysis of the same 8 trials: OR=0.73 [.62, .87]; p=.0004. When the model was expanded to capture the impact of both high dose and low dose treatment (see Fig. 1), high dose vitamin D (700 to 1000 IU vitamin D per day) reduced the odds of falling by 34% (OR=0.66 [.53, .82] p=.0002), while low dose vitamin D did not (OR=1.14 [.69, 1.87]; p=.61) [32].

Notably, in the original publication of this meta-analysis [16], the authors performed a sensitivity analysis including 15 trials of any study design and fall assessment quality (n= 17,786) and documented a non-significant 7% fall reduction with vitamin D (RR=0.93; 95% CI 0.87–1.01). Even at the comprehensive analysis level, significant variation among the 15 trials (Q-test: p=0.009), could be explained by dose (700 IU +/day; n=17,281; pooled RR was 0.92 (95% CI, 0.85–1.00)), and further among trials that tested a higher dose by trial quality (Q-test: p=0.005). Further, based on the primary analysis [16], the benefit of fall prevention was present in all subgroups of the senior population at the higher dose of vitamin D. At the higher dose of 700 to 1000 IU vitamin D, there was a 38% reduction in the risk of falling with a treatment duration of 2 to 5 months and a sustained significant effect of 17% fall reduction with treatment duration of 12 to 36 months, and the benefit was independent of type of dwelling and age. There was a suggestion that vitamin D_3 was superior to vitamin D_2 for fall prevention. Although the number of studies for active vitamin D and fall prevention was small, the authors pooled these trials separately and found a significant benefit on fall prevention (−22%), which adds to the evidence that improved vitamin D status will reduce the risk of falling in older individuals.

1.8 Summary of the IOM report recommendations of vitamin D and fall prevention

The IOM did a thorough review on the effect of vitamin D on fall prevention. Their synopsis is that the evidence of vitamin D on fall prevention is inconsistent, which is in contrast to all published and peer-reviewed meta-analyses [16, 60–67] and recent guidelines by the Agency for Healthcare Research and Quality (AHRQ) for the U.S. Preventive Services Task Force [66], the American Geriatric Society/British Geriatric Society Clinical Practice Guideline [68], position paper on vitamin D by the IOF [69], and the Endocrine Society [70].

The IOM overall analysis of 12 RCTs (n=14,101) showed a significant benefit of vitamin D on fall prevention (OR=0.89; 95% CI 0.80–0.99), as did the majority of their subset analyses, clearly supporting the use of vitamin D in the prevention of falling. The set of analyses which showed

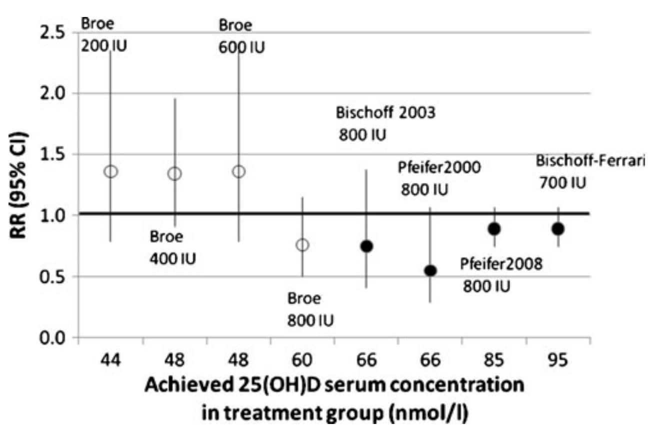

Fig. 2 Fall prevention by achieved 25(OH)D levels. Circles show the relative risk of falling in 5 double-blind RCTs testing vitamin D supplementation with or without calcium supplementation against calcium or placebo documenting achieved 25(OH)D levels in the treatment groups. Markers filled indicate trials with oral vitamin D3 (cholecalciferol) and markers unfilled indicate trials with oral vitamin D2 (ergocalciferol) [16, 32]. By visual inspection, fall reduction only occurs in trials that achieve 25(OH)D levels of at least 60 nmol/l in their treatment groups. Achieved serum 25-hydroxyvitamin D concentrations of 60 nmol/l or more resulted in 23% fall reduction (pooled RR=0.77; 95% CI; 0.65–0.90), while less than 60 nmol/l resulted in no fall reduction (pooled RR=1.35, 95% CI, 0.98–1.84) [10]

no benefit were based on only 4 studies, which cannot be considered reliable indicators of true treatment efficacy, as these trials either used low dose vitamin D [72], had less than 50% adherence [73], had a low-quality fall assessment [74] or used one large bolus dose of vitamin D among seniors in unstable health [75].

1.9 Desirable 25-hydroxyvitamin D status for muscle health

A threshold for serum 25(OH)D level needed for muscle function and fall prevention in older subjects has been evaluated in few studies. A dose–response relationship between lower extremity function and serum 25(OH)D levels has been found in two epidemiologic studies among older individuals [9, 10]. From these analyses a threshold of 50 nmol/l has been suggested for optimal function in one study [9], while in the larger study [10], a threshold beyond which function would not further improve was not identified, but most of the improvement was seen coming from very low 25(OH)D levels to a minimal threshold of 60 nmol/l [10]. Consistently, one meta-analysis of double-blind RCTs found a differential benefit of achieved 25(OH)D levels below 60 nmol/l *versus* levels 60 nmol/l or above, with a benefit demonstrated only in the higher group. Achieved serum 25-hydroxyvitamin D concentrations of 60 nmol/l or more resulted in 23% fall reduction (pooled RR=0.77; 95% CI; 0.65–0.90), while less than 60 nmol/l resulted in no fall reduction (pooled RR=1.35, 95% CI, 0.98–1.84) [10]; see Fig. 2.

Lending further support to the importance of an adequate dose of vitamin D, several double-blind RCTs have documented fracture prevention with 700–800 IU vitamin D per day [48, 49, 74, 76] but not with 400 IU per day [77–79].

2 Conclusion

Vitamin D is relevant to muscle health as supported by several lines of evidence summarized in this article. Based on available data, the VDR is present in muscle tissue and vitamin D effects on muscle are direct including both genomic and non-genomic effects. Strong evidence is available from clinical trials in the senior population suggesting that vitamin D supplementation at a high enough dose reduces the risk of falling. Thus, given the available evidence today, vitamin D supplementation for fall prevention should not be delayed as a recommendation among the senior population. More studies are needed to test whether higher doses of vitamin D than currently recommended (600 to 800 IU/day) contribute to a greater benefit on muscle, including both muscle function and fall prevention. Further, additional studies are needed to further defined vitamin D effects at the cellular level in muscle and whether VDR expression can be enhanced by treatment.

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