Vitamin D and muscle function

Heike A. Bischoff-Ferrari

Department of Rheumatology and Institute for Physical Medicine
University Hospital Zurich, Switzerland

Address for correspondence:
Heike A. Bischoff-Ferrari, M.P.H.
Department of Rheumatology and Institute for Physical Medicine
University Hospital Zurich
Gloriastrasse 25, 8091 Zurich, Switzerland
Ph. +41 (044) 2552699
Fax +41 (044) 2554388
E-mail: hbischof@hsph.Harvard.edu; Heike.Bischoff@usz.ch

Maintenance of musculoskeletal function and fall prevention are important public health targets in a rapidly aging population (1). Sarkopenia is prevalent in older persons and resulting in falls among 30% percent of those 65 years or older, and 40-50% of those 80 years or older (2, 3).

Several beneficial effect of vitamin D have been described, the most established one being improved bone mineral density and fracture prevention (4-6). On the other hand, muscle weakness is also a prominent feature of the clinical syndrome of vitamin D deficiency (7, 8) and may plausibly mediate fracture risk through an increased susceptibility to falls (7, 9-13). In fact, vitamin D appears to directly improve muscle strength (14, 15) and effects on muscle strength occur within 8-12 weeks (10, 11, 16).

A possible explanation for the beneficial effect of vitamin D on fall risk is that 1,25-dihydroxyvitamin D, the active vitamin D metabolite, binds to a highly specific nuclear receptor in muscle tissue (17, 18) leading to improved muscle strength and thus to a reduced risk of falling. It is currently believed that, apart from rapid genome-independent calcium fluxes, 1,25-dihydroxyvitamin D elicits its biological response through the activation of the vitamin D receptor (VDR), which leads to de novo protein synthesis, affecting muscle cell growth (7, 11).

In one study, which illustrates this hypothesis, treatment with 1-alpha-hydroxyvitamin D increased the relative number and size of type II muscle fibers of elderly women within three months of treatment (11). Furthermore, two RCTs included in the meta-analysis above found a positive effect of vitamin D on body sway (16) and musculoskeletal function (10) in addition to the documented reduction in falls, supporting that fall prevention with vitamin D is likely to be mediated by improved musculoskeletal function. Pfeifer and colleagues found a 9% decrease in body sway following a two-month treatment with vitamin D (800 IU per day) plus calcium (1200 mg per day) compared to calcium alone (1200 mg per day) (16). Similarly, Bischoff and colleagues documented a 5-11% improvement in grip strength, knee extensor and flexor strength, and the timed up&go test following a three-month treatment with vitamin D (800 IU per day) plus calcium (1200 mg per day) compared to calcium alone (1200 mg per day) (10).

One meta-analysis addressed the effect of vitamin D on the risk of falling in older persons (19). Based on 5 RCTs (n = 1237), vitamin D reduced the risk of falling by 22% (pooled corrected OR = 0.78; 95% CI [0.64, 0.92]) compared to calcium or placebo (10, 16, 20-22). Subgroup analyses suggested that the reduction in risk was independent of the type of vitamin D, duration of therapy, and gender. However, the results from one trial suggested that 400 IU of vitamin D may not be clinically effective in preventing falls in the elderly (22), while two trials that used 800 IU of vitamin D per day plus calcium reduced the risk of falling (10, 16). For the two trials with 259 subjects using 800 IU of cholecalciferol, the corrected pooled OR was 0.65 (95% CI [0.40, 1.00]) (19). A recent double-blind RCT testing the long-term effect of 700 IU vitamin D plus 500 mg calcium compared to placebo confirmed a benefit on falls among community-dwelling older women (n = 246) with a 46% reduction in the odds of falling (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.30-0.97) (23). Fall reduction was most pronounced in less active women (OR, 0.35; 95% CI, 0.15-0.81), while the effect in community-dwelling older men was neutral (OR, 0.93; 95% CI, 0.50-1.72, n = 199). The neutral effect in men maybe explained by higher physical activity and higher 25-hydroxyvitamin D [25(OH)D] levels among men in this trial compared to women. Furthermore, the data suggested a possible benefit of vitamin D on the risk of falling among less active men.

A threshold for optimal 25(OH)D and lower extremity function has been addressed recently (15) examining the association between serum 25(OH)D levels and lower-extremity function in NHANES III including 4100 ambulatory older adults (15). Functional assessment included the 8-foot-walk test and sit-to-stand test (24, 25). Both tests depend on lower extremity strength, and mirror functions needed in everyday life. For the 8-foot walk test, compared to the lowest quintile of 25(OH)D, the highest quintile showed an average decrease by 5.6% (test for trend: $p < 0.001$). For the sit-to-stand test, compared to the lowest quintile of 25(OH)D the highest quintile showed an average decrease by 3.9% (test for trend: $p = 0.017$).

In the regression plots of the NHANES III analysis, performance speed continued to increase throughout the reference range of 25(OH)D (22.5 to 94 nmol/l) with most of the improvement occurring in 25(OH)D levels going from 22.5 to approximately 40 nmol/l (15). Further improvement was seen in the range of 40-94 nmol. These results were similar for subgroups of active and inactive individuals, men and women, three ethnic groups (Caucasians, African Americans and Mexican Americans), and persons with higher (> 500 mg/day) and lower calcium intakes (500 mg/day).

Thus, for all subgroups of ambulatory older individuals the data for lower extremity strength suggested that serum 25(OH)D levels of at least 40 nmol/l are desirable, but 75-100 nmol/l are best. This is supported by data published in abstract from the Longitudinal Aging Study Amsterdam including 1351 Dutch men and women aged 65 and older. In that study, a physical performance score (chair stands, a walking test, and a tandem stand) improved most from very low levels of serum 25(OH)D up to 50 nmol/l, and less pronounced but continuously beyond 50 nmol/l (26).

The optimal target of 75 nmol/l 25(OH)D for lower extremity function is supported by threshold assessment for bone mineral density in younger and older adults (6), fracture efficacy in

older adults (27), as well as a recent expert consensus for optimal bone health (28). The minimal dose of vitamin D to achieve both fall (19) and fracture prevention (27) has been identified as 700-800 IU vitamin D per day (cholecalciferol).
In summary, it has become a public health priority to raise the consciousness of the community towards ensuring sufficient vitamin D status for both fall and fracture prevention, as well as maintenance of muscle strength and lower extremity function. Fall and fracture benefits have been observed with intakes of at least 700-800 IU vitamin D (cholecalciferol) per day and a target level for optimal lower extremity strength and bone health has been suggested to be 75 nmol/l (30 ng/ml) 25(OH)D.

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