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70th Anniversary Conference on ‘Vitamins in early development and healthy aging: impact on infectious and chronic disease’

Symposium 1: Vitamins and cognitive development and performance Serum 25-hydroxyvitamin D and muscle atrophy in the elderly

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The objective of this review is to consider the mechanisms by which vitamin D affects muscle and the evidence that vitamin D status is important for muscle performance and fall prevention in older adults. Vitamin D receptors have been identified in human skeletal-muscle cells. Activation of these receptors by 1,25-dihydroxyvitamin D is involved in the action of vitamin D on the myocyte. Several studies have examined the effect of supplemental vitamin D on muscle strength, balance and falls. Among those examining muscle strength, results have been either positive for vitamin D or null. A recent meta-analysis of seventeen such trials revealed no significant effect of vitamin D overall, but a significant improvement in strength was observed in the trials in which the mean starting level of 25-hydroxyvitamin D was 25 nmol/l or below. Evidence for an effect of vitamin D on balance, measured as sway, is less abundant but more consistently positive. Many trials have evaluated the effect of supplemental vitamin D on falls. Overall, there is about a 20% lower risk of falling with supplementation. One meta-analysis considered the vitamin D dose administered and concluded that doses up through 15 µg (600 IU) were ineffective and doses of 17.5–25 µg/d (700–1000 IU/d) significantly lowered fall risk. The minimal 25-hydroxyvitamin D level needed for benefit was 60 nmol/l.

25-hydroxyvitamin D: Vitamin D: Muscle performance: Falls

Aging is accompanied by loss of muscle mass. Each decade, older women lose an average of 0.6 kg lean tissue mass and men lose 1.6 kg⁽¹⁾. Loss of muscle mass results in reduced muscle strength and this, in turn, leads to an increased risk of falling. The term sarcopenia was coined in 1989 by Rosenberg to describe the decline in muscle mass that occurs with aging⁽²⁾. Nine years later, Baumgartner operationalised the term to: appendicular skeletal muscle mass (muscle weight (kg)/height² (m²) being less than 2 SD below the mean of a young, same-sex reference group⁽³⁾. By this definition, the prevalence of sarcopenia increased from 13 to 24% in persons under the age of 70 years to over 50% in persons over the age of 80 years⁽³⁾. Moreover, he documented the fact that sarcopenia was significantly associated with self-reported physical

disability in both men and women, independent of ethnicity, age, morbidity, obesity, income and health behaviours. This study was influential in drawing attention to the extent of the problem and to its ramifications. More recently, a variety of definitions have been proposed but no one is used by all.

Exercise has well-established powerful trophic effects on muscle mass and function. Low intensity self-administered home-based exercise programmes have lowered risk of falling in elders^(4,5) and should always be encouraged. The focus of this paper, however, is on whether vitamin D status affects muscle performance and risk of falling and whether supplementing current intakes of vitamin D may improve muscle performance and lower risk of falling.

Abbreviations: 25OHD, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D; VDR, vitamin D receptor.

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Scope and consequences of falls in the elderly

A major consequence of muscle wasting and atrophy is that it increases risk of falling. Falls are common events and ones that have very serious clinical consequences in the elderly. With aging, fall rates increase by 10% per decade and by the age of 65 years, one in three persons falls each year and by the age of 80 years, one in two falls⁽⁶⁾. Of those who fall, 20–30% sustain moderate or severe injuries, at least half of which are fractures⁽⁶⁾. Community dwelling elders who have sustained one non-injurious fall have a 3.1-fold increased risk of becoming long-term residents of a nursing home and those who have sustained two or more non-injurious falls have a 5.5-fold increase risk⁽⁷⁾. Direct total cost for all fall injuries for people aged 65 and older in the United States exceeded \$19 billion in 2000⁽⁸⁾. Based on demographic projections, the annual direct and indirect cost of fall injuries may rise to \$54.9 billion in 2020⁽⁹⁾.

Proposed mechanisms linking vitamin D to muscle performance

Vitamin D in its activated form, 1,25-dihydroxyvitamin D (1,25(OH)₂D), acts on muscle by binding to classical nuclear vitamin D receptors (VDR). This binding induces the heterodimerisation of active VDR and a steroid receptor, the retinoic × receptor, forming the VDR/retinoic × receptor/cofactor complex. This complex then binds to vitamin D response elements to regulate gene expression of mRNA and, subsequently, *de novo* protein synthesis. Mice lacking the VDR show a skeletal muscle phenotype with smaller muscle fibres and persistent immature muscle-gene expression during adult life⁽¹⁰⁾. Evidence of the existence of VDR in human muscle stems from a variety of techniques including Western-blot and immunocytochemical analysis using specific antibodies, biochemical characterisation and detection of VDR-mRNA by reverse transcription-PCR^(11–13). VDR in human muscle, measured by immunohistochemical staining have been shown to decline as a function of aging⁽¹⁴⁾. It is not universally agreed, however, that VDR exist in human muscle⁽¹⁵⁾.

At the non-genomic level, 1,25(OH)₂D acts rapidly at a cell membrane-associated receptor to exert its effects. In chick skeletal muscle cells, this process may involve translocation of the classic nuclear VDR to the cell surface⁽¹²⁾. Alternatively, 1,25(OH)₂D may bind to a cell surface 1,25(OH)₂D receptor, Membrane Associated Rapid Response Steroid⁽¹⁶⁾ or to another novel 1,25(OH)₂D surface receptor⁽¹⁷⁾. It is agreed that 1,25(OH)₂D acts at the cell surface to regulate Ca influx by G-protein activation of phospholipase C and adenylate cyclase. This in turn activates the mitogen-activated protein kinase superfamily that regulates muscle cell growth.

Muscle performance and balance

Vitamin D plays a prominent role in muscle health in human subjects. The clinical disorder of vitamin D deficiency is characterised by profound muscle weakness

particularly in proximal muscles, and by muscle pain and impaired gait^(18,19). Several cross-sectional studies indicate a positive association between serum 25-hydroxyvitamin D (25OHD) concentration and muscle performance in older persons. In 4100 ambulatory adults aged 60 years and older participating in The Third National Health and Nutrition Examination Survey, lower extremity muscle performance, measured as the eight-foot walk test and the repeated sit-to-stand test, was poorest in subjects with the lowest 25OHD levels, below 20 nmol/l, and was progressively higher at increasing 25OHD levels throughout and even beyond the 25OHD reference range⁽²⁰⁾. A similar association was observed in a prospective cohort of older Dutch men and women⁽²¹⁾. In this study, performance reached its maximum at a mean 25OHD level of 50 nmol/l. This was in contrast to The Third National Health and Nutrition Examination Survey analysis in which performance reached its maximum at 25OHD levels above the upper end of the reference range⁽²⁰⁾. In the Third National Health and Nutrition Examination Survey, the apparent benefit was independent of gender, level of physical activity and level of Ca intake. Ensrud *et al.*⁽²²⁾ have described a U-shaped association of 25OHD with frailty in the baseline study measures in older women in the Study of Osteoporotic Fractures. In these women, frailty was minimal at 25OHD levels in the range of 50–75 nmol/l (the base of the U). In a similar analysis in older men in the Osteoporotic Fractures in Men Study, 25OHD was inversely associated with frailty throughout the full range of 25OHD levels, 12–135 nmol/l, although the steepest decline occurred in the range of 12–50 nmol/l⁽²³⁾.

Randomised, controlled vitamin D intervention trials with muscle performance outcomes have presented a mixed picture, with some studies being positive for selected measures and others being null. Stockton *et al.*⁽²⁴⁾ concluded from their meta-analysis that vitamin D had no significant effect on lower extremity muscle strength except in individuals with starting serum 25OHD levels <25 nmol/l. These studies do not provide strong support for a major role for supplemental vitamin D in improving muscle mass or strength in elders with 25OHD levels in the range 25–75 nmol/l, although this possibility remains.

Body sway is used as a measure of balance. Sway, assessed with the subject standing quietly on a force plate, measures ground-reacting force and moments in three orthogonal directions is a reproducible measure of balance and it is a test easily performed by the elderly. These measurements enable the calculation of the maximum displacement in the anteroposterior and medial–lateral directions, the average speed of displacement and other parameters⁽²⁵⁾. In adults aged 60 years and older, the root mean square amplitude in the medial–lateral direction was a strong predictor of falling more than once per year⁽²⁶⁾. Two independent randomised controlled trials have evaluated the effect of vitamin D on sway. Both trials compared the effect of 20 µg (800 IU) of vitamin D₃ plus 1000 mg of Ca/d compared with Ca alone, on sway in elderly adults. The vitamin D groups had an up to 28% improvement (reduction) in body sway^(27,28) over periods of 2 and 12 months, when compared with the Ca alone groups. These studies implicate a role for vitamin D

supplementation in improving balance in elders. This may be an important means by which vitamin D lowers risk of falling.

Falls

A number of organisations now recommend vitamin D to lower risk of falls in the elderly, including the International Osteoporosis Foundation⁽²⁹⁾, the Endocrine Society⁽³⁰⁾ and the US Preventive Services Task Force⁽³¹⁾. In a meta-analysis of randomised controlled trials in community dwelling elders, the US Preventive Services Task Force identified a 17% decrease in risk of falling in the vitamin D compared with the placebo group. In a systematic review, Murad *et al.*⁽³²⁾ identified a similar 14% decrease in fall risk with vitamin D compared with placebo. In a meta-analysis limited to high-quality trials (defined on the basis of quality and duration of falls ascertainment during the study), Bischoff-Ferrari *et al.*⁽³³⁾ examined the impact of the dose of vitamin D administered in the trials. That analysis, involving eight trials and 2426 individuals, revealed that doses of vitamin D up to 15 µg/d (600 IU/d) were ineffective, whereas higher doses that ranged from 17.5–25 µg/d (700–1000 IU/d) reduced risk of falling by about 20%. A recent reanalysis of those trials by the same investigators indicated a 34% risk reduction for the higher 17.5–25 µg/d (700–1000 IU/d) dose trials (OR 0.66 (95% CI 0.53, 0.82)) and no reduction with lower doses of vitamin D (OR 1.14 (95% CI 0.69, 1.87)), with a borderline significant interaction term ($P = 0.06$)⁽³⁴⁾. The reviews cited above reach similar conclusions that vitamin D supplementation in adequate dosage can reduce risk of falling in elders with vitamin D insufficiency. In contrast, the recent Institute of Medicine report (see p. 161) found that ‘... the greater part of the causal evidence indicated no significant reduction in fall risk related to vitamin D intake or achieved level in blood.’⁽³⁵⁾

At this point, the minimum level of 25OHD required for maximal fall-risk reduction is not certain, but the best estimate is that it is about 60 nmol/l. Increases above this level have not added additional protection against falling. In a comparative study of the effect of 20 v. 50 µg/d (800 v. 2000 IU/d) in elderly on fall risk in acute hip fracture patients, the incidence of first falls did not differ significantly in the two treatment groups⁽⁵⁾. Their starting 25OHD levels were 30 nmol/l, and levels at 12 months were 90 nmol/l in the 20 µg/d (800 IU/d) group and 118 nmol/l in the 50 µg/d (2000 IU/d) group. Thus, both groups substantially crossed the proposed threshold of 60 nmol/l and had equal and probably maximal protection against falling. One pragmatic trial testing the effect of an annual oral dose of 12.5 mg (500 000 IU) of vitamin D v. placebo demonstrated that vitamin D actually increased risk of falling; the reason(s) for this are not clear because of the minimal amount of ancillary information and measurements available from the participants⁽³⁶⁾.

The dose of vitamin D needed to achieve a given 25OHD level varies inversely with the starting level of 25OHD and with BMI and other factors that have not been well defined. On average, however, 1 µg (40 IU) of added

vitamin D₃ will increase the circulating 25OHD level by about 1 nmol/l. Dosing at intervals of daily, weekly and monthly is effective. Less frequent oral dosing, specifically 12.5 mg (500 000 IU) annually, is not recommended in view of the finding of Sanders *et al.*⁽³⁶⁾ that it increased falls (and fractures) in older adults.

Conclusions

In conclusion, vitamin D appears to act on muscle tissue through its actions on the VDR but the precise mechanisms involved have not been fully defined. Its effects on performance are most apparent in individuals with lower initial 25OHD levels. Vitamin D also affects balance, but the mechanisms for this are less clear. Adequate vitamin D status is important to lower the risk of falling in older men and women. It appears at this time that a circulating 25OHD level of at least 60 nmol/l is needed to minimise fall risk, but additional research is needed to confirm this.

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