Serum 25-hydroxyvitamin D and functional outcomes in the elderly

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ABSTRACT
The objective of this article was to consider key evidence that treatment of vitamin D insufficiency has measurable clinical benefits for the musculoskeletal system in the elderly. The functional outcomes considered were increased bone mass, decreased rates of bone loss, improved muscle performance, reduced risk of falls, and reduced fracture incidence. Available evidence suggests that the elderly need a mean serum concentration of $\geq 65$ nmol/L of vitamin D to improve muscle performance and reduce the risk of falling and $\geq 75$ nmol/L to reduce the risk of fracture. Many elderly persons in the United States and elsewhere have serum 25-hydroxyvitamin D concentrations below these levels. For this reason, supplementation is likely to provide significant benefit to this segment of the population.

INTRODUCTION
The prevalence of osteoporotic fractures in the US population aged 50–99 y will increase in the next few decades as the number of elderly persons increases (1). Elderly persons had $>2$ million fractures in 2005, and research indicates that this figure will increase by $\approx 50\%$ to $>3$ million in 2025, primarily because of the increased number of elderly persons (1). Investigators have estimated the associated medical costs in 2005 dollars to be $17$ billion in 2005 and $25.3$ billion in 2025 (1).

Many factors—including declining bone mass, muscle mass, and muscle strength and increased risk of falls—contribute to fracture risk in the elderly. Bone mass in old age is a function of the peak bone mass achieved during the person’s mid-20s and the subsequent rates of bone loss. Bone mass loss in women becomes more rapid during menopause, although it continues after that period as calcium absorption efficiency declines and parathyroid hormone (PTH) and, subsequently, bone resorption levels rise. Men lose bone mass at a steady rate after age 50 y. Aging is also accompanied by loss of muscle mass. Each decade, older women lose 0.6 kg of lean tissue and men lose 1.6 kg, on average (2). Loss of muscle mass results in reduced muscle strength and this, in turn, leads to an increased risk of falling. By age 65 y, 1 in 3 persons falls each year, and by age 80 y, 1 in 2 falls (3). Of those who fall, 20% to 30% sustain moderate or severe injuries; at least half of these injuries are fractures (3).

Many experts recognize that vitamin D status is suboptimal in older adults. I define vitamin D deficiency in this paper as serum 25-hydroxyvitamin D [25(OH)D] concentrations $\leq 25$ nmol/L (the lower limit of the reference population for many assays), vitamin D insufficiency as serum concentrations of 25 to 75 nmol/L (4), and vitamin D sufficiency as 25(OH)D concentrations of $\geq 75$ nmol/L.

The third National Health and Nutrition Examination Survey (NHANES III) estimated that up to 30% of persons aged 60 y and older who reside in lower latitudes have vitamin D insufficiency in the winter, and up to 26% residing in higher latitudes have vitamin D insufficiency in the summer (5). Other studies have found that the prevalence of vitamin D deficiency is even higher in homebound elderly (6).

The objectives of this article were to consider key evidence that treatment with vitamin D has measurable benefits for the musculoskeletal system in the elderly. The functional outcomes considered were improved muscle performance, reduced risk of falls, decreased bone loss, and reduced fracture incidence.

MUSCLE PERFORMANCE
In its activated form, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], acts on muscle by binding to the vitamin D receptors (VDRs). Researchers have identified 2 different VDRs in the nucleus and cell membrane of muscle (7). At the genomic level, 1,25(OH)$_2$D binds to its nuclear receptor, resulting in activation of the VDR. This activation induces the heterodimerization of active VDR and a steroid receptor, retinoic receptor (RXR), forming the VDR/RXR/cofactor complex. This complex then binds to vitamin D response elements to regulate gene expression of messenger RNA and, subsequently, de novo protein synthesis (8).

At the nongenomic level, vitamin D has rapid effects mediated by the cell membrane VDR, which results in second messenger signaling or phosphorylation of intracellular proteins (9). Specifically, vitamin D in muscle activates protein kinase C and results in calcium release, increasing the calcium pool, which is essential for muscle contraction. Clinical studies support the concept that vitamin D insufficiency is associated with poor...
lower extremity performance (10, 11). Several randomized, controlled intervention trials have found that vitamin D supplementation in amounts that bring the treated group’s mean serum 25(OH)D level to 66–84 nmol/L improves lower extremity muscle performance in the elderly (Table 1: 12). We need further research to determine whether increasing mean serum 25(OH)D to concentrations >84 nmol/L would lead to additional benefits for muscle in the elderly.

**FALLS**

Supplementation with vitamin D can lead to a reduced risk of falling (12–15, 18). For example, Flicker et al (13) randomly assigned 625 assisted-living facility residents, with a mean age of 83 y and with starting 25(OH)D concentrations in the insufficient range, to receive treatment with 30 µg (1200 IU) vitamin D₃ or placebo daily. The treated group had a reduced risk of falls (0.73; 95% CI: 0.57, 0.95). Moreover, the effect of vitamin D was greater in participants who took at least half of the supplements compared with those who took less than half (0.63; 95% CI: 0.48–0.82), which suggests a dose effect. Another study also found indications of a dose effect after showing that 20 µg (800 IU) of vitamin D₃ daily reduced falls in very elderly nursing home residents but lower doses of 5 µg (200 IU) and 10 µg (400 IU) did not (14).

In contrast, 2 large recent trials found no effect of supplementation vitamin D on the incidence of falls (17, 19). One of these, the Randomized Evaluation of Calcium and Vitamin D (RECORD) Group trial, was a secondary fracture prevention trial that also collected information on falls (17). Participants were mobile before their initial fracture but the authors did not specify their residential status. In this 5-y trial, subjects received their supplements and a medical history questionnaire (asking about falls in the previous week) through the mail every 4 mo (17). The authors found that quarterly supplementation with the equivalent of 20.8 µg (833 IU) of vitamin D₃ daily, with or without 1000 mg Ca/d, had no effect on fall rates (17). Although the return rate for the questionnaires was high (94%), the investigators captured information on falls that occurred only during the relatively limited period of 1 wk out of every 4 mo. A more significant limitation of this trial was that compliance with the supplements was poor (<50% at the 2-y point).

Several factors might explain why trials assessing the impact of vitamin D supplementation on the risk of falling in the elderly are more likely to have positive results when conducted in participants living in institutions than when conducted in those living in the community. First, ascertainment of falls is likely to be far more accurate in trials conducted in an environment where staff monitor the residents than in trials in the community, which require that participants have sufficient memory, motivation, and executive function to report their own falls. In addition, compliance is likely to be higher when staff administer the treatments than when subjects must remember to take the pills and have sufficient executive function to record the action in a compliance calendar. When compliance is higher, the likelihood of benefit is greater. For these reasons, the study results described above do not imply that elderly persons must live in institutions to benefit from supplemental vitamin D, but rather that vitamin D supplements benefit vitamin D–deficient and insufficient elderly persons who actually take their supplements.

Research has not yet identified the minimal level of circulating 25(OH)D required for maximal benefit in fall prevention. The 25(OH)D concentrations achieved in falls trials are listed in Table 1 (14, 15, 17). These trials indicate that mean values of 75 and 99 nmol/L were beneficial. Still higher values might confer greater benefit, but evidence to support this is not currently available. An important caveat concerning the achieved 25(OH)D concentrations shown in Table 1 is that the studies cited used different 25(OH)D assays and thus the results are not standardized. Researchers in the future should examine the potential influences of age, physical activity level, calcium intake, gonadal hormone concentrations, renal function, and sex on the impact of vitamin D on muscle and risk of falling to define the profile of the older people most likely to benefit from vitamin D supplementation.

**IMPACT OF VITAMIN D ON BONE MASS AND BONE LOSS**

Vitamin D has metabolic effects that ultimately influence bone mass. Vitamin D insufficiency leads to reduced active transport of calcium across the intestine. This results in a decline in the circulating ionized calcium concentration, which in turn promotes the secretion of PTH. PTH acts on the skeleton and other target tissues to mobilize calcium and normalize the circulating ionized calcium concentration. In the process, PTH promotes bone resorption and bone loss. Serum 25(OH)D concentrations

<table>
<thead>
<tr>
<th>Trial</th>
<th>Vitamin D dose and preparation</th>
<th>Duration of trial</th>
<th>25(OH)D concentration achieved</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg (IU)/d</td>
<td></td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>Muscle performance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato (12)</td>
<td>25 (1000) D₃</td>
<td>3 y</td>
<td>84</td>
<td>+</td>
</tr>
<tr>
<td>Pfeiffer (16)</td>
<td>20 (800) D₃</td>
<td>2 mo</td>
<td>66</td>
<td>+</td>
</tr>
<tr>
<td>Bischoff (15)</td>
<td>20 (800) D₃</td>
<td>3 mo</td>
<td>66</td>
<td>+</td>
</tr>
<tr>
<td><strong>Falls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bischoff (15)</td>
<td>17.5 (700) D₃</td>
<td>3 y</td>
<td>99</td>
<td>+</td>
</tr>
<tr>
<td>Broe (14)</td>
<td>20 (800) D₃</td>
<td>5 mo</td>
<td>75</td>
<td>+</td>
</tr>
<tr>
<td>Flicker (13)</td>
<td>20 (800) D₃</td>
<td>2 y</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Grant (17)</td>
<td>20 (800) D₃</td>
<td>5 y</td>
<td>62</td>
<td>Null</td>
</tr>
</tbody>
</table>

1 25(OH)D, 25-hydroxyvitamin D; +, significantly reduced the number of falls; NA, not available.
are inversely associated with PTH concentrations (20), leading some researchers to define vitamin D sufficiency by using as a biochemical criterion the 25(OH)D concentration needed to suppress PTH to its plateau level. Many investigators have estimated this level to be 75 to 80 nmol/L (4, 21–23).

Several clinical studies have examined the relation between vitamin D and bone mass. In the NHANES III data, higher serum concentrations of 25(OH)D are associated with higher bone mass of the hip in older (and younger) men and women (24). Several randomized, placebo-controlled trials have shown that supplementation with vitamin D₃ reduces rates of bone loss (25), particularly in the winter months (26) in older adults. Although statistically significant, the effect of vitamin D on change in bone mass (1-2%) is small; this effect on its own is not sufficient to substantially lower fracture risk.

**IMPACT OF VITAMIN D ON FRACTURES**

This supplement to the Journal contains an extensive review and a formal meta-analysis of the impact of vitamin D supplementation on fracture risk; however, I would like to make a few comments about available evidence. In a 2005 meta-analysis of placebo-controlled vitamin D intervention trials, Bischoff-Ferrari et al (27) found that higher concentrations of 25(OH)D during treatment were associated with greater reductions in hip and all nonvertebral fracture risk. Since that report’s publication, several researchers have published the results of large trials. 25(OH)D concentrations from trials of treatment with vitamin D are shown in Table 2 (17, 28–36). In aggregate, these data suggest that 25(OH)D concentrations at or above 75 nmol/L are associated with greater suppression of serum PTH and greater fracture risk reduction in elderly subjects. Neither the RECORD Group trial (17) nor the Women’s Health Initiative (33) achieved 25(OH)D concentrations high enough to demonstrate whether persons need concentrations of ≥75 nmol/L to lower their fracture risk. The Larsen trial (36) found that vitamin D₃ had a significant protective effect, even though the study achieved a mean 25(OH)D concentration of only 47 nmol/L. On the basis of the weight of the evidence, several investigators recommend 75 nmol/L as the minimal goal for the elderly (4), although a limitation of current interpretations is the fact that these clinical trials used different assays for 25(OH)D.

Several authors have addressed whether people need calcium supplements to obtain skeletal benefits from supplemental vitamin D (37, 38). The anti-fracture efficacy trials that administered calcium along with vitamin D are listed in Table 2. Because the trials with positive results that included calcium and vitamin D supplementation also generally gave participants enough vitamin D (and had sufficient compliance) to raise mean 25(OH)D concentrations to 75 nmol/L or higher, it is difficult to segregate the relative contributions of these 2 nutrients. The Institute of Medicine’s Standing Committee on the Scientific Evaluation of Dietary Reference Intakes recommends a daily intake of 1200 mg Ca/d for men and women aged ≥51 y (39). Because the impact of vitamin D in clinical trials can vary with the study population’s calcium intake, future studies should assess the amount of vitamin D needed for maximal benefit to the musculoskeletal system under standardized calcium intake conditions to make cross-study comparisons possible and to define the impact of vitamin D.

**CONCLUSIONS AND RESEARCH QUESTIONS**

In elderly individuals with vitamin D insufficiency, supplementation with vitamin D reduces bone loss; it also improves muscle performance and lowers the risk of falling. The combined effects on bone and muscle lead to reduced fracture risk. Researchers have not definitively identified the circulating 25(OH)D concentration needed for maximal muscle function in the elderly, but studies conducted to date indicate that it is ≥65 nmol/L. For fracture risk reduction in the elderly, the weight of the evidence indicates that the minimum amount required is ≈75 nmol/L (4). An adequate intake of calcium is important for bone health in its own right and it seems prudent for clinicians to ensure that their vitamin D–deficient and insufficient elderly patients receive adequate calcium as well as vitamin D to ensure sufficiency.

Many research questions about vitamin D and musculoskeletal function remain unanswered. Future research needs to define

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose and preparation</th>
<th>25(OH)D concentration achieved</th>
<th>Change in PTH level</th>
<th>Significant reduction in nonvertebral fractures?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawson-Hughes (30)²</td>
<td>17.5 (700) D₃</td>
<td>112</td>
<td>-28</td>
<td>Yes</td>
</tr>
<tr>
<td>Chapuy (28)²</td>
<td>20 (800) D₃</td>
<td>100</td>
<td>47</td>
<td>Yes</td>
</tr>
<tr>
<td>Chapuy (29)²</td>
<td>20 (800) D₃</td>
<td>100</td>
<td>-33</td>
<td>Yes</td>
</tr>
<tr>
<td>Trevedi (31)</td>
<td>20.5 (820) D₃</td>
<td>74</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Law (32)</td>
<td>23.3 (933) D₂</td>
<td>74</td>
<td>-14</td>
<td>No</td>
</tr>
<tr>
<td>Meyer (35)</td>
<td>10 (400) D₃</td>
<td>64</td>
<td>-6</td>
<td>No</td>
</tr>
<tr>
<td>Grant (17)²</td>
<td>20 (800) D₃</td>
<td>63</td>
<td>-13</td>
<td>No</td>
</tr>
<tr>
<td>Jackson (33)</td>
<td>10 (400) D₃</td>
<td>59</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Lips (34)</td>
<td>10 (400) D₃</td>
<td>54</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Larsen (unmasked) (36)²</td>
<td>10 (400) D₃</td>
<td>47</td>
<td>NA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹ NA, not available.
² Administered both calcium and vitamin D supplements.
REFERENCES