

Original Investigation | LESS IS MORE

# Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline

## A Randomized Clinical Trial

Heike A. Bischoff-Ferrari, MD, DrPH; Bess Dawson-Hughes, MD; E. John Orav, PhD; Hannes B. Staehelin, MD; Otto W. Meyer, MD; Robert Theiler, MD; Walter Dick, MD; Walter C. Willett, MD, DrPH; Andreas Egli, MD

**IMPORTANCE** Vitamin D deficiency has been associated with poor physical performance.

**OBJECTIVE** To determine the effectiveness of high-dose vitamin D in lowering the risk of functional decline.

**DESIGN, SETTING, AND PARTICIPANTS** One-year, double-blind, randomized clinical trial conducted in Zurich, Switzerland. The screening phase was December 1, 2009, to May 31, 2010, and the last study visit was in May 2011. The dates of our analysis were June 15, 2012, to October 10, 2015. Participants were 200 community-dwelling men and women 70 years and older with a prior fall.

**INTERVENTIONS** Three study groups with monthly treatments, including a low-dose control group receiving 24 000 IU of vitamin D<sub>3</sub> (24 000 IU group), a group receiving 60 000 IU of vitamin D<sub>3</sub> (60 000 IU group), and a group receiving 24 000 IU of vitamin D<sub>3</sub> plus 300 µg of calcifediol (24 000 IU plus calcifediol group).

**MAIN OUTCOMES AND MEASURES** The primary end point was improving lower extremity function (on the Short Physical Performance Battery) and achieving 25-hydroxyvitamin D levels of at least 30 ng/mL at 6 and 12 months. A secondary end point was monthly reported falls. Analyses were adjusted for age, sex, and body mass index.

**RESULTS** The study cohort comprised 200 participants (men and women ≥70 years with a prior fall). Their mean age was 78 years, 67.0% (134 of 200) were female, and 58.0% (116 of 200) were vitamin D deficient (<20 ng/mL) at baseline. Intent-to-treat analyses showed that, while 60 000 IU and 24 000 IU plus calcifediol were more likely than 24 000 IU to result in 25-hydroxyvitamin D levels of at least 30 ng/mL ( $P = .001$ ), they were not more effective in improving lower extremity function, which did not differ among the treatment groups ( $P = .26$ ). However, over the 12-month follow-up, the incidence of falls differed significantly among the treatment groups, with higher incidences in the 60 000 IU group (66.9%; 95% CI, 54.4% to 77.5%) and the 24 000 IU plus calcifediol group (66.1%; 95% CI, 53.5%-76.8%) group compared with the 24 000 IU group (47.9%; 95% CI, 35.8%-60.3%) ( $P = .048$ ). Consistent with the incidence of falls, the mean number of falls differed marginally by treatment group. The 60 000 IU group (mean, 1.47) and the 24 000 IU plus calcifediol group (mean, 1.24) had higher mean numbers of falls compared with the 24 000 IU group (mean, 0.94) ( $P = .09$ ).

**CONCLUSIONS AND RELEVANCE** Although higher monthly doses of vitamin D were effective in reaching a threshold of at least 30 ng/mL of 25-hydroxyvitamin D, they had no benefit on lower extremity function and were associated with increased risk of falls compared with 24 000 IU.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01017354

*JAMA Intern Med.* 2016;176(2):175-183. doi:10.1001/jamainternmed.2015.7148  
Published online January 4, 2016. Corrected on February 8, 2016.

← Editorial page 171

+ Supplemental content at  
jamainternalmedicine.com

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Heike A. Bischoff-Ferrari, MD, DrPH, Department of Geriatrics and Aging Research, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland (heike.bischoff@usz.ch).

Impaired lower extremity function is a major risk factor for falls, hip fractures, frailty, and loss of autonomy.<sup>1-3</sup> Given the imminent demographic change resulting in a significant growth of the senior segment of the population, strategies that prevent functional decline and the cascade of undesirable and costly consequences are urgently needed.<sup>4</sup>

Vitamin D supplementation has been proposed as a possible preventive strategy in delaying functional decline through its direct effect on muscle strength.<sup>5-7</sup> However, definitive data are lacking on the effectiveness of vitamin D supplementation and dose requirements related to the improvement of lower extremity function.

Mechanistically, several lines of evidence link vitamin D to muscle strength and lower extremity function.<sup>7</sup> First, proximal muscle weakness is a feature of clinical vitamin D deficiency.<sup>8</sup> Second, the vitamin D receptor is expressed in human muscle tissue, as documented in 6 studies<sup>9-14</sup> but not in a seventh study.<sup>15</sup> Third, the results of studies<sup>6,16,17</sup> among older individuals suggest that vitamin D receptor activation in muscle promotes *de novo* protein synthesis preferentially in type II fast twitch muscle fibers relevant to the prevention of falls.

At a clinical level, seniors at risk of vitamin D deficiency demonstrated a benefit of vitamin D supplementation on lower extremity function in some randomized clinical trials (RCTs)<sup>18-20</sup> but not in other RCTs.<sup>21-23</sup> The findings of a 2011 meta-analysis<sup>24</sup> of 17 RCTs suggested that a benefit of vitamin D on lower extremity strength may be seen primarily among those with vitamin D deficiency. Consistently, meta-analyses of double-blind RCTs support a benefit of vitamin D supplementation in the prevention of falls<sup>25,26</sup> and hip fractures<sup>27,28</sup> among seniors 65 years and older at high risk of vitamin D deficiency. However, these benefits have been found to be questionable in meta-analyses<sup>29-34</sup> that were not restricted to seniors 65 years and older at risk of vitamin D deficiency and extending to open-design trials.

In a pilot trial among 20 young postmenopausal women, daily calcifediol administration (20 µg/d) increased levels of 25-hydroxyvitamin D, hereafter 25(OH)D, from a mean of 13.2 to 69.5 ng/mL at the 4-month follow-up (to convert 25[OH]D level to nanomoles per liter, multiply by 2.496).<sup>35</sup> Compared with 800 IU of vitamin D per day, which increased levels above 20 ng/mL in most women,<sup>35,36</sup> this dosage was accompanied by a significant 2.8-fold increased odds of maintained or improved lower extremity function.<sup>35</sup>

In this trial, we investigated our hypothesis that higher monthly doses of vitamin D or a combination with calcifediol (which is approximately a 2-3 times more potent liver metabolite of vitamin D<sup>37</sup>) would increase levels of 25(OH)D in most study participants to at least 30 ng/mL and thereby reduce the risk of functional decline. For our study population, we selected seniors 70 years and older with a prior fall, who are a high-risk group for vitamin D deficiency and functional decline.

## Methods

### Participants and Study Design

By newspaper advertisement, we recruited home-dwelling men and women 70 years and older with a low-trauma fall in

the previous 12 months. We screened 463 individuals and enrolled 200 participants. Study eligibility criteria included maintaining mobility with or without a walking aid, having the ability to use public transportation to attend the clinic visits, and scoring at least 27 on the Mini-Mental State Examination to ensure that participants understood the study procedures and voluntarily agreed to participate by providing written informed consent. Key exclusion criteria were supplemental vitamin D use exceeding 800 IU/d and unwillingness to discontinue additional calcium and vitamin D supplementation (other exclusion criteria are listed in the **Figure 1** legend).

The study was approved by the Cantonal Ethical Commission of Zurich, Switzerland, and all participants provided written informed consent. The full study protocol can be found in **Supplement 1**. Participant enrollment, all data collection, and examinations took place at the Centre on Aging and Mobility at the University of Zurich. All staff members and study participants were masked to treatment allocation. The screening phase was December 1, 2009, to May 31, 2010, and the last study visit was in May 2011. The dates of our analysis were June 15, 2012, to October 10, 2015.

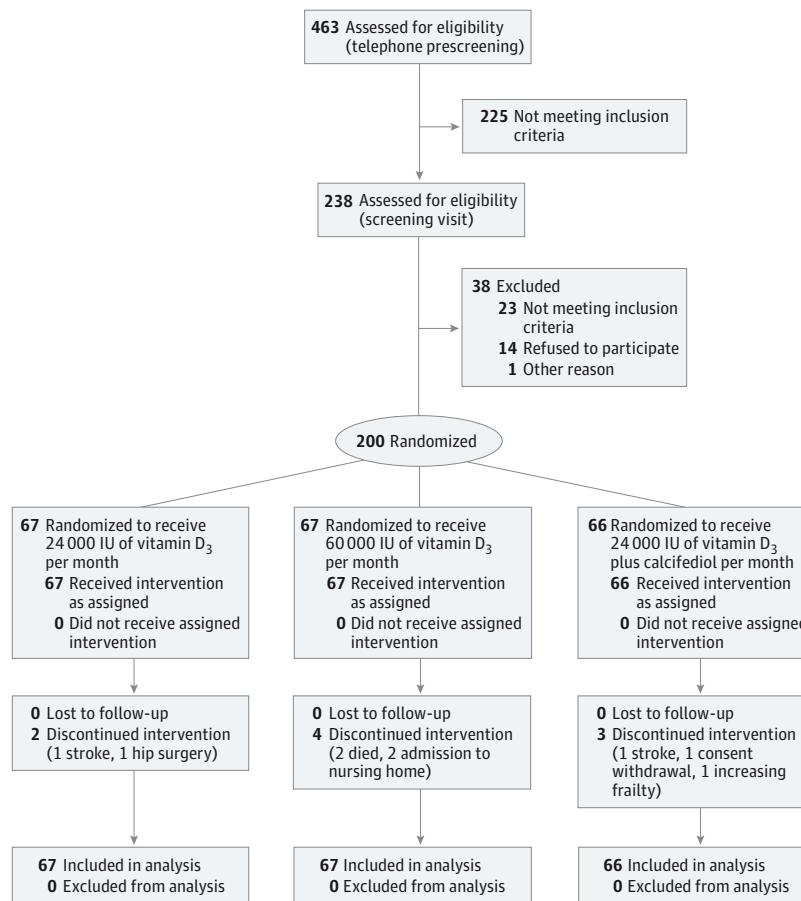
### Supplementation

In this 12-month, single-center, double-blind clinical trial, participants were randomized to 1 of 3 study groups receiving monthly supplementation with vitamin D<sub>3</sub>. The first group was a control group receiving 24 000 IU of vitamin D<sub>3</sub> (24 000 IU group) (one 5-mL drink solution of 24 000 IU of vitamin D<sub>3</sub> once per month, equivalent to the current recommendation of 800 IU/d, plus 3 placebo capsules once per month). The second group received 60 000 IU of vitamin D<sub>3</sub> (60 000 IU group) (one 5-mL drink solution containing 60 000 IU of vitamin D<sub>3</sub> once per month, equivalent to 2000 IU/d, plus 3 placebo capsules once per month). The third group received 24 000 IU of vitamin D<sub>3</sub> plus 300 µg of calcifediol (24 000 IU plus calcifediol group) (one 5-mL placebo drink solution once per month, plus 2 vitamin D<sub>3</sub> capsules containing 12 000 IU each and 1 capsule containing 300 µg of calcifediol, the liver metabolite of vitamin D, once per month). Drink solutions of vitamin D<sub>3</sub> and calcifediol and placebo capsules (DSM Nutritional Products; <http://www.dsm.com/corporate/about/business-entities/dsm-nutritional-products.html>) had identical appearances and taste, and assays confirmed the expected contents. The potency and safety of vitamin D<sub>3</sub> vs 300 µg of calcifediol were previously evaluated.<sup>37</sup>

### Randomization, Masking, and Treatment Allocation

Randomization was computer based in blocks of 6 and stratified by sex by an independent biostatistician. The randomization list was sent directly and exclusively to the cantonal pharmacy in Zurich, Switzerland, that performed the masking. The study treatment was then shipped to an independent randomization center (hospital pharmacy) in charge of treatment allocation. The randomization center was located at the same hospital as the recruitment site but in another area with restricted access (ie, with no access by study team members). Participants, their treating physicians, and any individual involved in the coordination and implementation of the trial were masked to treatment allocation.

Figure 1. Consolidated Standards of Reporting Trials Diagram and Inclusion and Exclusion Criteria



Inclusion criteria were mobility with or without a walking aid, ability to use public transportation to attend the clinic visits, and a score of at least 27 on the Mini-Mental State Examination. Exclusion criteria were supplemental vitamin D use exceeding 800 IU/d and unwillingness to discontinue additional calcium and vitamin D supplementation during the course of the trial. Other exclusion criteria were the following: current cancer, malabsorption syndrome, heavy alcohol consumption, uncontrolled hypocalcemia, severe visual or hearing impairment, use of medications affecting calcium metabolism, diseases causing hypercalcemia (eg, sarcoidosis), planned travel to sunny locations for longer

than 2 months per year, maximum calcium supplement dose of 250 mg/d (with no additional vitamin D), use of medications affecting serum 25-hydroxyvitamin D level (eg, phenobarbital), body mass index (calculated as weight in kilograms divided by height in meters squared) of 40 or higher, diseases predisposing to falls (eg, Parkinson disease, hemiplegia after stroke, and inflammatory arthritis), hypercalcemia (serum calcium level >10.4 mg/dL [to convert calcium level to millimoles per liter, multiply by 0.25]), and kidney disease (estimated creatinine clearance <15 mL/min/1.73 m<sup>2</sup> or kidney stone within 10 years [to convert creatinine clearance to mL/s/m<sup>2</sup>, multiply by 0.0167]).

### Dropouts and Adherence to the Study Medication

Nine participants discontinued treatment (2 in the 24 000 IU group, 4 in the 60 000 IU group, and 3 in the 24 000 IU plus calcifediol group), although all participants remained in the trial and were followed up for all end points (Figure 1). Adherence to the study medication exceeded 98.0% in all treatment groups from months 0 to 6 and exceeded 94.0% in all treatment groups from months 7 to 12, which was confirmed by counts of returned drink bottles and blister packs.

### Measurements

Participants attended 3 full clinical visits (at baseline, 6 months, and 12 months) plus a safety visit at 2 weeks to determine serum calcium and creatinine levels and the ratio of urinary calcium to creatinine. The baseline assessment involved functional tests, including the Short Physical Performance Battery

(SPPB), physical examination, medical history, blood and urine samples, and appendicular muscle mass using intelligent dual x-ray absorptiometry (iDXA; GE Healthcare).<sup>38</sup> Except for iDXA, all assessments were repeated at 6 and 12 months; the iDXA was repeated only at 12 months. Between clinical visits, study nurses called participants monthly to assess falls, adverse events, and adherence to the study medication.

The SPPB score (our primary outcome) was used to assess lower extremity function by walking speed, successive chair stands, and a balance test and has been validated extensively.<sup>39</sup> In the original trial protocol, we outlined 2 strategies to measure functional decline. During the implementation of the trial, we changed our strategy to exclusively use the SPPB score as the primary measure of functional decline. This decision was based on the feedback from our masked study physiotherapist that many participants reported pain when

being tested for knee extensor and flexor strength, raising significant concerns about the validity of the measure. Accordingly, our analysis plan proceeded only with the SPPB score as the measure of functional decline and the primary end point measure. The alternative score was not analyzed.

We also calculated the proportion of participants who achieved 25(OH)D levels of at least 30 ng/mL. The study was designed to enroll 210 participants to have 85% power to detect 30% differences in the SPPB score improvement and in achieved 25(OH)D levels of at least 30 ng/mL.

The secondary outcome reported in this study was based on falls, defined as “unintentionally coming to rest on the ground, floor, or other lower level,”<sup>40(p1619)</sup> while coming to rest against furniture or a wall was not counted. Falls were assessed by diary and monthly telephone calls to all participants by the study staff.

Other prespecified secondary end points not included in this study are listed in the trial protocol (Supplement 1) and will be reported elsewhere. Several exploratory end points were also identified in the trial protocol, and we report on reaction time, grip strength,<sup>20</sup> muscle mass, and parathyroid hormone level. Comorbidity was assessed by the Charlson Comorbidity Index, including 22 conditions.<sup>41</sup>

### Analyses

Fasting blood and urine samples were obtained between 8:00 AM and 9:30 AM at all 4 visits (baseline, 2 weeks, 6 months, and 12 months). The 25(OH)D serum levels were measured by a sensitive and selective high-performance liquid chromatography-tandem mass spectrometry method<sup>42,43</sup> that was included in the National Institute of Standards and Technology/National Institutes of Health Vitamin D Metabolites Quality Assurance Program.<sup>44</sup> Serum calcium and creatinine levels and the ratio of urinary calcium to creatinine were measured using an analyzer machine (c 501; Cobas).

### Statistical Analysis

Changes over time in the SPPB score ( $\Delta$  from baseline) were compared between study groups using repeated-measures linear regression, adjusting for baseline SPPB score, age, sex, and body mass index (BMI) to increase power based on prior studies<sup>23,45</sup> showing an association of each variable with our study outcomes. We used a statistical procedure (MIXED in SAS, version 9.4; SAS Institute Inc) to allow for serial correlation in the SPPB score at 6 and 12 months. To examine progressive improvements in one treatment group compared with others, we used an indicator variable for time, indicator variables for the treatment groups, and interaction terms between time and treatment. Similar analyses were used for reaction time and grip strength. Because lean mass was not measured at 6 months, simpler linear regression models were used to compare changes in arm and leg lean mass from baseline to 12 months (eTable 1 in Supplement 2). Simple logistic regression (adjusting for age, sex, and BMI) was used to compare our other primary outcome of achieved 25(OH)D levels of at least 30 ng/mL between the study groups.

For the secondary outcome, we compared the incidence of falls between baseline and 6 months, 6 and 12 months, and baseline and 12 months using a logistic regression model with the 0 vs 1 indicator for any fall as the outcome. Finally, we used the

number of falls during the first 6 months of follow-up in a linear regression, with indicators for treatment group and covariates to adjust for age, sex, and BMI. We truncated the number of falls at 5 per participant to reduce skewness and then used linear regression to preserve interpretability. The analysis was repeated with the number of falls between 6 and 12 months and with the total number of falls as the outcomes. Although the multiple testing increased the potential for false-positive results, we considered both early and late effects important.

Because the prespecified primary analysis of the SPPB score over time was limited to the single *P* value for the interaction, we did not adjust for the multiple testing. However, caution is appropriate when interpreting the *P* values for our secondary and exploratory outcomes.

Based on our initial analyses, the dose of vitamin D (ie, treatment group) was insufficient to explain the outcomes. Therefore, in an observational analysis, we divided the cohort according to quartiles of achieved 25(OH)D levels at 12 months, anticipating that higher levels would predict better outcomes.

## Results

### Baseline Characteristics of Participants

At baseline, all 200 participants had reported a fall in the year before enrollment. Their mean (SD) age was 78 (5) years, and 67.0% (134 of 200) were female. While 42.0% (84 of 200) of participants were vitamin D replete at baseline ( $\geq 20$  ng/mL), 58.0% (116 of 200) were vitamin D deficient at baseline ( $< 20$  ng/mL), and 13.0% (26 of 200) were severely deficient ( $< 10$  ng/mL). None of the baseline characteristics in Table 1, including the SPPB score, physical activity,<sup>46</sup> and the prevalence of sarcopenia,<sup>38</sup> differed by treatment group.

### Changes in 25(OH)D Levels by Treatment Group

Absolute changes in 25(OH)D levels are shown in Figure 2. After adjustment for baseline 25(OH)D level, age, sex, and BMI, the 24 000 IU group increased 25(OH)D levels by 12.7 ng/mL (95% CI, 10.6-14.9 ng/mL) at 6 months and by 11.7 ng/mL (95% CI, 9.6-13.8 ng/mL) at 12 months. The 60 000 IU group increased 25(OH)D levels by 18.3 ng/mL (95% CI, 16.2-20.5 ng/mL) at 6 months and by 19.2 ng/mL (95% CI, 17.1-21.4 ng/mL) at 12 months. The 24 000 IU plus calcifediol group increased 25(OH)D levels by 27.6 ng/mL (95% CI, 25.4-29.8 ng/mL) at 6 months and by 25.8 ng/mL (95% CI, 23.6-27.9 ng/mL) at 12 months. The changes for the 60 000 IU group and the 24 000 IU plus calcifediol group vs the 24 000 IU group were significant at 6 and 12 months ( $P < .001$ ). As summarized in Table 2, the percentage of participants with achieved 25(OH)D levels of at least 30 ng/mL was significantly higher at 12 months in the 60 000 IU group and the 24 000 IU plus calcifediol group compared with the 24 000 IU group. All treatment groups had similar reductions in intact parathyroid hormone levels (eAppendix in Supplement 2).

### Primary End Point of the SPPB Score by Treatment Group

Over time, the mean changes in the SPPB score did not differ significantly among the treatment groups ( $P = .26$ ) (Table 2). For 1 of the 3 SPPB score components (5 successive chair stands), there was a significant difference between the treatment groups, with



Table 1. Demographics by Treatment Group<sup>a</sup>

Variable	24 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	60 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	24 000 IU of Vitamin D <sub>3</sub> Plus Calcifediol per Month (n = 66)
Age, mean (SD) [range], y	78.0 (5.0) [71-90]	78.0 (5.3) [71-92]	77.0 (4.7) [71-90]
Female sex, No. (%)	45 (67.2)	45 (67.2)	44 (66.7)
25(OH)D level, mean (SD), ng/mL	18.7 (9.8)	20.9 (9.2)	18.4 (7.6)
Intact parathyroid hormone level, mean (SD), pg/mL	53.1 (18.9)	50.6 (23.4)	51.6 (18.0)
BMI, mean (SD)	26.4 (3.7)	26.1 (4.5)	26.2 (3.9)
Height, mean (SD), cm	162.2 (8.2)	161.2 (7.8)	163.3 (8.8)
Weight, mean (SD), kg	69.2 (9.8)	68.0 (13.8)	69.9 (11.5)
Prevalence of sarcopenia, No. (%) <sup>b</sup>	11 (16.4)	14 (20.9)	10 (15.2)
Arm muscle mass based on iDXA, mean (SD), g	4493.3 (1049.1)	4365.2 (1157.3)	4643.0 (1296.1)
Leg muscle mass based on iDXA, mean (SD), g	13 694.6 (2266.3)	13 571.3 (2984.3)	14 100.6 (2900.2)
Charlson Comorbidity Index, mean (SD)	0.58 (0.86)	0.65 (1.16)	0.52 (0.79)
MMSE score, mean (SD)	28.6 (0.9)	28.5 (1.0)	28.7 (1.9)
Physical activity, mean (SD), METs per mo <sup>46</sup>	91.2 (72.5)	112.1 (176.1)	92.4 (76.4)
SPPB score, mean (SD)	9.96 (1.53)	9.81 (1.60)	9.34 (1.57)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); iDXA, intelligent dual x-ray absorptiometry (GE Healthcare); METs, metabolic equivalent tasks; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; 25(OH)D, 25-hydroxyvitamin D.

SI conversion factors: To convert 25(OH)D level to nanomoles per liter, multiply by 2.496; to convert parathyroid hormone level to nanograms per liter, multiply by 1.0.

<sup>a</sup> None of the baseline variables varied significantly among the 3 treatment groups.

<sup>b</sup> Sarcopenia was assessed based on appendicular muscle mass alone according to work by Baumgartner et al<sup>38</sup> and by Bischoff-Ferrari et al.<sup>47</sup>

less improvement in the 2 high-dose groups compared with the 24 000 IU group ( $P = .04$ ) (eTable 1 in Supplement 2). The findings for other functional and muscle mass end points were qualitatively similar.

### Secondary End Points by Treatment Group

Of the 200 participants, 60.5% (121 of 200) fell during the 12-month treatment period. Among those, the 60 000 IU group (66.9%; 95% CI, 54.4%-77.5%) and the 24 000 IU plus calcifediol group (66.1%; 95% CI, 53.5%-76.8%) had significantly higher percentages of fallers compared with the 24 000 IU group (47.9%; 95% CI, 35.8%-60.3%) at 12 months ( $P = .048$ ) (Table 2).

Consistent with the percentage of fallers, the mean number of falls differed marginally by treatment group over the 12-month follow-up ( $P = .09$ ) (Table 2). The 60 000 IU group (mean, 1.47;  $P = .02$  vs the 24 000 IU group) and the 24 000 IU plus calcifediol group (mean, 1.24;  $P = .22$  vs the 24 000 IU group) had a higher mean number of falls compared with the 24 000 IU group (mean, 0.94). A similar pattern was observed during months 0 to 6 and months 7 to 12.

### Treatment Effect Stratified by Baseline Vitamin D Level

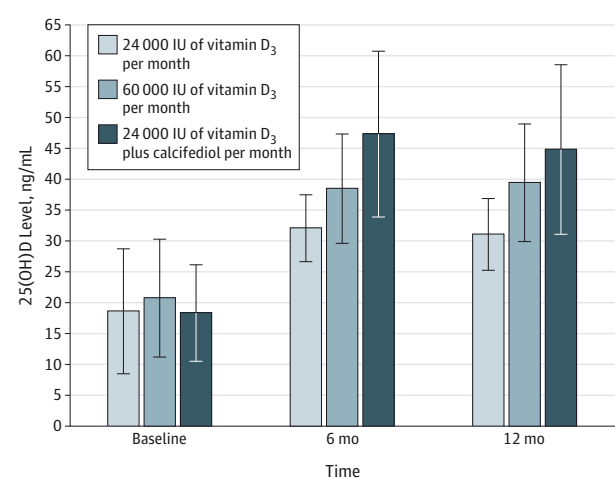
The percentage of participants achieving 25(OH)D levels of at least 30 ng/mL at 6 and 12 months differed by treatment group only in those who were vitamin D deficient at baseline. Seniors who were vitamin D replete at baseline were most vulnerable to 60 000 IU of vitamin D<sub>3</sub>, demonstrating the most falls (mean, 1.65;  $P = .02$  vs the 24 000 IU group) (Table 3). The treatment effect did not differ by baseline vitamin D level for functional decline and the incidence of falls.

### Observational Analyses by Quartiles of Achieved 25(OH)D Levels at 12 Months

#### SPPB Score

At 12 months, seniors reaching moderate 25(OH)D levels (30.4-37.4 ng/mL) had the best SPPB score improvement from baseline

Figure 2. Unadjusted 25(OH)D Levels by Treatment at Baseline, 6 Months, and 12 Months



At the 6-month and 12-month follow-ups, the mean 25(OH)D levels differed significantly by treatment ( $P < .001$ ). 25(OH)D indicates 25-hydroxyvitamin D; error bars, SD. To convert 25(OH)D level to nanomoles per liter, multiply by 2.496.

(0.45; 95% CI, 0.11 to 0.79;  $P = .01$ ). However, this increase was not significantly different from that of the highest quartile (0.12; 95% CI, -0.24 to 0.48;  $P = .18$ ) (eTable 2 in Supplement 2).

### Secondary End Points

Seniors reaching the highest quartile of 25(OH)D level (44.7-98.9 ng/mL) at the 12-month follow-up had a 5.5-fold (odds ratio, 5.52; 95% CI, 2.10-14.50) higher odds of falling compared with those reaching the lowest quartile of 21.3 to 30.3 ng/mL of 25(OH)D ( $P < .001$ ) (eTable 2 in Supplement 2). Furthermore, seniors reaching the highest quartile of 25(OH)D level at 12 months had the most falls (mean, 1.59) compared with those reaching the lowest quartile of 25(OH)D level (mean, 0.84) ( $P = .01$ ).

Table 2. Treatment Effect on the Prevention of Functional Decline and Falls<sup>a</sup>

Variable	24 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	60 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	24 000 IU of Vitamin D <sub>3</sub> Plus Calcifediol per Month (n = 66)	P Value for Difference Between Treatments in Change Over Time
<b>Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL, % (95% CI)</b>				
Unadjusted at baseline	14.9 (8.2 to 25.6)	19.4 (11.6 to 30.6)	12.1 (6.2 to 22.4)	.51 <sup>b</sup>
Adjusted at 6 mo	63.8 (50.7 to 75.1)	83.0 (71.3 to 90.5) <sup>c</sup>	93.5 (84.5 to 97.4) <sup>c</sup>	<.001 <sup>b</sup>
Adjusted at 12 mo	54.7 (41.6 to 67.2)	80.8 (68.5 to 89.1) <sup>c</sup>	83.3 (71.4 to 90.9) <sup>c</sup>	.001 <sup>b</sup>
<b>Primary End Point of Mean SPPB Functional Decline Score</b>				
Unadjusted at baseline, mean (SD)	9.96 (1.53)	9.81 (1.60)	9.34 (1.57)	
Adjusted change (95% CI) at 6 mo	0.17 (-0.06 to 0.41)	0.16 (-0.08 to 0.40)	0.16 (-0.08 to 0.40)	.26 <sup>d</sup>
Adjusted change (95% CI) at 12 mo	0.38 (0.07 to 0.68)	0.10 (-0.21 to 0.41)	0.11 (-0.19 to 0.43)	
<b>Secondary End Point of Prevention of Falls, Value (95% CI)</b>				
Adjusted % of fallers by incidence of first fall				
At 0-6 mo	35.0 (24.3 to 47.5)	39.5 (28.1 to 52.0)	49.0 (36.9 to 61.2)	.26 <sup>b</sup>
At 7-12 mo	26.6 (17.3 to 38.6)	41.3 (29.8 to 53.9)	38.5 (27.4 to 50.9)	.17 <sup>b</sup>
At 0-12 mo	47.9 (35.8 to 60.3)	66.9 (54.4 to 77.5) <sup>c</sup>	66.1 (53.5 to 76.8) <sup>c</sup>	.048 <sup>b</sup>
Adjusted mean No. of falls				
At 0-6 mo	0.52 (0.26 to 0.79)	0.86 (0.50 to 1.12)	0.67 (0.40 to 0.93)	.19 <sup>b</sup>
At 7-12 mo	0.46 (0.20 to 0.72)	0.69 (0.43 to 0.95)	0.71 (0.45 to 0.97)	.31 <sup>b</sup>
At 0-12 mo	0.94 (0.60 to 1.29)	1.47 (1.13 to 1.82) <sup>c</sup>	1.24 (0.89 to 1.58)	.09 <sup>b</sup>

Abbreviations: BMI, body mass index; SPPB, Short Physical Performance Battery; 25(OH)D, 25-hydroxyvitamin D.

SI conversion factor: To convert 25(OH)D level to nanomoles per liter, multiply by 2.496.

<sup>a</sup> All regression models were adjusted for baseline age, sex, and body mass index. Change over time in our primary study outcome was compared between the 3 study groups using a repeated-measures linear regression model. For the primary and secondary outcomes, we compared the percentage of fallers in a logistic regression model, adjusting for age, sex, and BMI. For the number of falls, we used linear regression, with indicators for treatment group as the main predictors and covariates to adjust for age, sex, and BMI.

<sup>b</sup> P values are from a 3-group comparison using linear regression (number of falls) or logistic regression (number of participants with achieved 25(OH)D levels ≥30 ng/mL), adjusting for age, sex, and BMI.

<sup>c</sup> Significant pairwise difference from 24 000 IU. There were no significant pairwise differences between 60 000 IU and 24 000 IU plus calcifediol.

<sup>d</sup> P value is from the interaction between treatment group and time, adjusting for baseline SPPB score, age, sex, and BMI. The outcome measures in each model (6-month change and 12-month change) are presented.

Regardless of 25(OH)D baseline level and independent of age, sex, and BMI, participants receiving 60 000 IU of vitamin D<sub>3</sub> had an 18.7% (95% CI, 10.4%-31.4%) probability of reaching the detrimental highest quartile of 25(OH)D level at 12 months (range, 44.7-98.9 ng/mL), and participants receiving 24 000 IU plus calcifediol had a 40.1% (95% CI, 27.7%-53.9%) probability. In contrast, no participants in the 24 000 IU group reached the highest quartile of 25(OH)D level at the 12-month follow-up. The same pattern was seen at the 6-month follow-up.

### Biochemical Safety

The mean serum calcium and creatinine levels and the mean urinary calcium excretion did not differ by treatment group at baseline, 6-month follow-up, and 12-month follow-up (eTable 3 and eTable 4 in Supplement 2). A transient increase in calcium excretion was seen in the 60 000 IU group and the 24 000 IU plus calcifediol group only at the 2-week visit.

### Discussion

In this RCT, seniors in the higher-dose vitamin D<sub>3</sub> groups (60 000 IU or 24 000 IU plus calcifediol) experienced no improvement in lower extremity function, had the highest per-

centages of fallers, and demonstrated the most falls compared with seniors in the control group (24 000 IU). This detrimental effect was seen during the first 6 months of the trial and was maintained during the last 6 months and was supported by our observational analysis. These findings suggest that participants who reached the highest quartile of 25(OH)D level (44.7-98.9 ng/mL) at the 12-month follow-up had the greatest odds of falling and the most falls compared with those who reached the lowest quartile (21.3-30.3 ng/mL). For the dosages examined in our study, participants receiving the 2 higher doses were most likely to reach the detrimental highest quartile at the 6-month and 12-month follow-ups, independent of baseline level. Corroborating the concept of a lack of benefit with the 2 higher doses of vitamin D, parathyroid hormone levels were not suppressed by higher doses of vitamin D compared with 24 000 IU.

High oral doses of vitamin D have been evaluated in 2 earlier trials with prospective fall assessment<sup>21,23</sup> and in 1 trial that assessed falls retrospectively.<sup>48</sup> In a trial among 173 frail seniors after acute hip fracture, 2000 IU of vitamin D/d vs 800 IU/d did not improve lower extremity function or reduce falls over a 12-month follow-up (28%; 95% CI, -4% to 68%).<sup>23</sup> The achieved mean 25(OH)D level at 12 months was 44.6 ng/mL in the 2000 IU/d group compared with 35.4 ng/mL in the 800 IU/d

**Table 3. Treatment Effect on the Prevention of Functional Decline and Falls, Stratified by Baseline Vitamin D Level<sup>a</sup>**

Variable	24 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	60 000 IU of Vitamin D <sub>3</sub> per Month (n = 67)	24 000 IU of Vitamin D <sub>3</sub> Plus Calcifediol per Month (n = 66)	P Value for Difference Between Treatments in Change Over Time
<b>Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL Among Seniors With 25(OH)D Levels &lt;20 ng/mL at Baseline, % (95% CI)</b>				
Unadjusted at baseline	0	0	0	NA
Adjusted at 6 mo	53.3 (37.5 to 68.5)	70.4 (52.6 to 83.6)	90.8 (77.4 to 96.6)	.003
Adjusted at 12 mo	43.6 (28.4 to 60.2)	73.6 (55.1 to 86.3)	80.9 (65.0 to 90.6)	.004
<b>Primary End Point of Participants With Achieved 25(OH)D Levels ≥30 ng/mL Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline, % (95% CI)</b>				
Unadjusted at baseline	23.9 (10.9 to 44.8)	28.3 (14.0 to 48.8)	21.7 (9.1 to 43.4)	.83
Adjusted at 6 mo	84.6 (63.3 to 94.6)	94.7 (80.9 to 98.7)	97.4 (80.7 to 99.7)	.14
Adjusted at 12 mo	72.8 (51.4 to 87.2)	87.1 (70.5 to 95.0)	89.2 (68.3 to 96.9)	.23
<b>Primary End Point of Mean SPPB Functional Decline Score Among Seniors With 25(OH)D Levels &lt;20 ng/mL at Baseline</b>				
Unadjusted at baseline, mean (SD)	9.93 (1.44)	9.51 (1.70)	9.71 (1.50)	
Adjusted change (95% CI) at 6 mo	0.15 (-0.15 to 0.45)	0.34 (0.02 to 0.67)	0.14 (-0.16 to 0.45)	.39
Adjusted change (95% CI) at 12 mo	0.46 (0.06 to 0.87)	0.36 (-0.09 to 0.80)	0.18 (-0.23 to 0.58)	
<b>Primary End Point of Mean SPPB Functional Decline Score Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline</b>				
Unadjusted at baseline, mean (SD)	10.13 (1.66)	10.11 (1.39)	10.32 (1.63)	
Adjusted change (95% CI) at 6 mo	0.34 (-0.03 to 0.71)	0.06 (-0.28 to 0.39)	0.25 (-0.16 to 0.66)	.60
Adjusted change (95% CI) at 12 mo	0.41 (0.04 to 0.86)	-0.07 (-0.49 to 0.35)	0.07 (-0.42 to 0.55)	
<b>Secondary End Point of Prevention of Falls, Adjusted % (95% CI) of Fallers by Incidence of First Fall Among Seniors With 25(OH)D Levels &lt;20 ng/mL at Baseline</b>				
At 0-6 mo	38.3 (24.4 to 54.4)	43.0 (27.4 to 60.1)	43.5 (29.0 to 59.3)	.88
At 7-12 mo	25.6 (14.4 to 41.4)	38.0 (23.3 to 55.2)	49.0 (33.8 to 64.4)	.11
At 0-12 mo	44.4 (29.6 to 60.2)	67.5 (50.0 to 81.2)	75.1 (59.5 to 86.1)	.02
<b>Secondary End Point of Prevention of Falls, Adjusted % (95% CI) of Fallers by Incidence of First Fall Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline</b>				
At 0-6 mo	24.8 (12.0 to 44.4)	54.2 (36.8 to 70.6)	32.0 (16.2 to 53.5)	.047
At 7-12 mo	22.0 (10.1 to 41.4)	43.2 (27.0 to 61.0)	29.8 (14.5 to 51.5)	.19
At 0-12 mo	45.1 (27.0 to 64.7)	68.0 (49.8 to 82.0)	51.5 (31.0 to 71.5)	.19
<b>Secondary End Point of Prevention of Falls, Adjusted Mean No. (95% CI) of Falls Among Seniors With 25(OH)D Levels &lt;20 ng/mL at Baseline</b>				
At 0-6 mo	0.61 (0.25 to 0.97)	0.79 (0.41 to 1.17)	0.73 (0.37 to 1.08)	.79
At 7-12 mo	0.43 (0.06 to 0.80)	0.72 (0.32 to 1.11)	0.90 (0.53 to 1.26)	.20
At 0-12 mo	0.98 (0.52 to 1.44)	1.39 (0.90 to 1.88)	1.41 (0.96 to 1.86)	.33
<b>Secondary End Point of Prevention of Falls, Adjusted Mean No. (95% CI) of Falls Among Seniors With 25(OH)D Levels ≥20 ng/mL at Baseline</b>				
At 0-6 mo	0.39 (0.03 to 0.81)	1.03 (0.65 to 1.41)	0.60 (0.15 to 1.05)	.06
At 7-12 mo	0.42 (0.07 to 0.75)	0.73 (0.43 to 1.04)	0.46 (0.10 to 0.82)	.29
At 0-12 mo	0.78 (0.25 to 1.31)	1.65 (1.17 to 2.13)	1.03 (0.46 to 1.60)	.03

Abbreviations: NA, not applicable; SPPB, Short Physical Performance Battery; 25(OH)D, 25-hydroxyvitamin D.

SI conversion factor: To convert 25(OH)D level to nanomoles per liter, multiply by 2.496.

<sup>a</sup> For this table, we divided the study cohort into participants with (n = 116) and without (n = 84) vitamin D deficiency and repeated the treatment analyses of

Table 2. For most end points, the findings were similar to the overall results in Table 2. However, there was a suggestion that the mean number of falls differed most by treatment among those who had higher vitamin D levels at baseline. We found no statistically significant interaction between treatment and vitamin D deficiency at baseline for any of the primary and secondary end points.

group.<sup>23</sup> In another trial of 2256 senior women at high risk of hip fracture (similar to our trial), an annual bolus of 500 000 IU of vitamin D vs placebo increased the risk of falling (rate ratio, 1.15; 95% CI, 1.02-1.30).<sup>21</sup> The bolus group achieved 25 (OH)D levels of 48 ng/mL at the 1-month follow-up and 36 ng/mL at the 3-month follow-up, which is the time frame in which most falls occurred in the trial.<sup>21</sup> In both of these trials, high-dose vitamin D resulted in mean 25(OH)D levels overlapping the highest achieved quartile in our trial.<sup>21,23</sup> In a third trial of 2686 community-dwelling seniors 65 to 85 years old, a vitamin D<sub>3</sub> bolus of 100 000 IU every 4 months for 5 years significantly reduced the risk of any new fracture by 22% but did not reduce the risk of falling (relative risk, 0.93; 95% CI,

0.76-1.14).<sup>48</sup> However, falls were only assessed retrospectively for the last year of follow-up, and the treatment group reached a mean 25(OH)D level of 30 ng/mL.<sup>48</sup>

While our data are consistent with these prior studies, the physiology behind a possible detrimental effect of a high monthly bolus dose of vitamin D on muscle function and falls remains unclear and needs further investigation. The possibility that high-dose monthly vitamin D may have increased physical activity and thereby the opportunity to fall was explored in our analyses but did not explain our findings. Alternatively, our results may have been caused by chance. However, this explanation is unlikely given the uniformity of our treatment findings for all muscle-related end points during the first and last 6

months of our trial, as well as given the consistency with our observational analyses on achieved blood levels.

Two ongoing trials use the same cumulative dose as the 60 000 IU group in our trial. These are the Vitamin D and Omega-3 Trial (VITAL; <http://www.vitalstudy.org>) and the Vitamin D<sub>3</sub>-Omega-3-Home Exercise-Healthy Ageing and Longevity Trial (DO-HEALTH; <http://do-health.eu/wordpress>). However, their dosing schedule is daily rather than monthly, and the patient characteristics differ from those of seniors in our trial. These trials will provide important opportunities to verify and expand our findings to other end points.

This trial has several strengths. It was powered adequately for the end points investigated, and fall rates (ascertained by diary and monthly telephone calls) were consistent with the literature.<sup>49-52</sup> We compared 24 000 IU of vitamin D per month (equivalent to 800 IU of vitamin D per day, which is often considered the standard of care<sup>53-55</sup> and is considered the current recommended daily allowance by the Institute of Medicine<sup>34</sup>) against 2 higher monthly doses of vitamin D. Corroborating our treatment findings that high-dose vitamin D increases the risk of falling, our observational analysis consistently showed that achieving the highest quartile of 25(OH)D level at the 12-month follow-up may not be advantageous for the prevention of falls. Furthermore, the study population is representative of a large part of the senior population 70 years and older

still living independently at home, with a Mini-Mental State Examination score of at least 27 and sufficient mobility to use public transportation but at increased risk of functional decline due to a prior fall event. However, because of these selection criteria, our findings may not apply to younger seniors and to individuals with more limited cognitive or functional abilities and may have limited our power to detect the primary end point of functional decline.

A further limitation of our study is the lack of a placebo group. Therefore, our trial supports low-dose over high-dose vitamin D supplementation but cannot establish a benefit of low dose over placebo.

## Conclusions

Compared with a monthly standard-of-care dose of 24 000 IU of vitamin D<sub>3</sub>, two monthly higher doses of vitamin D (60 000 IU and 24 000 IU plus calcifediol) conferred no benefit on the prevention of functional decline and increased falls in seniors 70 years and older with a prior fall event. Therefore, high monthly doses of vitamin D or a combination with calcifediol may not be warranted in seniors with a prior fall because of a potentially deleterious effect on falls. Future research is needed to confirm our findings for daily dosing regimens.

### ARTICLE INFORMATION

**Accepted for Publication:** October 27, 2015.

**Published Online:** January 4, 2016.  
doi:10.1001/jamainternmed.2015.7148.

**Correction:** This article was corrected on February 8, 2016, to fix an error in the Corresponding Author address.

**Author Affiliations:** Department of Geriatrics and Aging Research, University Hospital Zurich, Zurich, Switzerland (Bischoff-Ferrari, Meyer, Egli); Centre on Aging and Mobility, University of Zurich, Zurich, Switzerland (Bischoff-Ferrari, Meyer, Theiler, Egli); Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts (Dawson-Hughes); Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Orav); Department of Geriatrics, University of Basel, Basel, Switzerland (Stahelin); Department of Orthopedic Surgery, University of Basel, Basel, Switzerland (Dick); Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (Willett).

**Author Contributions:** Dr Bischoff-Ferrari had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bischoff-Ferrari, Dawson-Hughes, Orav, Theiler, Dick.

**Acquisition, analysis, or interpretation of data:** Bischoff-Ferrari, Dawson-Hughes, Orav, Stahelin, Meyer, Willett, Egli.

**Drafting of the manuscript:** Bischoff-Ferrari, Orav.

**Critical revision of the manuscript for important intellectual content:** Bischoff-Ferrari, Dawson-Hughes, Stahelin, Meyer, Theiler, Dick, Willett, Egli.

**Statistical analysis:** Bischoff-Ferrari, Orav.

**Obtained funding:** Bischoff-Ferrari.

**Administrative, technical, or material support:**

Bischoff-Ferrari, Dawson-Hughes, Egli.

**Study supervision:** Bischoff-Ferrari, Stahelin, Theiler, Dick.

**Conflict of Interest Disclosures:** Dr Bischoff-Ferrari reported receiving speaker fees from and serving on advisory boards for Merck Sharp & Dohme AG, Amgen, WILD, DSM Nutritional Products, Roche Diagnostics, Nestlé, Pfizer, and Sanofi. No other disclosures were reported.

**Funding/Support:** The primary funding sources for this trial were professorship grant PPOOB-114864 from the Swiss National Science Foundation and The VELUX Foundations. Supplementary funding was provided by investigator-initiated funds from Merck Sharp & Dohme AG, WILD, and DSM Nutritional Products.

**Role of the Funder/Sponsor:** The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

### REFERENCES

- Cummings SR, Nevitt MC; Study of Osteoporotic Fractures Research Group. Non-skeletal determinants of fractures: the potential importance of the mechanics of falls. *Osteoporos Int*. 1994;4 (suppl 1):67-70.
- Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med*. 1997;337(18):1279-1284.
- Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-M156.

- Visser M, Schaap LA. Consequences of sarcopenia. *Clin Geriatr Med*. 2011;27(3):387-399.

- Ceglia L. Vitamin D and skeletal muscle tissue and function. *Mol Aspects Med*. 2008;29(6):407-414.

- Ceglia L, Niramitmahapanya S, da Silva Morais M, et al. A randomized study on the effect of vitamin D<sub>3</sub> supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *J Clin Endocrinol Metab*. 2013;98(12):E1927-E1935. doi:10.1210/jc.2013-2820.

- Bischoff-Ferrari HA. Relevance of vitamin D in muscle health. *Rev Endocr Metab Disord*. 2012;13(1):71-77.

- Al-Shoha A, Qiu S, Palnitkar S, Rao DS. Osteomalacia with bone marrow fibrosis due to severe vitamin D deficiency after a gastrointestinal bypass operation for severe obesity. *Endocr Pract*. 2009;15(6):528-533.

- Bischoff HA, Borchers M, Gudat F, et al. In situ detection of 1,25-dihydroxyvitamin D<sub>3</sub> receptor in human skeletal muscle tissue. *Histochem J*. 2001;33(1):19-24.

- Bischoff-Ferrari HA, Borchers M, Gudat F, Dürmüller U, Stähelin HB, Dick W. Vitamin D receptor expression in human muscle tissue decreases with age. *J Bone Miner Res*. 2004;19(2):265-269.

- Boland R. Role of vitamin D in skeletal muscle function. *Endocr Rev*. 1986;7(4):434-448.

- Costa EM, Blau HM, Feldman D. 1,25-Dihydroxyvitamin D<sub>3</sub> receptors and hormonal responses in cloned human skeletal muscle cells. *Endocrinology*. 1986;119(5):2214-2220.

- Simpson RU, Thomas GA, Arnold AJ. Identification of 1,25-dihydroxyvitamin D<sub>3</sub>



- receptors and activities in muscle. *J Biol Chem*. 1985;260(15):8882-8891.
14. Ceglia L, da Silva Morais M, Park LK, et al. Multi-step immunofluorescent analysis of vitamin D receptor loci and myosin heavy chain isoforms in human skeletal muscle. *J Mol Histol*. 2010;41(2-3):137-142.
  15. Wang Y, DeLuca HF. Is the vitamin D receptor found in muscle? *Endocrinology*. 2011;152(2):354-363.
  16. Sørensen OH, Lund B, Saltin B, et al. Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. *Clin Sci (Lond)*. 1979;56(2):157-161.
  17. Freedman LP. Transcriptional targets of the vitamin D3 receptor—mediating cell cycle arrest and differentiation. *J Nutr*. 1999;129(2S)(suppl):581S-586S.
  18. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int*. 2009;20(2):315-322.
  19. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res*. 2000;15(6):1113-1118.
  20. Bischoff HA, Stähelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res*. 2003;18(2):343-351.
  21. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial [published correction appears in *JAMA*. 2010;303(23):2357]. *JAMA*. 2010;303(18):1815-1822.
  22. Latham NK, Anderson CS, Lee A, Bennett DA, Moseley A, Cameron ID; Fitness Collaborative Group. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). *J Am Geriatr Soc*. 2003;51(3):291-299.
  23. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Arch Intern Med*. 2010;170(9):813-820.
  24. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. *Osteoporos Int*. 2011;22(3):859-871.
  25. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ*. 2009;339:b3692.
  26. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. *JAMA*. 2004;291(16):1999-2006.
  27. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med*. 2012;367(1):40-49.
  28. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009;169(6):551-561.
  29. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol*. 2014;2(4):307-320.
  30. Bolland MJ, Grey A, Gamble GD, Reid IR. Vitamin D supplementation and falls: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol*. 2014;2(7):573-580.
  31. DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ*. 2010;340:b5463.
  32. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess (Full Rep)*. 2007(158):1-235.
  33. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev*. 2009;(2):CD000227.
  34. Institute of Medicine. Dietary reference ranges for calcium and vitamin D. <http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx>. Published 2010. Accessed February 13, 2012.
  35. Bischoff-Ferrari HA, Dawson-Hughes B, Stöcklin E, et al. Oral supplementation with 25(OH)D<sub>3</sub> versus vitamin D<sub>3</sub>: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. *J Bone Miner Res*. 2012;27(1):160-169.
  36. Gallagher JC, Sai A, Templin T II, Smith L. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. *Ann Intern Med*. 2012;156(6):425-437.
  37. Jetter A, Egli A, Dawson-Hughes B, et al. Pharmacokinetics of oral vitamin D<sub>3</sub> and calcifediol. *Bone*. 2014;59:14-19.
  38. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998;147(8):755-763.
  39. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94.
  40. Buchner DM, Hornbrook MC, Kutner NG, et al. Development of the common data base for the FICSIT trials. *J Am Geriatr Soc*. 1993;41(3):297-308.
  41. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
  42. Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope-dilution liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D<sub>2</sub> and D<sub>3</sub>. *Clin Chem*. 2005;51(9):1683-1690.
  43. Saenger AK, Laha TJ, Bremner DE, Sadrzadeh SM. Quantification of serum 25-hydroxyvitamin D<sub>2</sub> and D<sub>3</sub> using HPLC-tandem mass spectrometry and examination of reference intervals for diagnosis of vitamin D deficiency. *Am J Clin Pathol*. 2006;125(6):914-920.
  44. National Institute of Standards and Technology NIST/National Institutes of Health. Vitamin D Metabolites Quality Assurance Program. <http://www.nist.gov/mml/csd/vitdqap.cfm>. Accessed November 9, 2015.
  45. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence: unifying the approach to geriatric syndromes. *JAMA*. 1995;273(17):1348-1353.
  46. Nelson KM, Reiber G, Boyko EJ; NHANES III. Diet and exercise among adults with type 2 diabetes: findings from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care*. 2002;25(10):1722-1728.
  47. Bischoff-Ferrari HA, Orav JE, Kanis JA, et al. Comparative performance of current definitions of sarcopenia against the prospective incidence of falls among community-dwelling seniors age 65 and older [published online June 12, 2015]. *Osteoporos Int*.
  48. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D<sub>3</sub> (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469.
  49. Giusti A, Barone A, Razzano M, Pizzonia M, Oliveri M, Pioli G. Predictors of hospital readmission in a cohort of 236 elderly discharged after surgical repair of hip fracture: one-year follow-up. *Aging Clin Exp Res*. 2008;20(3):253-259.
  50. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. *J Gerontol A Biol Sci Med Sci*. 2000;55(9):M498-M507.
  51. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev*. 1985;7:178-208.
  52. Bookvar KS, Halm EA, Litke A, et al. Hospital readmissions after hospital discharge for hip fracture: surgical and nonsurgical causes and effect on outcomes. *J Am Geriatr Soc*. 2003;51(3):399-403.
  53. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R; US Preventive Services Task Force. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2010;153(12):815-825.
  54. American Geriatrics Society and British Geriatrics Society. Updated fall prevention guidelines. [http://www.patientsafety.solutions.com/docs/February\\_2011\\_Updated\\_Fall\\_Prevention\\_Guidelines.htm](http://www.patientsafety.solutions.com/docs/February_2011_Updated_Fall_Prevention_Guidelines.htm). Published February 2011. Accessed February 13, 2012.
  55. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. *Osteoporos Int*. 2010;21(7):1151-1154.