Vitamin D for Prevention of Falls and their Consequences in Older Adults

Developed by the Workgroup of the Consensus Conference on Vitamin D for the Prevention of Falls and their Consequences
The goal of this Consensus Statement is to help primary care practitioners achieve adequate vitamin D intake from all sources in their older patients with the goal of reducing falls and fall-related injuries.

The workgroup graded the quality of evidence and assigned an evidence level using established criteria. Based on the evidence for fall and fracture reduction in the clinical trials of older community-dwelling and institutionalized persons and meta-analyses, the workgroup concluded that a serum 25(OH)D concentration of 30 ng/ml (75 nmol/L) should be a minimum goal to achieve in older adults, particularly in frail adults who are at higher risk for falls, injuries and fractures. The workgroup concluded that the goal – to reduce fall injuries that are related to low vitamin D status – could be achieved safely and would not require practitioners to measure serum 25(OH)D concentrations for older adults in the absence of underlying conditions that increase the risk for hypercalcemia.

The Consensus Statements are divided into an introduction followed by two sections. Section 1 consists of Recommendations to Reduce Falls and Fractures. Section 2 presents Strategies for Optimizing Vitamin D Status. The Section 2 recommendations on vitamin D intake are based on vitamin D from all sources: dietary intake, unprotected skin sun exposure, and supplements.

A summary of this document, “Recommendations Abstracted from the American Geriatrics Society Consensus Statement on Vitamin D for Prevention of Falls and their Consequences,” is published in the Journal of the American Geriatrics Society and is available online at www.geriaticscareonline.org.
SECTION 1. Recommendations to Reduce Falls and Fractures

The first section focuses on the clinical trials that tested the effects of vitamin D supplementation on reducing fall injuries. The trials varied in vitamin D supplement dose, adherence to the vitamin D regimen, and achieved vitamin D levels. The vitamin D supplement doses in the trials that were associated with reduced falls and fall injuries varied by meta-analysis, with a range of 600 to 1000 IU daily. Because fewer studies tested daily doses above 800 IU, estimates of benefit from the meta-analyses are lower than the results of individual higher dose studies.

The Statements recommend that all older adults have a minimum daily supplement of 1000 IU daily, with calcium supplementation, to reduce falls and fractures. The recommendations take into account two major factors in evaluating the evidence. First, in the trials that measured serum concentrations, many subjects in the vitamin D supplement groups had 25(OH)D concentrations below current recommended levels. Adherence to vitamin D supplementation to achieve a mean blood level over 24 ng/ml (60 nmol/L) in the intervention groups was needed to prevent falls. Second, dosages of less than 600 IU did not prevent falls. As the vitamin D supplement dose increased, or serum 25(OH)D level increased above these thresholds, the risk of falls or fractures decreased. The workgroup endorsed 1000 IU as a minimum daily supplement after a long discussion of the potential benefit of recommending a dose higher than was used in most of the intervention trials that showed protection from falls or fractures.

The workgroup chose this higher minimum supplement for the following reasons:

1. In clinical practice, adherence to supplementation will likely be lower than in clinical trials that demonstrated fall and fracture reduction.

2. The vast majority of older adults in the United States will require higher supplementation to achieve minimum desirable levels. Based on calculations from the Institute of Medicine’s 2011 publication, “Dietary reference intakes for calcium and vitamin D’s dose response estimates,” only about half of adults >71 years of age will achieve a 25(OH)D blood level of 30 ng/ml (75 nmol/L) with a daily supplement of 1000 IU. (IOM, 2011) (see Table 5)

3. African Americans and obese subjects are under-represented in the intervention studies cited. These populations have lower baseline serum levels of vitamin D and will require higher vitamin D intake to reach serum levels of 30 ng/ml (75 nmol/L).

4. For persons without underlying conditions that increase the risk of hypercalcemia (e.g., advanced renal disease, certain malignancies, sarcoidosis), there is no known risk from taking 1000 IU vitamin D supplements per day.
SECTION 2. Strategies for Optimizing Vitamin D Status

The workgroup concluded that 30 ng/ml (75 nmol/L) was the minimum desirable 25(OH)D concentration for older adults. The workgroup concurred with the Osteoporosis Canada Statement (Hanley DA, 2010), the majority opinion of the International Osteoporosis Foundation (Dawson-Hughes, 2010) and the Endocrine Society (Holick, 2011) that 30 ng/ml (75 nmol/L) was the minimum desirable 25(OH)D level. More than 75% of the older adult population of the US falls below this serum level (see Table 3). In studies that demonstrated a reduction in falls and fractures, the average concentrations of 25(OH)D achieved were consistently above 24 ng/ml (60 nmol/L). Most importantly, the Agency for Healthcare Research and Quality (AHRQ) meta-analysis found that the stronger fracture protection of vitamin D reported in trials of institutionalized subjects may have been due to the higher achieved 25(OH)D levels. (Cranney A, 2007) The AHRQ report stated: “The combined estimate from trials with higher end-of-study serum 25(OH)D concentrations (>30 ng/ml or 74 nmol/L) was consistent with a significant reduction in the risk of fractures.” (Cranney A, 2007)

The IOM report focused on providing public health recommendations to the US Food and Drug Administration (FDA) for food labeling. (The report is titled “Dietary Reference Intakes for Calcium and Vitamin D.”) In contrast, the workgroup focused on providing guidance to practitioners caring for older, frail adults, many of whom rarely have direct exposure to the sun.

The total vitamin D intake needed to assure that the vast majority of older adults (age >71 years) achieve serum concentrations of >30 ng/ml (75 nmol/L) are much higher than 800 IU daily. This consensus statement used the dose-response estimates developed by the IOM (IOM, 2010) to determine total daily intake (see Figure 5 and Table 5).

Based on IOM equations of serum response to vitamin D intake, 4,000 IU daily input from all sources — meaning all dietary sources, unprotected skin sun exposure, and supplements — will ensure that 92% of the population of older adults will achieve levels >30 ng/ml (75 nmol/L). To assure that 80% of the older adult population achieves a level >30 ng/ml (75 nmol/L), daily total intake must be 2,500 IU, which produces a mean 25(OH)D level of about 34 ng/ml (85 nmol/L), with the lowest 5% of the population achieving levels at or below 24 ng/ml (60 nmol/L).

The workgroup recognizes that over the next several years, ongoing clinical trials may give more precise estimates of supplement doses needed, and levels of 25(OH)D required to minimize falls and injuries. Practitioners who are faced with advising older and frail adults — who are at higher risk for falls and injuries in the immediate or near future — can now recommend vitamin D supplements to maximize likelihood of benefit without risk of toxicity.
METHODOLOGY

General Methods and Literature Search

The National Institutes of Health (NIH) convened a conference in 2007, entitled “Vitamin D and Health in the 21st Century,” that presented an evidence-based review of the efficacy of vitamin D supplementation in preventing adverse outcomes. At this conference, the summary findings of the AHRQ commissioned meta-analysis of the effects of vitamin D supplementation were presented. (Cranney 2007) The meta-analysis for falls – which assessed vitamin D 700-1000 IU with calcium – found a significant reduction in the incidence of falls (OR=0.84, 95% CI=0.76-0.93).

Following the publication of the reports presented at the NIH meeting (Brannon, 2008) the American Geriatrics Society convened a workgroup to develop a consensus statement that would assist practitioners caring for older adults. The project was supported by the National Center for Injury Prevention and Control of the Centers for Disease Control and Prevention (CDC). The workgroup members were chosen on the basis of their leadership in vitamin D research and their clinical experience. All meta-analyses published prior to the meeting and the randomized controlled trials (RCTs) cited in these meta-analyses were collected for review. A Medline literature search was also conducted of all meta-analyses and RCTs published between January 2006 and February 2009 following the research strategy utilized by Cranney and coworkers. (Cranney, 2008)

In November, 2010, the IOM released its report, Dietary Reference Intakes for Calcium and Vitamin D. The workgroup decided to review and revise the present statement because of this new information. It was in response to the IOM’s report that the workgroup again reviewed the evidence and reformatted the recommendations into the two sections described above:

The revised statement cites the dose-response equations developed by the IOM; these equations have been included in the tables.

The following organizations with special interest and expertise in vitamin D and older persons provided peer review of a preliminary draft of this guideline: American College of Physicians, American Academy of Orthopaedic Surgeons, American College of Clinical Pharmacy, American College of Obstetricians and Gynecologists, American Geriatrics Society, American Medical Directors Association, American Osteopathic Association, American Society for Bone and Mineral Research, American Society of Nutrition, International Society for Clinical Densitometry, National Osteoporosis Foundation, Endocrine Society.

Evidence Synthesis and Classification of Evidence-based Statements

Workgroup members reviewed the standard tables and evaluated the evidence based on the recently developed Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. (Guyatt, 2008)
INTRODUCTION

Vitamin D is vital for the optimal function of numerous physiological systems. It is produced in the skin by exposure to ultraviolet-B (UV-B) light in sunlight. The vitamin is then hydroxylated in the liver to 25-hydroxyvitamin D 25(OH)D, an important storage form of the vitamin as well as the measured indicator of vitamin D functional status. The active metabolite, 1,25-dihydroxyvitamin D3, is produced through further hydroxylation of 25(OH)D by 1-alpha-hydroxylase in the kidneys and other organs in an autocrine manner. Casual exposure to sunlight provides about 60% of most people’s vitamin D acquisition from all sources. (Barger Lux 2000) Little vitamin D is naturally present in food, but in the US, milk, cereals, and some orange juice and breads are fortified with vitamin D. Most multivitamin supplements contain 400-1,000 international units (IU) of vitamin D. (See Table 2.)

In the third National Health and Nutrition Examination Survey (NHANES), for years 1988 to 1994, the mean daily intake of vitamin D from food and supplements in American adults >50 years of age was found to be low. (Table 3)

A recent update of NHANES reported vitamin D input from food and supplements from the years 2005-06. The total diet and supplement intakes for adult American males over 50 years was 380 IU, and for females, 402 IU. This represents an increase of only 60-70 units a day over a span of more than 10 years. (Reagan 2010)

Table 2: Dietary, Supplemental, and Pharmaceutical Sources of Vitamin D2 and Vitamin D3†

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>Vitamin D Content (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Sources</td>
<td></td>
</tr>
<tr>
<td>Sunlight</td>
<td>Highly variable and difficult to estimate range 0-1000 IU of vitamin D3/ day</td>
</tr>
<tr>
<td>Salmon</td>
<td>100-250 IU of vitamin D3 or D2</td>
</tr>
<tr>
<td>Fresh, wild, farmed (3.5 oz)</td>
<td>300-600 IU of vitamin D3</td>
</tr>
<tr>
<td>Sardines, canned (3.5 oz)</td>
<td>300 IU of vitamin D3</td>
</tr>
<tr>
<td>Mackerel, canned (3.5 oz)</td>
<td>250 IU of vitamin D3</td>
</tr>
<tr>
<td>Tuna, canned (3.6 oz)</td>
<td>230 IU of vitamin D3</td>
</tr>
<tr>
<td>Fortified foods</td>
<td></td>
</tr>
<tr>
<td>Fortified milk, yogurts, orange juice</td>
<td>100 IU/8 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified cheeses</td>
<td>100 IU/3 oz, usually vitamin D3</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>100 IU/serving, usually vitamin D3</td>
</tr>
</tbody>
</table>

Adapted from Holick M. Vitamin D deficiency. NEJM 2007;357:266-81. Table 1.

†IU denotes international unit; 1 IU equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.

‡About 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.

*When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D2; cholecalciferol indicates that the product contains vitamin D3.
Table 3: Estimated mean daily intake of vitamin D from food, supplements, and both among US residents 50 or more years of age, 1988-1994

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>Data years 1988-1994</th>
<th>Race/Ethnicity</th>
<th>Women (IU/day)</th>
<th>Men (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and Supplements</td>
<td>White</td>
<td>334.8</td>
<td>324.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mexican American</td>
<td>238.0</td>
<td>245.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>237.6</td>
<td>238.4</td>
<td></td>
</tr>
<tr>
<td>Data years 1988-1994</td>
<td>Food</td>
<td>All Ethnic Groups</td>
<td>180</td>
<td>224</td>
</tr>
<tr>
<td></td>
<td>Supplement</td>
<td></td>
<td>220</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>Food and Supplements</td>
<td></td>
<td>400</td>
<td>428</td>
</tr>
</tbody>
</table>


Adults in the United States are at marked risk of low vitamin D status, defined as serum 25(OH)D concentrations less than 30 ng/ml (75 nmol/L). (Dawson-Hughes, 2005) According to NHANES 2000-2004, 78.2% of American men >70 years and 76.7% of women across all ages had vitamin D concentrations <30 ng/ml (75 nmol/L). (Calvo, 2004) (Table 4)

While there is no evidence that age alone is a risk factor for low vitamin D status, serum 25(OH)D concentrations may be slightly lower with very advanced age. (Sherman, 1990; Gallagher, 1998; Orwoll, 2009) One study found that 31% of men between the ages of 80-84 years had serum concentrations of 25(OH)D <20 ng/ml (50 nmol/L) while 40% of men >85 years old had serum concentrations in this range. (Orwoll, 2009) Decreased exposure to sunlight in long-term care settings, and the reduction in 7-dehydrocholesterol levels in the skin are both associated with lower vitamin D levels in older people. (Holick, 2007)

Lower 25(OH)D serum concentrations have been associated with many other factors, including geographic latitude, season, genetic variants, female sex, lack of exercise (probably a proxy measure for sun exposure), skin pigmentation, concealing clothing, use of sunscreen, high body mass, and lower consumption of vitamin D-fortified milk. (Schneider, 2006; Yetley, 2008; Moniz, 2005; Orwoll, 2009; Looker, 2008; Finch, 1998; Ilahi, 2008, Calvo, 2004)

Among all individuals >12 years old, age-standardized mean 25(OH)D concentrations significantly declined from NHANES III (1988–1994) to NHANES 2000–2004. The absolute decline was 4.8-8 ng/ml (12-20 nmol/L) in males, and 2-5.2 ng/ml (5-13 nmol/L) in females, depending on season. After adjustment for differences in the assays between NHANES III and NHANES 2000–2004, the difference was reduced to 2-3.6 ng/ml (5-9 nmol/L) in males and from 0.3-2.4 ng/ml (0.7-6.1 nmol/L) in females. The difference was no longer significant for females although it remained significant for males. (Looker, 2008)
Seasonal Variation in Vitamin D in Older Adults

The Cardiovascular Health Study of 2,300 adults in the US found substantial seasonal variation in vitamin D levels. 25(OH)D levels were highest in September and lowest in March - the mean seasonal difference in 25(OH)D levels was 9.6 ng/ml (24 nmol/L). Men, subjects living in higher latitudes, and those with greater physical activity levels had larger seasonal differences. (Shoben, 2011) A best estimate of the seasonal variation in total vitamin input associated with a 10 ng/ml (25 nmol/L) increase in 25(OH)D levels in the summer is about 1000 IU day from sun exposure. This estimate of the contribution of sun exposure to total vitamin D input is used in Section 2, Table 6.

It is not possible to predict if serum concentrations of 25(OH)D in older adults in the US have changed since 2004. The factors that reduce 25(OH)D concentrations – larger proportion of older adults with obesity or high body mass, increased use of sun protection, and reduction in milk consumption – are countered by the increasing use of vitamin D supplementation. (Regan, 2010) NHANES data from the 2003-2006 report document that total intake of vitamin D from food and supplements has increased in the range of 125-175 IU since NHANES 1988-94. There is no data reporting how sun exposure and sunscreen use has changed in older adults in the past decade; these trends would counteract the small increase in vitamin D intake from food and supplements. Therefore, serum levels of 25(OH)D from NHANES (2000-2004) were used as the best estimate to develop recommendations for vitamin D input in older adults.

Table 4: Unadjusted serum 25(OH)D Concentration in Adults over 70 years of Age by Sex and Race/Ethnicity: NHANES 2000-2004

<table>
<thead>
<tr>
<th>PERCENT WITH SERUM 25(OH)D</th>
<th>&lt;15 ng/ml (≤37.5 nmol/L)</th>
<th>SE1</th>
<th>&lt;20 ng/ml (≤50 nmol/L)</th>
<th>SE1</th>
<th>&lt;30 ng/ml (≤75 nmol/L)</th>
<th>SE1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All races</td>
<td>11.4</td>
<td>1.4</td>
<td>26.6</td>
<td>1.9</td>
<td>78.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Non-Hispanic white†</td>
<td>9.0 (9.2)</td>
<td>1.5</td>
<td>23.0 (23.3)</td>
<td>2.1</td>
<td>75.7 (76.0)</td>
<td>1.8</td>
</tr>
<tr>
<td>Non-Hispanic black†</td>
<td>31.7 (31.4)</td>
<td>4.4</td>
<td>57.7 (57.5)</td>
<td>5.0</td>
<td>93.2 (93.2)</td>
<td>1.9</td>
</tr>
<tr>
<td>Mexican American†</td>
<td>17.6 (14.4)</td>
<td>3.3</td>
<td>45.4 (40.3)</td>
<td>7.1</td>
<td>88.4 (86.7)</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All races</td>
<td>16.5</td>
<td>1.3</td>
<td>33.6</td>
<td>1.8</td>
<td>76.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Non-Hispanic white†</td>
<td>13.2 (13.5)</td>
<td>1.5</td>
<td>28.5 (29.1)</td>
<td>2.0</td>
<td>73.3 (73.7)</td>
<td>1.7</td>
</tr>
<tr>
<td>Non-Hispanic black†</td>
<td>46.3 (46.4)</td>
<td>4.3</td>
<td>68.0 (68.1)</td>
<td>3.8</td>
<td>94.6 (94.6)</td>
<td>1.8</td>
</tr>
<tr>
<td>Mexican American†</td>
<td>32.8 (27.9)</td>
<td>4.8</td>
<td>55.2 (50.2)</td>
<td>6.5</td>
<td>88.8 (87.2)</td>
<td>3.2</td>
</tr>
</tbody>
</table>

1Standard error of percent
2Percent shown in parentheses are adjusted for season using logistic regression.

Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008;88(suppl):558S-64S. Adapted from Supplemental Table S2.
Adverse Musculoskeletal Outcomes Associated with Low Vitamin D Serum

Serum concentrations <30 ng/mL (<75 nmol/L) have been associated with balance problems (Pfeifer, 2000; Sambrook, 2004), impaired lower extremity function (Bischoff-Ferrari, 2004a), higher fall rates (Flicker, 2003; Faulkner, 2006), lower bone mineral density (BMD) (Bischoff-Ferrari, 2004b), and muscle weakness. (Holick, 2006a; Bischoff-Ferrari, 2006a; Bischoff, 2003)

Bischoff Ferrari and colleagues reviewed multiple studies (including RCTs, prospective and cross-sectional epidemiological studies, and evidence from dose-response relations and mechanistic data) regarding the association between serum 25(OH)D levels and several health conditions to create Figure 1, shown below. This figure illustrates the associations between serum 25(OH)D levels and BMD, fracture risk, time to walk 8 feet, and alveolar attachment loss in the jaw, a measure of periodontal disease. (Bischoff-Ferrari, 2006a) (The vitamin D relationship with colon cancer is not a focus of this Statement.)

Figure 1. Relationship between vitamin D levels and BMD, gait speed, alveolar attachment, and fractures.*

Falls are the leading cause of deaths and emergency department visits from unintentional injury among Americans >65 years of age. A third of people >65 years living in the community and up to half of nursing home residents fall each year. (Hornbrook, 1994; Hausdorff, 2001) According to the CDC, fall injuries among older adults resulted in 16,650 deaths and 1.8 million emergency department visits in the U.S. in 2006, a rate of five emergency department visits per year for every 100 people aged 65 and older. (www.cdc.gov/ncipc/wisgars; May 11, 2009)

*Solid lines relate to the left axis and dashed lines relate to the right axis. For bone mineral density (BMD), data from older white subjects are used. The 8-foot walk test was used he caption.disease (subjects >50 years). Colon cancer is not a focus of this document. (Bischoff-Ferrari HA, et al. Am J Clin Nutr 2006;84:18-28)
One of the most serious fall outcomes is hip fracture, an injury that often results in long-term functional impairment, early nursing home admission, and premature death. (Stevens, 2005) Over 95% of hip fractures are caused by falling, (Parkkari, 1991) usually from falling sideways onto the hip. (Hayes 1993) In 2009, there were 271,000 hospital admissions for hip fractures among people age 65 and older. (National Hospital Discharge Survey 2009) In 2010, after adjusting for inflation, the direct medical costs of falls among older adults were estimated to be $28.2 billion. (Stevens, 2006) The economic and societal impact of fall injuries, coupled with the aging of the American population, makes fall prevention a significant public health concern.

In the past ten years, evidence has been accumulating that enhancing dietary input and sun exposure with vitamin D supplements can significantly reduce the number of falls and their consequences. A recent meta-analysis supports these results, reviewing doses ranging from 400-800 IU/day cholecalciferol or 800-1,000 IU ergocalciferol with or without calcium. Higher doses were associated with greater benefit. (Bischoff-Ferrari, 2009a) The US Preventive Task Force (USPTF) on Preventing Falls identified vitamin D supplementation and exercise as the two specific interventions that reduce falls. The USPTF meta-analysis of vitamin D supplementation reported a reduction in falls of 17%. (Michael, 2010) Also, the Osteoporosis Canada Statement on Vitamin D in Health and Disease also concluded that, overall, vitamin D supplementation reduced falls by 17%. (Hanley, 2010)

Purpose of Vitamin D Consensus Statements

The goal of this publication is to develop clinical guidance regarding the use of vitamin D supplements (with or without calcium) in the prevention of falls and fractures in this older population. The information is essential for all health care providers, including primary care physicians, internists, geriatricians, nurse practitioners, and other clinicians and policy makers involved in providing health care for older adults.

Patients with advanced chronic renal failure stage IV - VI (CKD level 4-6; MDRD eGFR <30 ml/1.72 m2 min).

The workgroup focused on vitamin D recommendations and did not attempt to assess the recommendations for calcium intake. Practitioners are advised to follow the evolving literature on the safety and potential side effects of calcium supplementation in older adults.

Two guidelines have specifically commented on older adults at high risk for fractures. The American Medical Directors Association (AMDA) clinical guidelines for vitamin D supplementation to reduce falls and fractures in nursing home or institutionalized adults recommends supplementation with either vitamin D3 (one 50,000 IU capsule monthly), or 1,000 IU daily (www.AMDA.org). The Osteoporosis Canada statement recommends daily vitamin D intake of 800–2,000 IU for high-risk and older adults “with potential for consideration of higher doses.” (Hanley, 2010) The USPTF concluded that vitamin D was an effective single intervention for the prevention of falls. As noted above, the USPTF meta-analysis found a 17% reduction in falls with vitamin D supplementation. The median daily supplement in the studies included in their meta-analysis was 800 IU. (Michael, 2010)
**STATEMENT 1a:** Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU/day as well as calcium supplementation to community-dwelling older adults (>65 years) in order to reduce the risk of fractures and falls. *(Strong recommendation for fractures based on high quality of evidence from RCTs and meta-analyses; strong recommendation for falls based on moderate evidence from RCTs and a preponderance of benefit over harm)*

**STATEMENT 1b:** There are insufficient data at this time to support a recommendation for increased vitamin D supplementation without calcium for older persons residing in the community or in institutional settings. *(No recommendation is made due to very low availability and quality of evidence.)*

Oral vitamin D supplementation 400-800 IU/day or higher was associated with a relative risk of fracture of 0.80 for nonvertebral fractures and 0.82 for hip fractures in a recent large meta-analysis of 11 trials. *(Figure 2a)* *(Bischoff-Ferrari, 2009a)* Higher dosages were associated with a reduction in nonvertebral fractures of 29%, while rates of fractures in institutionalized older individuals decreased by 15%. **Figure 2b** illustrates a recalculation of the Bischoff-Ferrari meta-analysis of dose-response data by the IOM. The new meta-regression analysis found that the 95% confidence interval, 0.89-1.02 (P=0.13 per 100 IU/day difference in dose), resulted in a non-significant effect of increasing doses of vitamin D in the Bischoff-Ferrari meta-analysis. This workgroup disagrees with the IOM conclusions of nonsignificance, and presents its argument in the discussion following **Statement 3** below.

The workgroup believed that a clear statement for clinicians and older adults was needed. The Bischoff-Ferrari meta-analysis *(Figure 2a)* estimated the actual vitamin D supplement in each trial based on reported adherence with each trial protocol. The vitamin D input from supplements that subjects reported was considerably lower than the study protocol, reflecting variable subject adherence to protocols. Given the realities of variable patient adherence to clinician recommendations, and the wide safety margin of vitamin D supplements, the workgroup made the recommendation for vitamin D supplementation of at least 1,000 IU (average daily supplement) to reduce falls and fractures. The workgroup acknowledges that the statement recommends a dose greater than the evidence from the RCTs and meta-analyses would suggest. For a clinician determining what dose to recommend to older patients, **Statement 1** provides a safe minimum recommendation. It should be recognized that this minimum recommendation may not be adequate for seniors who have negligible dietary intakes and little or no unprotected skin exposure to sunlight. Statements 3 and 4 provide more detailed recommendations on how to achieve the recommended total vitamin D input from all sources.
Calcium: In most trials, calcium dosages ranged between 500-1200 mg/day, with 1000-1200 mg/day most commonly prescribed. The 2008 National Osteoporosis Foundation Guidelines recommend 1,200 mg/day of calcium for adults >50 years of age as well as 800-1,000 IU vitamin D (D2 or D3)/day. (www.NOFS.org, 2008; Dawson-Hughes, 2005) The meta-analysis of three trials of vitamin D without calcium (n=2,997 subjects) found no risk reduction in total fractures (OR 0.98, 95%CI 0.79-1.23,). (Cranney, 2007) A 2009 meta-analysis that analyzed vitamin D with and without calcium co-administration found that although vitamin D alone reduced the fracture rate, actual calcium input had not been clearly recorded in the studies analyzed, and should be assumed to have been in the range of 500 mg/day. (Bischoff-Ferrari, 2009a)

Evidence Profile

• Aggregate evidence quality for Statement 1a: high, based on meta-analyses, randomized controlled trials, and dosing trials in the target population; aggregate evidence quality for Statement 1b: low, based on lack of clearly recorded intake of calcium in the great majority of reports
• Benefit: reduction in falls and fractures in older individuals living in the community
• Risk of harm: no persuasive risk
• Cost: minimal
• Benefit-harm assessment: preponderance of benefit over harm
• Value judgments: none
• Role of patient preferences: minimal
• Policy level: strong recommendation

STATEMENT 2: Clinicians are strongly advised to recommend vitamin D supplementation of at least 1,000 IU/day with calcium to older adults residing in institutionalized settings in order to reduce the risk of fracture and falls.

(Strong recommendation for this intervention, based on a high level of evidence from meta-analyses and RCTs, and a strong preponderance of benefit over harm)

Meta-analyses and randomized controlled trials have reported reduced risk of falls and fractures in older adults residing in long-term care settings who receive vitamin D supplementation plus calcium. (Bischoff-Ferrari, 2009a, 2009b and 2005; Cranney, 2007, Izaks, 2007; Flicker, 2005; Chapuy, 2002; Chapuy, 1994) In these studies, higher doses (>600 mg) of vitamin D were associated with reduced fracture risk. As was found in community-dwelling older individuals, the benefits of vitamin D supplementation strongly exceeded risk. The cost to institutions is low, with minimal hidden loss of opportunity for other programs. Supplements can be administered monthly to further reduce the increase in nursing burden. To maximize uptake from all sources, long-term care facilities should offer diets high in vitamin D and calcium.
Fewer falls may result in better quality of life, fewer fractures and other injuries, thereby reducing costs to institutions. Delaying the loss of mobility and decline in activities of daily living that accompanies falls and fractures will reduce both the time and the burden of direct care in the institutional setting.

Evidence Profile
- Aggregate evidence quality: high, based on meta-analyses, RCTs, and dosing trials in the target population
- Benefit: reduction in falls and fractures in older individuals living in long-term care institutions
- Harm: none
- Cost: minimal
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: none
- Role of patient preferences: minimal
- Policy level: strong recommendation
**STATEMENT 3:** Clinicians should review older patients’ vitamin D intake from all sources (diet, supplements, and sunlight) and discuss strategies to achieve a total vitamin D input associated with fall and fracture prevention. *(Strong recommendation for this intervention, based on a moderate level of evidence from national epidemiologic studies, metabolic and pharmacokinetic studies, meta-analyses, RCTs, small dosing studies, toxicity reports and reviews, and a strong preponderance of benefit over harm)*

Clinicians are advised to ensure that older people receive sufficient vitamin D supplementation to achieve 25(OH)D serum levels of >30 ng/ml (75 nmol/L) in both community-residing older adults and those in long-term care. This recommendation is based on metabolic and pharmacokinetic studies (Heaney, 2003; Heaney, 2008; Ilahi, 2008), meta-analyses and multiple RCTs that showed reductions in falls, fractures, and bone loss. (Dawson-Hughes, 1997; Chapuy 1994; Chapuy 2002; Trivedi, 2003; Prince, 2008; Flicker, 2005; Broe, 2007; Bischoff, 2003; Bischoff- Ferrari, 2009; Pfeiffer, 2000; Pfeiffer, 2008; Izaks, 2007; Cranney, 2007; Kuchuk 2009) The workgroup concurs with the Osteoporosis Canada Statement (Hanley DA, 2010), the majority opinion of the International Osteoporosis Foundation (Dawson-Hughes, 2010) and the Endocrine Society (Holick, 2011) that 30 ng/ml (75 nmol/L) is the minimum desirable 25(OH)D level.

The workgroup relied on the AHRQ report (Cranney, 2007) which was commissioned to inform the IOM review to make recommendations for supplements and minimum 25(OH)D concentrations. Based on the AHRQ-Ottawa analysis, with text included in Text Box 1, the workgroup supported 30 ng/ml (75 nmol/L) 25(OH)D as the minimum serum level goal.

**Text Box 1:** AHRQ-Ottawa (Pg.169) Cranney, 2007

Combining the results from 13 randomized trials of vitamin D2/D3 +/- calcium resulted in a non-significant reduction in total fractures that persisted when only trials of higher quality was combined. When combining seven trials of vitamin D3 (400-800 IU) plus calcium, there was a reduction in the risk of total and hip fractures. However, in a subgroup analysis, this benefit was only evident when combining trials of institutionalized elderly subjects. One possible explanation is that the mean serum 25(OH)D level achieved in trials of institutionalized participants was higher than in the trials on community dwellers, and provided a greater level of vitamin D repletion. **The combined estimate from trials with higher end-of-study serum 25(OH)D concentrations (>30 ng/ml/75nmol/L) was consistent with a significant reduction in fractures.** This needs to be interpreted with caution given the variability in the 25(OH)D assays and incomplete assessment of vitamin D status in the fracture trials.
The workgroup conclusions differed from those of the IOM report, Dietary Reference Intakes for Calcium and Vitamin D, which stated that there was no benefit to 25(OH)D above 20 ng/ml (50 nmol/L) in older adults. As noted in Table 4, three-quarters of the US population >70 years of age have serum concentrations of 25(OH)D that are below the level recommended as desirable for preventing fractures (30 ng/ml or 75 nmol/L). More than one-quarter of American men and one-third of women >70 years have levels below 20 ng/ml (50 nmol/L). African American adults have greater risk of low levels of serum 25(OH)D. (Yetley, 2008) In studies that demonstrated a reduction in falls and fractures, the average concentrations of 25(OH)D achieved were consistently above 26 ng/mL (65 nmol/L). Figure 3 illustrates the reduction in falls with achieved serum 25(OH)D levels >24 ng/ml (60 nmol) (with higher estimated dosages delivered). Point estimates of risk reduction were greater in studies with the highest achieved 25(OH)D concentrations. (Bischoff-Ferrari, 2007; Bischoff-Ferrari, 2009a; Bischoff-Ferrari, 2009b; Izaks, 2007) In these RCTs, about half of the subjects in the vitamin D supplemented groups had 25(OH)D serum concentrations below the levels recommended for musculoskeletal health.

We have included figures from the IOM report which questioned the Bischoff-Ferrari meta-regression analysis for clinicians to review. (Figures 2b and 3) The IOM report dismissed the Bischoff-Ferrari analysis and performed an alternative meta-regression analysis. The IOM found that the 95% confidence interval for the slope of the dose/ fracture risk indicated non-significance (CI: 0.89-1.02; p=0.13) as did the slope of serum 25(OH)D level/ fracture risk effect (CI: 0.80-1.05, p=0.17). That is, there was no linear effect of either increasing supplementation or increasing serum response on fall rates. Following the IOM report, Bishoff-Ferrari published a letter to the editor with a revised figure, without the misleading regression line. (Bischoff Ferrari, 2011) The IOM committee responded with a rebuttal of the methods used in the Bischoff-Ferrari meta-analysis. (Gallagher 2011)

The workgroup did not question the meta-regression analysis performed by the IOM. A simple visual review of the individual trials, however, showed that 4 trials with serum levels of 24 ng/ml (60 nmol/L) or greater demonstrated reduced fall rates. The three trials with serum levels below 25 ng/ml (60 nmol/L) all had higher relative risk for falls.

The workgroup concluded that higher supplement doses and higher serum levels of 25(OH)D > 25 ng/ml (60 nmol/L) provide protection. The workgroup disagreed with the conclusion of the IOM that there was no evidence of benefit of serum levels >25 ng/ml (60 nmol/L). The workgroup also concluded that few clinicians looking at Figure 3 would conclude that a serum level of 20 ng/ml (50 nmol/L) would provide maximum protection for falls.

Clinicians who care for older adults, and who want to reduce the risk for falls and fractures in the next two or three years, must weigh the evidence available at this time (2012) and advise supplement and total intake that is safe and likely to be effective for their patients who may suffer a fracture before definitive studies are reported.

The target level recommended (>30 ng/ml; 75 nmol/L) is a physiologically conservative estimate. Outdoor summer workers typically achieve serum concentrations twice that level (Barger-Lux, 2002; Heaney, 2003). Also, given the fact that humans evolved in equatorial East Africa (wearing no clothes), values closer to 60 ng/ml (150 nmol/L) would likely have been the population norm. Moreover, meta-analyses of intervention studies show the bulk of the positive studies clustered around 25(OH)D levels of 24 ng/ml (60 nmol/L) or higher (Figure 2a). (Bischoff-Ferrari, 2009; Cranney, 2007)
Figure 2a: Meta-analysis of 11 trials of oral vitamin D supplementation (Bischoff-Ferrari, 2011).

Higher dosages were associated with a reduction in nonvertebral fractures of 29%. Fractures in institutionalized older individuals decreased by 15%.

Figure 2b: Relative risk of falls and vitamin D supplementation doses: correct meta-regressions with continuous predictors showing nonsignificance. ("Dietary Reference Intakes for Calcium and Vitamin D" A. Catharine Ross, et al. The National Academies Press Book. 2011; pg.4-28.)
Figure 3: Relative risk of falls and mean achieved serum 25(OH)D concentrations: correct meta-regressions with continuous predictors showing nonsignificance. ("Dietary Reference Intakes for Calcium and Vitamin D" A. Catharine Ross, et al. The National Academies Press Book. 2011; pg.4-29.)

Oral inputs needed to achieve 30 ng/ml (75 nmol/L) in the population of older adults carry no risk of toxicity. Assuming that the additional supplemental inputs recommended are adhered to, the highest increase realized will not exceed 60 ng/ml (150 nmol/L), which is still well below toxicity levels, even in the 5% of older adults with the highest baseline vitamin D levels who are already in the recommended range. There are no recorded cases of vitamin D intoxication at serum levels <200 ng/ml (500 nmol/L) or at oral inputs <30,000 IU/day. (Hathcock, 2007)

Values of 30 ng/ml (75 nmol/L) or higher are often labeled “sufficient” but it must be stressed that the boundary between sufficiency and insufficiency is not yet firmly fixed, and could move upwards as studies with higher achieved levels are performed and published.

While it is not difficult to identify and recommend a minimum 25(OH)D serum level consistent with musculoskeletal health, pinpointing a specific vitamin D supplementation dose for older adults is more problematic. The following are current barriers to specific dosage recommendations for clinicians treating older people:

1. The intervention trials that showed a reduction in falls and fractures provided fixed doses of vitamin D, but did not target or assess 25(OH)D serum concentrations. There is strong evidence that as the vitamin D dose, and the serum 25(OH)D concentrations, increase within intervention groups, the greater is the musculoskeletal protection (Figure 2a). However, there are no published
post-hoc analyses to ascertain whether subjects that achieved serum 25(OH)D levels >30 ng/ml (75 nmol/L) had reduced fall and fracture rates. No trials have been reported with falls or injury as outcomes, using vitamin D dosages of >2,000 IU/day. In contrast, standard drug trials are designed to administer specific drug dosages that will produce a desired physiological target, at which point clinical outcomes of this change can be assessed. Although it is plausible that maximum protection from falls and fractures can be attained by raising vitamin D input to achieve 25(OH)D serum levels >30 ng/ml (75 nmol/L) in every older adult, this remains to be confirmed.

2. Vitamin D supplementation produces a variability in individual serum 25(OH)D response that has not yet been explained. At this time, it is not possible to reliably predict the exact vitamin D supplement dosage that will achieve a 25(OH)D level above 30 ng/ml (75 nmol/L) in an individual patient. A recent review sponsored by the AHRQ (Chung, 2009) assessing the dose-response to vitamin D supplementation in adults determined that the heterogeneity among studies did not allow for a meta-regression analysis to determine a dose-response to vitamin D. (Figure 4).

![Figure 4: AHRQ dosing response to vitamin D: Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs. Reprinted with permission from Agency for Healthcare Research and Quality Evidence Report/Technology Assessment No. 183. Vitamin D and Calcium: A Systematic Review of Health Outcomes. (AHRQ Publication No. 09-E015). Fig. 24 (lower panel), p. 293. Reference (Chung, 2009).](image-url)

Each empty circle represents a single study. The area of the circle is equal to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D. Source: Agency for Healthcare Research and Quality (AHRQ) Publication No. 09-E015, August 2009. Figure 23, Page 292. Reference (Chung, 2009)
3. Two analyses found evidence of a diminishing response in 25(OH)D levels to increasing supplementation doses. (Aloia, 2008; IOM 2010) Vitamin D levels rise by approximately 1.0-1.6 ng/ml (2.5-4.0 nmol/L) for every 100 IU/day dosage increase up to a daily supplement of about 1000 IU vitamin D. The IOM report and Aloia both reported a curvilinear 25(OH)D dose response to increasing supplement doses. This curvilinear response provides a large safety margin with higher supplement doses.

While relatively low doses of vitamin D supplementation may be sufficient to boost very low serum 25(OH)D levels to 50 nmol/L, higher doses will be needed to reach serum levels >30 ng/ml.

![Figure 5. Predicted linear serum 25(OH)D response to total vitamin D intake. ("Dietary Reference Intakes for Calcium and Vitamin D" A. Catharine Ross, et al. The National Academies Press Book. 2011; pg.5-32.)](image)

For older adults >71 years: achieved 25(OH)D = 10.9 ln (total vitamin D intake), which explains 77.5 percent of the within-study variability and 92.2 percent of the between-study variability. Predicted CIs were \( y = 7.7 \ln \) (log natural) of total vitamin D intake for lower limit and \( y = 14.2 \ln \) of total vitamin D intake for upper limit. Source: IOM Report 2010 Figure 5-3.

4. Estimates of vitamin D supplement dose needed to achieve levels >30 ng/ml (75 nmol/L) in >95% of the older population range from 2,000 IU in one study based on extrapolations from lower doses (Cashman, 2008) to 4,000-5,000 IU/day in other reports using the actual doses. (Vieth, 2009; Aloia, 2008, IOM, 2010)
5. Two studies of older adults measured serum response to 2000 IU and 5000 IU daily doses. Bischoff-Ferrari supplemented older patients following a hip fracture with either 800 IU or 2000 IU daily. The mean body mass of the subjects was 62.2 kg. After one year, the 2,000 IU supplement group increased 25(OH)D levels from 13.1 to 44.7 ng/ml (32.8 to 111.7 nmol/L, and 93% of the group achieved 25(OH)D levels of 30 ng/ml (75 nmol/L). The 800 IU supplement group increased mean 25(OH)D levels from 12 ng/ml (30 nmol/L) to 35.4 ng/ml (88.5 nmol/L), and 70% of the 2000 IU group achieved 25(OH)D levels of 30 ng/ml (75 nmol/L). (Bischoff-Ferrari, 2010)

A single arm one-year trial administered vitamin D to nursing home residents by providing a daily bread roll that contained 5,000 IU vitamin D3 and 1250 mg of calcium. Mean body mass was 74.8 kg. Serum levels increased from a baseline of 28.5 nmol/L (11.4 ng/ml) to 125.6 nmol/L (50.2 ng/ml), and 92% of subjects achieved 25(OH)D levels of 75 nmol/L (30 ng/ml). (Mocanu, 2009)

A third trial in older adults tested the serum response to a monthly dose of 50,000 IU D3 (1,666 IU daily average intake). (Bacon, 2009) This 4-arm intervention trial included 2 arms with a 500,000 IU loading dose. (Figure 6) Note that Statement 5 explicitly recommends against a loading dose. The graph shown in Figure 6 illustrates the results divided into two groups referring to subjects with baseline 25(OH)D above and below 20 ng/ml (50 nmol/L). After five months of intervention, subjects with a baseline level below 20 ng/ml (50 nmol/L) achieved an average serum 25(OH)D level of approximately 30 ng/ml (75 nmol/L). In subjects with baseline 25(OH)D above 20 ng/ml (50 nmol/L), the intervention group serum 25(OH)D level averaged about 36 ng/ml (90 nmol/L). (Bacon 2009)

Figure 6. Effects of a monthly dose of 50,000 IU vitamin D3, with and without a loading dose, in older adults with baseline serum 25(OH)D levels above or below 20 ng/ml (50 nmol/L) (“High-dose oral vitamin D3 supplementation in the elderly”. Bacon CJ, et al. Osteoporos Int (2009) 20:1407–1415.)

The majority of the workgroup, in reviewing the data, concluded that a 4,000 IU daily input from all sources would be required to achieve 25(OH)D levels 30 ng/ml (75 nmol/L)
**TOTAL VITAMIN D INTAKE (AVERAGE DAILY IU)- EXCLUDING SUN EXPOSURE**

<table>
<thead>
<tr>
<th>Predicted 25(OH)D level (nmol/L)</th>
<th>1,000</th>
<th>1,500</th>
<th>2,000</th>
<th>2,500</th>
<th>3,000</th>
<th>3,500</th>
<th>4,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 25(OH)D level</td>
<td>75</td>
<td>80</td>
<td>83</td>
<td>85</td>
<td>87</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>Lowest (5th) percentile</td>
<td>53</td>
<td>56</td>
<td>59</td>
<td>60</td>
<td>62</td>
<td>63</td>
<td>64</td>
</tr>
<tr>
<td>Highest (95th) percentile</td>
<td>98</td>
<td>104</td>
<td>108</td>
<td>111</td>
<td>114</td>
<td>116</td>
<td>118</td>
</tr>
<tr>
<td>Percent of population achieving</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>level &gt; 75 nmol/L 25(OH)D</td>
<td>51%</td>
<td>65%</td>
<td>74%</td>
<td>79%</td>
<td>83%</td>
<td>85%</td>
<td>92%</td>
</tr>
</tbody>
</table>

**Table 5: Estimated 25(OH)D Concentrations in Adults >70 years, Based on Estimate of Average Daily Vitamin D Intake, using the IOM Dose-Response Equation.**

Adapted from IOM calculation of dose response for adults >70 years, as detailed in the legend to Figure 5. (IOM, 2011 Figure 5-3) add citation

6. Few older adults receive adequate sun exposure to achieve recommended serum vitamin D concentrations, and sun exposure is commonly overestimated. Unprotected skin exposure to the sun is explicitly not recommended as a strategy to achieve recommended vitamin D levels (see American Academy of Dermatology Statement; www.aad.org).

7. Darker skin pigmentation and high body mass are associated with lower levels of serum 25(OH)D. Obese adults and adults with high body mass have 25(OH)D levels approximately 5 ng/ml (12.5 nmol/L) lower than non-obese adults. Also, the serum response to vitamin D is about 20% lower in high body mass and obese adults, suggesting that replacement should be about 20% greater in these individuals. (Snijder MD, 2005, Blum M, 2008)

The workgroup agreed on two strategies to ensure that 92% of older adults would achieve serum 25(OH)D levels of >30 ng/ml (75 nmol/L):

1. Recommend an average daily input from all sources of 4,000 IU for all older adults. This level of vitamin D input should result in about 92% of older adults in the US achieving target 25(OH)D levels regardless of skin pigmentation, obesity or sun exposure. This total daily input is at the IOM updated UL and well below the risk for toxicity.

2. Individualize patient supplementation levels with adjustments for sun exposure, skin pigmentation, and high body mass or obesity.

The clear majority of the workgroup recommended strategy 1. This message is simple, and easy to remember and implement. Some workgroup members, however, felt that there was still insufficient evidence of protection on the individual level to recommend this specific input in all older adults.

The following principles support these recommendations:

- The current state of knowledge regarding the benefits and safety of vitamin D encourage the adoption of higher total vitamin D input in older adults.
The recommended dietary allowance (RDA) of 800 IU for older adults was based on the IOM determination of 20 ng/ml (50 nmol/L) as the minimum serum level for 25(OH)D. The workgroup concluded that the minimum for 25(OH)D should be 30 ng/ml (75 nmol/L).

The tolerable upper intake level for vitamin D supplementation (4,000 IU/day) is considered conservative by the IOM and most experts in the field of musculoskeletal health. The tolerable upper intake level should not limit clinicians caring for older adults.

More than three-quarters of older adults should increase their current input of vitamin D.

Table 6 provides suggestions for clinicians who have chosen to individualize vitamin D supplementation plans for their patients. The adjustments in the table are drawn from cross-sectional and intervention studies, and should be considered rough estimates. Refer to Table 1 for vitamin D2 and D3 levels in various foods, supplements, and pharmaceuticals.

<p>| CLINICAL REVIEW |</p>
<table>
<thead>
<tr>
<th>Baseline Supplement Needs</th>
<th>ADJUSTMENT</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting supplement dose</td>
<td>3000 IU/day</td>
<td>3000 IU</td>
</tr>
<tr>
<td>Food input (see TABLE 1)</td>
<td>Subtract estimated input of vitamin D from food</td>
<td>- IU</td>
</tr>
<tr>
<td>For most older adults, food input is small. Average input from food in US adults = 150-225 IU/day</td>
<td>Subtract estimated input of vitamin D from food</td>
<td>- IU</td>
</tr>
<tr>
<td>Daily multivitamins /or calcium/vitamin tablets</td>
<td>Subtract total daily vitamin D units</td>
<td>- IU</td>
</tr>
<tr>
<td>Unprotected sun exposure</td>
<td>During summer months only: Subtract 500-1000 IU/day with regular unprotected sun exposure during summer months</td>
<td>- IU</td>
</tr>
<tr>
<td>NOT recommended as a strategy: If exposure is uncertain, do not adjust supplement dose. Do not adjust for institutionalized residents Adjust dose only if individual has unprotected sun exposure (in bathing suit or shorts and short sleeved shirt) for 15 minutes in sun several days per week.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity or high body mass</td>
<td>Add 500 -800 IU/day</td>
<td></td>
</tr>
<tr>
<td>Obesity or high body mass (&gt;90 kg) is associated with lower vitamin D levels and ~20% lower 25(OH)D response to supplementation.</td>
<td>Add 500 -800 IU/day</td>
<td></td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>Add 300-600 IU/day</td>
<td></td>
</tr>
<tr>
<td>Mexican Americans and African Americans have lower vitamin D levels than non-Hispanic whites.</td>
<td>Add 300-600 IU/day</td>
<td></td>
</tr>
<tr>
<td>Total Additional Supplement Dose per Day</td>
<td>Do not exceed 4,000 IU/day except in cases of special populations (see next page)</td>
<td></td>
</tr>
</tbody>
</table>
SPECIAL POPULATIONS

For special populations, serum 25(OH)D levels may be useful in helping to verify adjusted dose

<table>
<thead>
<tr>
<th>Medications</th>
<th>Increase dose according to serum 25(OH)D</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Agents that bind vitamin D in the gut, e.g., cholestyramine</td>
<td></td>
</tr>
<tr>
<td>• Agents that accelerate the breakdown of vitamin D (e.g., inducers of the cytochrome P450 pathway such as phenytoin and phenobarbital)</td>
<td></td>
</tr>
<tr>
<td>Malabsorption syndromes</td>
<td></td>
</tr>
</tbody>
</table>

*Vitamin D supplements should not be taken at the same time as high fiber cereals (oatmeal, bran flakes) or fiber stool softeners since these bind to the vitamin. Absorption is enhanced by taking vitamin D supplements with meals. Patients with advanced renal failure and sarcoidosis are not covered in this guideline.

† This sun exposure adjustment is explicitly not a recommendation for extended, unprotected sun exposure as a strategy to achieve adequate vitamin D serum levels. Current guidelines for prevention of skin cancer and aging of the skin should be the determining factor in advice given to the patient.

Evidence Profile

• Aggregate evidence quality: moderate, based on national epidemiologic reports, meta-analyses of RCTs, and small to medium-sized dosing trials in the target population

• Benefit: reduction in falls and fractures in older individuals living in the community or in long-term settings

• Risk of harm: no persuasive risk

• Cost: minimal

• Benefit-harm assessment: preponderance of benefit over harm

• Value judgments: none

• Role of patient preferences: choice of frequency of supplementation, serum test to assess response to supplementation

• Policy level: recommendation
**STATEMENT 4a:** Routine laboratory testing for 25(OH)D serum concentrations before supplementation begins is not necessary.  
(Strong recommendation based on high quality of evidence from pharmacokinetic and metabolic studies)

Testing for vitamin D status is recommended for diagnostic purposes only in specific clinical situations, e.g., failure to thrive, malabsorption syndromes, presence of osteoporosis accompanied by failure to respond to bone anti-resorptive agents, and treatment with specific medications (see below). A serum calcium level should be reviewed before increasing vitamin D input, to assure the patient is not hypercalcemic.

Most older adults will have suboptimal vitamin D levels, and will benefit from additional supplementation. In the average patient, there is no need to “clinically manage” vitamin D by repeated laboratory testing, as vitamin D intake at or below 4,000 IU per day is both safe and effective in 95% of the population (see text under Statement 5). This recommendation is based on the cost and patient burden associated with testing with little additional benefit to the patient, and underscores the cost-effectiveness of higher doses.

**STATEMENT 4b:** It is not necessary for clinicians to routinely monitor 25(OH)D for safety or efficacy when supplementation is within the recommended limits.  
(Strong recommendation based on high quality of evidence from pharmacokinetic and metabolic studies)

In patients with total vitamin D (intake from all sources) of 4,000 IU/day, clinicians do not need laboratory assessments to determine if target concentrations of 25(OH)D have been achieved, unless problems with adherence are suspected. Increasing vitamin D input from all sources to 4,000 IU daily should achieve a 25(OH)D serum level of 30 ng/ml (75 nmol/L) in about 92% of the population. Projected levels of the top 5% of patients on 4000 IU total intake are 47 ng/mL (118 nmol/L). These levels are well below the lowest levels associated with toxicity (60 ng/mL (150 nmol/L)).

**Rationale for serum testing in certain cases**

For patients or practitioners who choose to recommend lower total intake, a serum level can either assure the patient and the practitioner that their current total intake is sufficient or that the patient should increase their total intake.

Monitoring vitamin D status may be advisable in situations where vitamin D metabolism may be altered, e.g., concomitant phenytoin use or in the setting of malabsorption (Gloth, 1991) or high body mass (greater than 90 kg).
**Monitoring should be considered in the following settings:**

1) Patients taking medications which either bind vitamin D in the gut or accelerate the breakdown of vitamin D (e.g. cholestyramine; inducers of the cytochrome P450 pathway such as phenytoin and phenobarbital)

2) Obesity: BMI >30 kg/m2 or body mass >90 kg*

3) Malabsorption syndromes

4) Patients who limit their vitamin D intake from all sources below recommended intake.

* (based on dose response findings by Blum 2008)

If vitamin D monitoring is considered necessary, 25(OH)D measurement is the preferred choice. PTH and 1,25(OH)2D have short half-lives and are sensitive to physiological perturbations (e.g., a recent calcium meal); these can create confusion rather than clarity. However, results of laboratory assessments of 25(OH)D serum concentrations may be inconsistent due to variation from one laboratory to another, or because of different types of assays (immunoassay, protein binding-based methods, liquid chromatography/mass spectrometry). (Orwoll, 2009; Binkley, 2004; Carter, 2004; Lips, 1999)

If there is a concern about the safety of vitamin D supplementation or treatment, the key diagnostic indicators are the circulating calcium concentration and urine calcium excretion.

Based on all available valid toxicity studies, an input of 4,000 IU/day of vitamin D from all sources is considerably below the proposed upper tolerable level of 10,000 IU/day. (Hathcock, 2007)

**STATEMENT 4c:** If clinicians choose to monitor 25(OH)D, they are advised to test after 4 months of vitamin D3 supplementation to confirm that appropriate levels have been achieved. (Strong recommendation based on high quality of evidence from pharmacokinetic and metabolic studies)

Based on pharmacokinetic data, a steady state is achieved only after 4-6 months (approximately 3-5 half-lives) of a stable dose of vitamin D3. (Bacon 2009, Ilahi M 2008) Measurements obtained before a steady state is achieved may result in unnecessary and erroneous adjustments in dosing. For vitamin D supplement dosing intervals of two weeks or more, samples should be obtained at around the midpoint between doses. This will give the best estimate of the average concentration between doses. (Heaney, 2003)

There is a moderate public health cost in unnecessary assessment of vitamin D serum concentrations. The older patients most likely to benefit from testing are those who may need higher vitamin D input from all sources, e.g., individuals with no direct sun exposure, high body mass, dark skin or obesity.
Evidence Profile

- Aggregate evidence quality: high, based on pharmacokinetic and metabolic studies
- Benefit: reduced public health and patient cost due to minimization of testing and use of most appropriate methods
- Harm: none
- Cost: laboratory serum test costs may exceed $200
- Benefit-harm assessment: preponderance of benefit over harm
- Value judgments: none
- Role of patient preferences: minimal
- Policy level: strong recommendation

STATEMENT 5: Due to the different pharmacokinetic profiles of vitamin D2 and vitamin D3, clinicians should recommend vitamin D3 supplementation intervals of 4 months or less, and vitamin D2 supplementation intervals of 14 days or less.

Clinicians should not recommend large bolus doses of vitamin D2 or D3 (300,000 IU or higher). (Strong recommendation for vitamin D3 dosing, based on high quality of evidence; vitamin D2, and annual dose recommendation by workgroup consensus, due to low quality of evidence)

The pharmacokinetic properties of vitamins D2 and D3 differ, with more consistent and higher serum concentrations of 25(OH)D associated with vitamin D3 supplementation. (Armas, 2004) Because longer intervals between doses of vitamin D2 will result in large fluctuations of serum 25(OH)D concentrations, the dosing interval with vitamin D2 should not exceed 14 days.

The long half-life of vitamin D3 (22 to 60 days) permits intermittent dosing at intervals of up to 4 months. No study has directly compared the effect of D2 versus D3 dosing (every 4 months) on falls or fracture. However, in a community study, D3 supplements of 100,000 IU every 4 months were found to reduce fractures compared to placebo. (Trivedi, 2003) In a study of institutionalized older adults, a D2 supplement of 100,000 IU every 4 months had no impact on falls. (Lyons, 2007)

Evidence against an annual dose of either D2 or D3 in autumn or winter

Two large community-based RCTs assessed the impact of annual doses of vitamin D compared to placebo. The D2 trial enrolled more than 9400 subjects and tested an annual injection of 300,000 IU vitamin D2 in autumn for a period of 3 years. (Smith 2007) The D3 trial enrolled more than 2200 subjects and tested an annual oral dose of 500,000 IU vitamin D3 in autumn or winter for 3-5 years. (Sanders 2010) Both trials reported increased fracture rates in the vitamin D supplement group.
While the evidence against annual supplements is limited, the finding of harm in two large community-based studies must be taken seriously. While waiting for clarification of a mechanism to explain this paradox, clinicians should recommend dosing frequencies that have shown benefit, not harm.

**D2 Supplementation**

Although a significant 25(OH)D response is seen within days of a monthly dose of vitamin D2 supplementation, the response declines to baseline at 14 days. (Armas, 2004) Further pharmacokinetic studies will provide greater confidence in dosing intervals for vitamin D2.

**D3 Supplementation**

Vitamin D3 is available as non-prescription, over-the-counter products in dosages of 400, 800, 1,000, 2,000, 5,000, and 10,000 IU. A 50,000 IU formulation is currently available on the internet. Vitamin D2 is available in a prescription form of 50,000 IU. This high-dose formulation of D2 is more expensive but may be more readily available at retail pharmacies. Vitamin D is also available in multivitamin preparations, in calcium supplements, in foods fortified with the vitamin, and in cod liver oil. However, practitioners should be aware that use of the prescription product at 50,000 IU vitamin D2 per dose, such as Drisdol®, is not approved by the FDA as means to influence serum 25(OH)D levels, and that this is an “off-label use” of the drug.

To achieve adequate supplemental doses of vitamin D through cod liver oil, the patient would be exposed to levels of vitamin A associated with increased risks of osteoporosis, hip fracture and malignancies. (Feskanich, 2002)

Administration of vitamin D in combination pills containing calcium supplements is not recommended as a primary strategy for achieving adequate vitamin D intake. Combination pills require dosing 2 or 3 times daily, with a maximum daily vitamin D intake of 600 to 800 IU. In a large clinical trial, combination pills had lower adherence and resulted in lower vitamin D intake compared to the same dose of vitamin D administered alone. (Grant, 2005) The real or attributed adverse gastrointestinal effects of calcium supplements, specifically constipation, may result in non-adherence and consequently inadequate vitamin D supplementation. Therefore, combination calcium plus vitamin D pills are not recommended as a primary source of vitamin D intake, but can be included in calculating average intake.

Vitamin D is a sterol with properties similar to cholesterol. For this reason, vitamin D should not be given with compounds or foods that are known to bind and prevent the absorption of cholesterol, such as steroid binding resins (cholestyramine), high fiber cereals (oatmeal and bran flakes), and fiber stool softeners. Absorption is thought to be enhanced by taking vitamin D with meals containing oils.

Vitamin D gel capsules contain various vegetable oils acting as a vehicle. Some patients are allergic to these oils, and react with symptoms such as diarrhea or, occasionally, rash. This allergic reaction may necessitate a switch to a different product formulation. (Updates regarding available formulations are published at the American Geriatrics Society website: www.americangeriatrics.org.)

Vegetarians who choose not to use vitamin D3 because of its animal derivation (from lanolin, the oil obtained from sheep’s wool) should be advised to take vitamin D2. People who follow kosher dietary law are permitted to consume either vitamin D3 or D2. Vitamin D3 is considered halal for those following Islamic dietary law if the source is guaranteed to be derived from wool sheared from live sheep.
Evidence Profile

• Aggregate evidence quality: high for vitamin D3 and low for vitamin D2, based on pharmacokinetic and metabolic studies
• Benefit: enhanced compliance and optimal serum 25(OH)D response
• Risk of harm: none
• Cost: none
• Benefit-harm assessment: preponderance of benefit over harm
• Value judgments: dietary and religious tenets
• Role of patient preferences: high
• Policy level: strong recommendation

STATEMENT 6: Because vitamin D3 supplements given daily, weekly, or monthly are equally effective at achieving target serum concentrations, physicians should discuss with their patients which supplementation schedule will achieve the best adherence. *(Strong recommendation based on a high level of evidence from meta-analyses, RCTs, and dosing studies, and a strong preponderance of benefit over harm)*

Each patient's preference as to the frequency of supplementation should be reviewed to increase adherence to the supplementation plan of the older individual.

Since the long half-life of vitamin D3 allows from one day to 4 months between supplements, clinicians should discuss dosing options with their older patients to help them maximize adherence and achieve the 25(OH)D levels desirable for musculoskeletal health. *(Ish-Shalom, 2008; Reginster, 2006; Kruk, 2006)*

Combination calcium plus vitamin D formulations are advantageous if patients are compliant with calcium supplementation, and will usually result in an average intake of 400 to 800 IU of vitamin D per day, assuming 100% adherence. However, one large study found that compliance was about 10% lower when vitamin D supplementation was combined with calcium in the same tablet, because of possible gastrointestinal side effects from this form of calcium supplements. *(Grant 2005)* Clinicians should discuss calcium compliance issues with patients before prescribing combination pills of calcium plus vitamin D. In some cases, the combination of a monthly high dose capsule and a combination calcium/vitamin D pill may be an effective strategy.

Adherence to vitamin D supplementation may be better if patients are not required to take daily supplements, according to investigations of patient adherence to medications in general. *(Kruk, 2006; Rossini 2005)* Also, available evidence indicates that oral administration of vitamin D is more efficient than injected supplements. *(Vieth, 1999; Leventis, 2009; Diamond, 2005)*
Evidence Profile

• Aggregate evidence quality: high, based on meta-analyses, RCTs, and dosing trials in the target population

• Benefit: better compliance with vitamin D supplementation for older individuals living in the community or in long-term settings

• Risk of harm: none

• Cost: minimal

• Benefit-harm assessment: preponderance of benefit over harm

• Value judgments: none

• Role of patient preferences: high

• Policy level: strong recommendation

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Peer Review

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Dr. Birge serves as a paid consultant to Amgen. He is also a member of the Speakers Bureau for Wyeth, Merck, and Novartis. Dr. Gloth serves as a paid consultant to Novartis, Wyeth, Endo Pharmaceuticals, and the Food and Drug Administration. He is also a speaker for Roche, Novartis, Glaxo-Smith-Kline, Wyeth, Merck, Endo Pharmaceuticals. Dr. Heaney serves as a paid consultant to the National Dairy Council and Conagra. He has also received a grant from Innophos. Dr. Heaney is a member of the Speakers Bureau for Amgen and Dairy Councils. Dr. Hollis serves as a paid consultant to DiaSorin. Dr. Kenny has received a research grant from Pfizer. Dr. Kiel serves as a paid consultant to Novartis, Merck, Amgen, GSK, Roche, Wyeth, Eli Lilly, Procter & Gamble, and Philips Lifeline. He has also received grants from Merck, Novartis, Amgen, Pfizer, and Hologic. Dr. Schneider serves as a paid consultant to Amgen, Eli Lilly, and Procter and Gamble; and member of the Speakers Bureau for Amgen and Eli Lilly. Dr. Vieth serves as a paid consultant to DSM Nutritional and DiaSorin. He is also a member of the Speakers Bureau for Merck and Company, Stieffel, Carlson Laboratories, and DiaSorin. And is related to an employee of Ddrops Company, Canada, and receives grant support from the Dairy Farmers of Canada.
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NOTE: This Chung reference is also known as AHRQ Tufts

NOTE: This Cranney reference is also known as the AHRQ-Ottawa report


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