

# Vitamin D and Fracture Reduction: An Evaluation of the Existing Research

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## Abstract

This article re-evaluates the literature on vitamin D and fracture reduction, highlighting the relevance of new understandings for fracture prevention. A new set of science-based research guidelines for clinical trials on vitamin D and fracture is proposed. The existing clinical trials on vitamin D and fracture are analyzed, focusing on studies that most closely meet the proposed guidelines. An estimation of the true fracture-reduction potential of therapeutic-level vitamin D supplementation is offered. The analysis outlined in this article leads to a series of striking conclusions. First, most of the available clinical trials and meta-analyses of vitamin D and fracture underestimate the true fracture reduction potential of vitamin D. Second, achievement of vitamin D serum sufficiency levels (now set in the United States, Europe, and many other places at a minimum of 32 ng/mL) could provide for a 50- to 60-percent fracture reduction. And third, providing for vitamin D sufficiency is the simplest, most life-supporting, and most cost effective means of significantly reducing the incidence of osteoporotic fractures worldwide. Given the urgent need, the Osteoporosis Education Project (OEP) has initiated a call for universal vitamin D repletion as the primary basis for osteoporotic fracture prevention worldwide. (*Altern Med Rev* 2008;13(1):21-33)

## Introduction

During 2006-2007, the Osteoporosis Education Project (OEP) undertook a comprehensive analysis of new scientific literature on vitamin D, with the goal of reassessing and rethinking the role of vitamin D in fracture prevention. The OEP concludes that the achievement of universal vitamin D sufficiency is the

foundation for, and the first prerequisite of, osteoporotic fracture prevention. This article summarizes the research findings that vitamin D is a more powerful fracture-prevention agent than previously suggested.

In the United States and other industrialized countries, fractures contribute significantly to the morbidity and mortality of older persons. Each year in the United States, more than 1.5 million low-trauma osteoporotic fractures occur, including more than 300,000 hip fractures. Hip fractures increase dramatically with age, and by age 90 an estimated one in three women and one in six men will have sustained a hip fracture.

The current aging of the world's populations is associated with a projected increase in fragility fractures. In 1990 it is estimated 1.66 million hip fractures occurred worldwide. The worldwide annual number is expected to rise to 6.26 million by 2050. Likewise, the economic impact of low-trauma fractures is significant and grows annually. For example, in the United States direct health-care expenditures in 2002 for osteoporotic fractures ranged from \$12.2-17.9 billion.<sup>1</sup>

There is widespread agreement among physicians and public health officials of the need for safe, cost-effective fracture-reduction strategies. The fracture-reduction research effort, however, is unbalanced. Other than studies on calcium supplementation, lifestyle and nutritional approaches have been largely overlooked – measures the U.S. Surgeon General declared should comprise the first step in fracture prevention.<sup>1</sup> The vast majority of scientific attention and research funding has been directed at the study of osteoporotic

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medications, which are costly, often associated with significant adverse side effects, and of varied efficacy.

Recent meta-analyses report “good evidence” that several pharmaceutical agents (alendronate, etidronate, ibandronate, risedronate, calcitonin, parathyroid hormone, and raloxifene) prevent vertebral fractures among high-risk populations compared with placebo (with reported reduction effects from 36-48 percent).<sup>2,3</sup> “Good evidence” for non-vertebral fracture reduction among high-risk populations is found only for alendronate and risedronate (reductions of 45-49 percent and 27 percent, respectively).<sup>3,4</sup> A meta-analysis of the stricter “intent-to-treat” studies, however, yields much lower risk-reduction estimates.<sup>5</sup> There is limited data whether these medications reduce the risk for fracture among low-risk populations, with some suggestion they may even increase fracture risk in these populations.<sup>2</sup>

## Current Scientific Knowledge about Vitamin D and its Relevance to the Study of Vitamin D and Fracture Prevention

### *The Vitamin D Paradigm Shift*

Extensive research over the past 20 years documents a remarkable “paradigm shift” in understanding of vitamin D. This new knowledge about vitamin D has significant implications for the study of vitamin D and fracture prevention.

It is now generally recognized that the body utilizes much more vitamin D than previously thought. In 2003, Dr. Robert Heaney, noted bone health researcher, established that healthy individuals utilize approximately 3,000-4,000 IU of vitamin D daily.<sup>6</sup>

Despite sun-phobia engendered by fear of skin cancer, the vast majority of vitamin D is obtained from sunlight exposure. For most individuals, 80-90 percent of vitamin D requirement is cutaneously produced from sunlight.<sup>6</sup> Furthermore, sun exposure results in production of much more vitamin D than previously thought. Studies show that bathing suit exposure during summer, until skin just begins to turn pink, results in skin production of 10,000-50,000 IU of cholecalciferol.<sup>7</sup>

Unlike other vitamins, vitamin D is a hormone precursor. It is known that vitamin D is produced in

the skin and hydroxylated in the liver to produce 25-hydroxyvitamin D (25(OH)D), and further hydroxylated in the kidney to form the active hormone, 1,25-dihydroxyvitamin D<sub>3</sub> (1,25(OH)<sub>2</sub>D). In addition, it is now known vitamin D can be converted into the active hormone by many tissues in addition to the kidney, and this active vitamin D hormone (1,25(OH)<sub>2</sub>D) plays many more roles within the human body than previously known. Vitamin D has long been known to control calcium and phosphorus absorption. It is also now known to be important in the control of cell proliferation, the promotion of cell differentiation, and the down-regulation of hyperproliferative cell growth, all of which protect from cancers. Vitamin D also enhances immunity, protects against inflammation, is cardio-protective, and is preventative of autoimmune conditions.<sup>8-11</sup>

### *New Insights into Vitamin D and Bone Health*

In regard to bone health, there are many manifestations of vitamin D deficiency/insufficiency beyond rickets, the classic disease of vitamin D deficiency. Sub-optimal calcium absorption, secondary hyperparathyroidism, increased bone resorption, decreased muscle strength, and increased risk of falling can be vitamin D deficiency/insufficiency disorders that increase fracture risk.

Research has quantified the blood level of vitamin D required for normalization of parathyroid hormone and optimum calcium absorption. Low vitamin D leads to decreased calcium absorption and lower blood calcium levels, which in turn causes an increase in parathyroid hormone. Rising parathyroid hormone stimulates bone breakdown to liberate calcium for transfer into the blood. This response to low vitamin D stabilizes blood calcium at the expense of bone. Studies in both the United States and Europe have found serum 25(OH)D levels of 32 ng/mL are needed to normalize parathyroid hormone and optimize calcium absorption.<sup>12-16</sup>

The amount of vitamin D necessary for normalization of parathyroid hormone and optimization of intestinal calcium absorption has also been quantified. Heaney demonstrated calcium absorption performance was 65-percent higher at serum vitamin D levels averaging 34 ng/mL than with lower vitamin D levels.

In a vitamin D-deficient state the small intestine absorbs no more than 10-15 percent of dietary calcium; whereas, in a vitamin D-sufficient state, 30-40 percent of ingested calcium is absorbed.<sup>6</sup> It should also be noted that researchers have documented cases where 48 ng/mL vitamin D was unable to normalize bone-damaging high parathyroid hormone levels.<sup>17</sup>

Research has quantified the blood level of vitamin D required for normalization of muscle strength and coordination. Vitamin D inadequacy leads to impaired musculoskeletal functioning, poor coordination, and increased risk of falling. Lower extremity neuromuscular function improves as serum 25(OH)D increases, up to at least the therapeutic range achieved in the more successful trials.<sup>12,18,19</sup> Clinical trials reaching sufficiency levels show a rapid reduction in fracture incidence, likely attributable in part to a rapid reduction in falls.

A rapid reduction in falls has been observed among elderly in long-term care with the administration of 800 IU vitamin D. Broe et al reported a 72-percent reduction in falls in an elderly population after five months of treatment with 800 IU vitamin D.<sup>20</sup> In a previous study, Bischoff-Ferrari et al found a 49-percent reduction in falls among geriatric-care elderly women using a combination of 800 IU vitamin D<sub>3</sub> and 1,200 mg calcium carbonate compared to those given 1,200 mg calcium carbonate without vitamin D.<sup>18</sup>

In osteoporotic fracture, vitamin D deficiency is the rule, not the exception. For example, a Minnesota hospital study of 82 minimal-trauma fracture patients ages 52-97 found 97 percent of the fractures were hip fractures and all but two patients had deficient vitamin D status (less than 30 ng/mL).<sup>21</sup> In a large British study, vitamin D deficiency was found in 95 percent of hip-fracture patients<sup>22</sup> and 78 percent of hip-fracture patients in a Boston study were vitamin D deficient.<sup>23</sup> Findings such as these have led some researchers to suggest vitamin D level is the best predictor of fracture risk.<sup>24</sup>

### Vitamin D Requirements Revisited

The amount of vitamin D supplementation or sunlight exposure needed to achieve minimum vitamin D sufficiency (commonly defined as a 32 ng/mL

25(OH)D blood level) depends on many factors and can vary significantly from individual to individual. Thus, the requirement for vitamin D supplementation needs to be individualized. Variables influencing vitamin D requirement are summarized in Table 1.

**Table 1. Variables Influencing Vitamin D Requirements**

Sunlight exposure
Skin pigmentation
Baseline vitamin D level
Intestinal absorption rates
Type of vitamin D supplement (D <sub>3</sub> is 3x more potent than D <sub>2</sub> )
Age (with age there is a reduced photoconversion of 7-dehydrocholesterol to vitamin D)
Genetic variation in vitamin D receptor activity

On average, the amount of vitamin D supplementation required to reach a therapeutic vitamin D blood level is higher than previously thought. If 32 ng/mL 25(OH)D blood level is accepted in the United States as the necessary minimum for preventing bone loss, a minimum daily intake of 2,600 IU of vitamin D<sub>3</sub> would meet the needs of 97 percent of U.S. residents.<sup>12</sup> The current governmental Adequate Intake (AI) level for vitamin D is far below this at 400 IU for adults ages 51-70 and 600 IU for adults over 70. A 2,600 IU intake also exceeds the official "lowest observed adverse effect level" (LOAEL) of 2,000 IU established by the U.S. Food and Nutrition Board.

Supplementation with 400 IU vitamin D has repeatedly been found to have no impact on fracture incidence. Supplementation with 800 IU vitamin D has been proven moderately effective for fracture reduction. The recent Bischoff-Ferrari et al meta-analysis of fracture prevention with vitamin D demonstrated this point. The pooling of 12 major studies showed supplementation with 400 IU vitamin D daily failed to influence fracture incidence, while 700-800 IU daily reduced hip fracture by 26 percent and all fractures by 23 percent.<sup>25</sup> Similar meta-analysis results were reported by

Tang et al.<sup>26</sup> The fracture reduction potential of higher-dose sufficiency level vitamin D has not been tested.

Vitamin D at an 800 IU daily dose results in minimum sufficiency levels of serum vitamin D (32 ng/mL) in some, but not all, subjects. Thus, studies using 800 IU dosages will not bring all participants to a sufficiency level of vitamin D. For example, the multi-year British RECORD trial intervention using 800 IU vitamin D for older adults raised vitamin D blood levels to an average of 24.8 ng/mL.<sup>27</sup> In a Swiss study, average vitamin D levels increased from 12.3 ng/mL to 26.2 ng/mL in ambulatory elderly given 800 IU D<sub>3</sub> daily for three months.<sup>18</sup> In both cases, vitamin D levels achieved were well below the effective therapeutic threshold of 32 ng/mL. Osteoporosis researcher Bischoff-Ferrari estimates 700-1,000 IU vitamin D supplementation for eight weeks will result in less than half of average healthy adults achieving serum vitamin D levels of 30 ng/mL.<sup>14</sup>

### ***Vitamin D More Important than Calcium for Fracture Prevention***

Current data suggests vitamin D is more important than calcium for fracture prevention. While many vitamin D and fracture clinical trials included calcium supplementation, some intervened with vitamin D only. These vitamin-D-only trials resulted in the same or better fracture reduction than the studies using both vitamin D and calcium, suggesting vitamin D is the operative intervention.

In 2003, British researchers examined vitamin D in a fracture trial. In this 2,686-person study, the equivalent of 800 IU vitamin D daily (in the form of 100,000 IU oral D<sub>3</sub> every four months for five years) produced a 33-percent overall fracture reduction at the common sites of osteoporotic fracture (hip, wrist, spine, or forearm).<sup>28</sup>

Bischoff-Ferrari et al reported an average 25-percent reduction in the risk of hip and non-vertebral fractures from trials using 700-800 IU vitamin D, with or without calcium. They conclude, "Thus, calcium additional supplementation may not be critical for non-vertebral fracture prevention once 700 to 800 IU of vitamin D are provided."<sup>25</sup> This, the authors note, presumes the dietary calcium intake is fairly high (an average 742 mg), as it was in the British trial.<sup>28</sup> A late 2007 meta-analysis of calcium and fracture risk reported

finding no fracture-reduction benefit of calcium supplementation.<sup>29</sup>

Looking at control of parathyroid hormone, Icelandic researchers also suggest the importance of vitamin D. Steingrimsdottir et al found parathyroid hormone to be more affected by vitamin D than calcium. They report, "Vitamin D may have a calcium sparing effect and as long as vitamin D status is ensured, calcium intake levels of more than 800 mg/day may be unnecessary for maintaining calcium metabolism." They further conclude, "Our results suggest that vitamin D sufficiency can ensure ideal parathyroid hormone values even when the calcium intake level is less than 800 mg/day, while high calcium intake (greater than 1,200 mg/day) is not sufficient to maintain ideal serum parathyroid hormone, as long as vitamin D status is insufficient."<sup>30</sup>

### ***Extra-Skeletal Benefits of Vitamin D***

A plethora of new research suggests the same blood level of vitamin D sufficiency found to prevent fracture ( $\geq 32$  ng/mL) also reduces the risk of other health afflictions. For several years researchers have noted strong evidence for a protective effect of vitamin D on a variety of disorders, including muscle weakness, numerous cancers, multiple sclerosis, and diabetes.<sup>9</sup> Garland et al estimated from known data points that 50 percent of colon cancer incidence in North America could be prevented by maintenance of a serum 25(OH)D level  $\geq 34$  ng/mL. Furthermore, they project a 30-percent reduction in breast cancer incidence in North America with lifelong maintenance of serum 25(OH)D levels equal to or above 42 ng/mL.<sup>31</sup>

In addition to colon and breast cancer, an inverse association between serum vitamin D concentration and the risk of various other cancers, including ovarian cancer and prostate cancer, has been documented.<sup>32</sup> Recently, William Grant, PhD, director of the Sunlight Nutrition and Health Research Center, compiled 651 papers on vitamin D and cancer and tabulated data on 28 cancers reported to be UVB/vitamin D sensitive in observational studies (W. B. Grant, SUNARC, San Francisco, private communication). In 2007, Lappe et al reported the findings of the first intervention trial examining vitamin D and cancer. In this four-year, population-based, double-blind, randomized, placebo-controlled trial, postmenopausal women given 1,100 IU

vitamin D experienced a 60- to 77-percent reduction in the risk of developing any type of cancer.<sup>33</sup>

New evidence has accumulated that vitamin D sufficiency plays an important role in immune competence, specifically in the innate immune system.<sup>34</sup> Verifying this, a recent three-year study of postmenopausal African-American women found vitamin D supplementation (800 IU/day for two years and then 2,000 IU/day for the third year) reduced the incidence of colds and influenza by more than two-thirds.<sup>35</sup>

### *Extent of Vitamin D Deficiency*

Vitamin D deficiency is widespread. It was recently established that at least one billion people worldwide are vitamin D deficient.<sup>36</sup>

☞ Two-thirds of postmenopausal women studied in rural Nebraska had vitamin D levels below 32 ng/mL.<sup>37</sup>

☞ In a Boston area study of women and men ages 65 and over, more than 90 percent had vitamin D levels below that required for optimum parathyroid hormone control.<sup>17</sup>

☞ Vast numbers of children are vitamin D deficient. For example, in Maine, 48 percent of Caucasian girls ages 9-13 were vitamin D deficient at the end of winter and 17 percent were still deficient at the end of summer.<sup>38</sup>

☞ More than one-half of African-Americans in the United States are either chronically or seasonally at risk of vitamin D deficiency. Melanin skin pigmentation absorbs vitamin-D-producing UVB radiation; thus, a dark-skinned person needs six times more sun exposure to produce the same amount of vitamin D as a lighter-skinned individual.<sup>8</sup>

☞ In Boston, 52 percent of African-American and Hispanic adolescent boys and girls are vitamin D deficient throughout the year.<sup>39</sup>

☞ The vitamin D status of 57 percent of Massachusetts General Hospital patients studied in 1998 was below the adequate, healthful level.<sup>40</sup>

☞ At Boston Medical Center, 32 percent of students and doctors ages 18-29 were vitamin D deficient at the end of winter.<sup>41</sup>

☞ Up to 90 percent of UK elderly and 86 percent of elderly Swiss are known to be vitamin deficient.<sup>36</sup>

☞ In Saudi Arabia, serum vitamin D concentrations in young people are very low, ranging from 2.4 ng/mL to 19.3 ng/mL.<sup>42</sup>

☞ In New Delhi, a study of 760 children from lower and upper economic sectors found the mean vitamin D level to be 11.8 ng/mL, indicating a high degree of vitamin D insufficiency among Indian school children.<sup>43</sup>

### **The Need for Vitamin D Research Guidelines**

Millions of dollars have been spent on numerous clinical trials assessing vitamin D supplementation and fracture reduction. Many of these studies have been flawed, however, causing researchers to erroneously conclude vitamin D is not effective at reducing fractures.

In a two-year British trial (n=3,314) by Porthouse et al only 60 percent of those assigned to take 800 IU vitamin D and 1,000 mg calcium daily actually took the supplements, vitamin D concentrations were not measured to determine the prevalence of insufficiency, and there was no effective control group, as the control group was instructed to increase vitamin D and calcium from dietary sources. Although the study was flawed, the researchers concluded that, "We found no evidence that calcium and vitamin D supplementation reduces the risk of clinical fractures in women with one or more risk factors for hip fracture."<sup>44</sup>

In the British multi-year RECORD Trial, 800 IU vitamin D was given with 1,000 mg calcium to 5,292 subjects. Wide-ranging methodological flaws, however, invalidate this large study of vitamin D and fracture incidence. The clinical trial defects include non-compliance and failure to reach a therapeutic serum level of vitamin D. Nearly half of all study participants did not comply with vitamin D and calcium supplement use. At 24 months, only 54 percent of participants were taking the supplements. There was no validation that study subjects reached a therapeutic vitamin D blood level. Evaluation of vitamin D levels in a small sample of 60 subjects found that, even with the 800 IU supplemental vitamin D, the average vitamin D blood level went from 15.2 ng/mL at baseline to 24.8 ng/mL – a level far below the known lower level of effectiveness of 32 ng/mL. Notwithstanding these invalidating flaws the RECORD Trial group concluded that supplementation



**Table 2. Proposed Scientific and Ethical Guidelines for Clinical Trials on Vitamin D and Fracture**

<p><b>Guideline #1</b>                  Vitamin D levels achieved in clinical trials should reach the known effective therapeutic level for optimizing calcium absorption, normalizing parathyroid hormone, and reducing low-trauma fractures. Currently, this vitamin D blood level is calculated to be 32 ng/mL.</p>
<p><b>Guideline #2</b>                  Achievement of vitamin D sufficiency should be verified for all study participants by blood testing for 25(OH)D levels.</p>
<p><b>Guideline #3</b>                  Only those study subjects who achieve serum vitamin D of 32 ng/mL or greater should be included in any calculation of fracture reduction.</p>
<p><b>Guideline #4</b>                  Vitamin D supplementation must be continued on a consistent basis for at least 12 months after the vitamin D sufficiency level has been reached.</p>
<p><b>Guideline #5</b>                  In clinical trials, vitamin D<sub>3</sub> (cholecalciferol) should be used and not vitamin D<sub>2</sub> (ergocalciferol). The latter is known to be only one-third as potent as cholecalciferol.</p>

with calcium and vitamin D was ineffective for fracture prevention.<sup>27</sup>

The recent 2006 U.S. Women’s Health Initiative Study was also poorly designed.<sup>45</sup> Although the trial was large (n=36,282), expensive (\$US 725 million), and long-term (seven years), the vitamin D intervention was only 400 IU daily. Although this low level of vitamin D might have appeared to be a reasonable dose when the Women’s Health Initiative Study was designed nearly two decades earlier, by its publication in 2006 the inadequacy of this level of vitamin D was well documented. In May 2005, a comprehensive meta-analysis of vitamin D and fracture reduction clearly established that 400 IU had no effect on fracture incidence.<sup>25</sup> Despite this revelation, the U.S. Women’s Health Initiative Study researchers still published findings that caused headlines around the country to read, “Calcium and Vitamin D Supplements Don’t Cut Fractures.”

To resolve these methodological limitations and to pave the way for a valid analysis of the actual fracture-reduction potential of vitamin D, the OEP has proposed “Scientific and Ethical Guidelines for Clinical Trials on Vitamin D and Fracture” (Table 2). The proposed guidelines follow and amplify an earlier call for vitamin D research guidelines proposed by others.<sup>46</sup>

Research has clarified that vitamin D<sub>3</sub> (cholecalciferol) is the preferred form of vitamin D for supplementation, rather than vitamin D<sub>2</sub> (ergocalciferol), vitamin D<sub>3</sub> being three times more potent.<sup>47</sup>

### Clinical Trials That Most Closely Adhere to the Guidelines

A search of the literature disclosed no clinical trials that follow all five of the criteria outlined in Table 2. Only a handful of studies follow several of them. The clinical trials that most closely adhere to the guidelines are outlined below and summarized in Table 3.

#### *The French Decalyos I Study* Study Design

The French Decalyos I Study was an 18-month trial of 3,270 elderly French women using 800 IU vitamin D<sub>3</sub> with 1,200 mg elemental calcium (as tri-calcium phosphate).<sup>48</sup> Only 1,762 women completed the study. Fracture reduction analysis was conducted on those completing the study.

Table 3. Vitamin D and Fracture Trials

Trial	Trial Overview (All are randomized controlled trials)	Trial Compliance	Serum Vitamin D (Therapeutic threshold is 32 ng/mL)	% Fracture Reduction
French Decalys I Study <sup>48</sup>	3,270 ambulatory elderly French women  18-month trial  Intervention: 800 IU D <sub>3</sub> w/tri-calcium phosphate (1,200 mg elemental calcium)	1,762 (54%) completed the trial  Supplement compliance appears good	16 ng/mL average vit D level at baseline  42 ng/mL average vit D level at completion of trial	32% ↓ in all non-vertebral fractures  43% ↓ in hip fractures
French Decalys I Study Extension <sup>49</sup>	3,270 ambulatory elderly French women  18-month extension of trial  Intervention: 800 IU of D <sub>3</sub> w/tri-calcium phosphate (1,200 mg elemental calcium)	Supplement compliance unclear but appears adequate	16 ng/mL average vit D level at baseline  42 ng/mL average vit D level at completion of trial	24% ↓ in all non-vertebral fractures  29% ↓ in hip fractures
French Decalys II Study <sup>50</sup>	610 ambulatory elderly French women  2-year trial  Intervention: 800 IU of D <sub>3</sub> w/tri-calcium phosphate (1,200 mg elemental calcium)	422 (69%) completed the trial  95% supplement compliance	9 ng/mL average vit D level at baseline  30 ng/mL average vit D level at completion of trial	Non-significant ↓ in non-vertebral fractures  31-38% ↓ in hip fractures depending on mode of calculation
British study of vitamin D and osteoporotic fracture <sup>28</sup>	2,686 community living men & women ages 65-85  5-year trial  Intervention: 100,000 IU tablets of vit D <sub>3</sub> every four months	75% of participants took the vit D supplement at least 80% of the time  66% compliance for final dose	4 yrs. into study, small sample tested for vit D level: 29 ng/mL average vit D level in those taking supplements  21 ng/mL average vit D in placebo group	33% overall ↓ of fracture at the common sites of osteoporotic fractures (hip, wrist, spine, forearm)
Boston area study <sup>17</sup>	389 community dwelling men & women (mean age 74)  3-year trial  Intervention: 700 IU D <sub>3</sub> and 500 mg elemental calcium (as citrate malate)	318 (82%) completed the trial  Supplement compliance appears good	30 ng/mL average vit D level at baseline  44 ng/mL average vit D level at completion of trial	60% ↓ in all non-vertebral fractures  60% ↓ in all osteoporotic fractures
Japanese study of sunlight exposure on BMD & hip fracture incidence among vitamin D deficient stroke patients <sup>51</sup>	258 stroke patients  12-month trial  Intervention: 50% of patients had 15 minutes/day of sunlight exposure to face and hands; 50% were sunlight deprived	Compliance w/ sunlight exposure appears good	6.8 ng/mL average vit D at baseline  20.8 ng/mL average at completion of trial	Six-fold ↓ in hip fracture incidence in the sunlight-exposed group  3.1% ↑ in BMD in sunlight-exposed group  3.3% ↓ in BMD in sunlight-deprived group
Japanese study of hip fracture reduction among Alzheimer's patients through sunlight exposure <sup>52</sup>	264 Alzheimer's patients  12-month trial  Intervention: 1,200 mg elemental calcium 2X/day to both groups; 50% of patients had 15 minutes/day of sunlight exposure to face, hands and forearms (total exposed skin area 426±32cm <sup>2</sup> ; 50% of patients were sunlight deprived)	Compliance w/sunlight exposure appears good	9.6 ng/mL average vit D at baseline  20.8 ng/mL average at completion of trial	4X more frequent non-vertebral fractures in sunlight-deprived group (11 compared to 3)  4X more frequent hip fractures in sunlight-deprived group (9 compared to 2)  2.7% ↑ in BMD in sunlight-exposed group  5.6% ↓ in BMD in sunlight-deprived group

### Vitamin D Blood Levels

Vitamin D blood levels were measured at baseline and completion. Serum vitamin D levels rose from an average of 16 ng/mL at baseline to an average of 42 ng/mL at study's end. Thus, in this study over one-half of the intervention group reached the vitamin D sufficiency level of 32 ng/mL.

### Study Finding on Fracture Reduction

A 32-percent reduction in non-vertebral fractures was demonstrated in the vitamin D and calcium group compared to the placebo group. There was a 43-percent reduction in hip fractures in the vitamin D and calcium group compared to the placebo group.

### OEP Comment on Study

This study meets several of the five proposed criteria. Over half of the participants reached a therapeutic level of vitamin D, the study was long-term, and vitamin D<sub>3</sub> was used. Fracture reduction statistics were only calculated for those completing the study. Although a significant number of participants did not achieve a therapeutic level of vitamin D, the degree of fracture reduction was impressive and comparable to, or better than, that reported in several bone drug trials. It is also interesting to note the reduction in fracture incidence was noticeable after only two months of supplement use.

### *The French Decalys I Study Extension* Study Overview

The original Decalys I 18-month study was extended an additional 18 months.<sup>49</sup> In the 18-month extension, 800 IU of vitamin D<sub>3</sub> was used with tricalcium phosphate (1,200 mg elemental calcium). The degree of compliance is unclear, but appears adequate.

### Vitamin D Blood Levels

Serum vitamin D levels increased from an average of 16 ng/mL to an average of 42 ng/mL. Thus, in this study over one-half of the individuals in the intervention group reached the vitamin D sufficiency level of 32 ng/mL.

### Study Finding on Fracture Reduction

A 29-percent reduction in hip fractures was achieved in the vitamin D and calcium group compared to the placebo group (active treatment analysis), with a 24-percent reduction in all non-vertebral fractures in the active treatment group compared to placebo.

### OEP Comment on Study

This study meets several of the five proposed criteria. Vitamin D levels were measured at baseline and at the end of the study. Over half of the participants reached a therapeutic level of vitamin D, the study was long-term, and vitamin D<sub>3</sub> was used. Although a significant number of participants did not achieve a therapeutic level of vitamin D, fracture reduction was impressive and comparable to, or better than, that reported in several bone drug trials.

### *The French Decalys II Study* Study Design

The French Decalys II Study was a two-year, placebo-controlled trial of 610 ambulatory elderly women.<sup>50</sup> Active treatment subjects were given 800 IU vitamin D<sub>3</sub> with 1,200 mg elemental calcium (as tricalcium phosphate). The study began with 610 participants and 422 (69%) completed the study. Compliance was good, with those who completed the study taking the supplements at least 95 percent of the time.

### Vitamin D Blood Levels

Serum vitamin D levels were measured at baseline and study end. Baseline vitamin D levels were low, averaging 9 ng/mL. Final vitamin D levels averaged 30 ng/mL with some individuals, but not a majority in the intervention group reaching the therapeutic threshold of 32 ng/mL serum level 25(OH)D.

### Study Finding on Fracture Reduction

This study resulted in a 31- to 38-percent reduction in hip fractures, depending on mode of calculation. The "intent-to-treat analysis" yielded a 31-percent reduction in hip fractures in the vitamin D and calcium group compared to the placebo group. A statistically non-significant decrease in total non-vertebral fractures in the active treatment group was achieved.

### OEP Comment on Study

This study meets several of the five proposed criteria. Less than 50 percent of participants failed to reach a therapeutic level of vitamin D. Although a significant number of participants did not achieve a therapeutic level of vitamin D, hip fracture reduction was impressive and comparable to that reported in several bone drug trials.

## **British Study of Vitamin D and Osteoporotic Fracture**

### Study Overview

In a five-year British study, 2,686 men and women ages 65-85 were divided into active treatment and control groups.<sup>28</sup> The active treatment group was instructed to take a 100,000 IU vitamin D<sub>3</sub> supplement every four months for five years. Over the study period, 75 percent of participants took the vitamin D supplement at least 80 percent of the time; compliance for the final dose was 66 percent.

### Vitamin D Blood Levels

Serum vitamin D levels were measured in only a small sample of study subjects (n=235) after the fourth year of the study. All those tested for vitamin D levels had taken at least 10 of the 12 vitamin D supplements assigned up to that time. Vitamin D blood levels in those taking the supplement averaged 29 ng/mL, while the placebo group averaged 21 ng/mL. The authors concluded that, although there was a 40-percent increase in vitamin D levels in the active treatment group, the level achieved was not high in absolute terms. In fact, parathyroid hormone concentrations were only slightly, and not significantly, lower in the active group. "This suggests that the 100,000 IU D<sub>3</sub> every four months may not have lowered parathyroid concentration adequately, and a more frequent (higher total) dose might be considered in future trials."<sup>28</sup>

### Study Finding on Fracture Reduction

This study resulted in a 33-percent overall reduction of fracture at the common sites of osteoporotic fracture (hip, wrist, spine, or forearm) in the vitamin D group compared to placebo.

### OEP Comment on Study

This trial met two of the five criteria. Less than 10 percent of study participants were measured for blood vitamin D levels and an effective therapeutic level of vitamin D was achieved in less than half the treatment group. Not enough vitamin D was given to control parathyroid hormone and effectively reduce fracture risk. Compliance was incomplete with only three-quarters of participants taking 80 percent of required doses or the final vitamin D dose. Notwithstanding these shortcomings, a 33-percent reduction of fractures at the common sites of osteoporotic fracture (hip, wrist, spine, or forearm) was achieved.

## **Boston Area Study**

### Study Overview

In a 389-person, three-year study in Boston, subjects (mean age of 74) were given either 700 IU vitamin D<sub>3</sub> and 500 mg elemental calcium (as calcium citrate-malate) or placebo.<sup>17</sup> The end point of the study was all non-vertebral fractures. Of 389 participants, 318 took the supplements per the study protocol.

### Vitamin D Blood Levels

Serum vitamin D levels were measured at baseline and study end. Levels rose from an average of 30 ng/mL at baseline to an average of 44 ng/mL. Thus, over half of the subjects reached the minimum vitamin D sufficiency level of 32 ng/mL.

### Study Finding on Fracture Reduction

Compared to placebo, the treatment group experienced a 60-percent reduction in risk of any first non-vertebral fracture and a 60-percent reduction in risk of fractures classified as osteoporotic. One hip fracture occurred in the placebo group, none in the treatment group.

### OEP Comment on Study

This study meets several of the five proposed criteria. Over half of the participants reached a therapeutic level of vitamin D. The study was long-term and vitamin D<sub>3</sub> was used, as was calcium citrate-malate, a highly absorbable form of calcium. Although a significant number of participants did not achieve a therapeutic level of vitamin D, non-vertebral fracture reduction was 60 percent, which is generally better than that reported in most fracture/drug trials. While there occurred too few hip fractures for valid assessment, the single hip fracture recorded was in the control group.

### Japanese Study of Sunlight Exposure on Hip Fracture Incidence among Stroke Patients

#### Study Overview

A 12-month, randomized, controlled, prospective study analyzed 258 stroke patients.<sup>51</sup> Half of the patients received regular sunlight exposure; the other half were sunlight deprived. Sunlight exposure in the treatment group consisted of 15 minutes/day exposure to face, hands and forearms. Compliance with sun exposure appeared to be good.

#### Vitamin D Blood Levels

Vitamin D levels were deficient in both groups at baseline. Baseline vitamin D levels averaged 17 nmol/L (6.8 ng/mL) and rose threefold to 52 nmol/L (20.8 ng/mL) in the sunlight-exposed group. Bone mineral density increased 3.1 percent in the sunlight-exposed group and decreased 3.3 percent in the sunlight-deprived group.

#### Study Finding on Fracture Reduction

There was a sixfold decrease in hip fracture incidence in the sunlight-exposed group. Six patients sustained hip fractures on the hemiplegic side in the sunlight-deprived group and one in the sunlight-exposed group.

### OEP Comment on Study

In this study, the vitamin D serum levels achieved from sun exposure were well below the therapeutic threshold of 80 nmol/L (32 ng/mL). Although not high in absolute terms, this threefold increase in vitamin D level provided for a sixfold decrease in fracture and optimization of individual vitamin D levels.

This study strongly suggests that raising vitamin D levels among severely vitamin D-deficient stroke patients can dramatically reduce fracture incidence. This sixfold decrease in fracture is far greater than that obtained with pharmaceutical therapies. In this study it is interesting to note that the number of falls was similar among sun-exposed and sun-deprived patients. Sun exposure and increased vitamin D levels reduced fracture incidence in stroke patients despite frequent falls.

### Japanese Study of Hip Fracture Reduction among Alzheimer's Patients

#### Study Overview

In a one-year, randomized, prospective study, 264 patients with Alzheimer's disease were assigned to either regular sunlight exposure or sunlight deprivation.<sup>52</sup> Sunlight exposure in the treatment group consisted of 15 minutes/day exposure to face, hands, and forearms (total exposed skin area approximately 426 cm<sup>2</sup>). Both study groups were given 1,200 mg elemental calcium. Study compliance appeared to be good.

#### Vitamin D Blood Levels

Vitamin D levels at baseline averaged 24 nmol/L (9.6 ng/mL) and rose to 52 nmol/L (20.8 ng/mL) in the sunlight-exposed group. Bone mineral density decreased 5.6 percent in the sunlight-deprived group and rose 2.7 percent in the sunlight-exposed group.

#### Study Finding on Fracture Reduction

Hip fractures were four times more frequent in the sunlight-deprived group (nine in the sunlight-deprived group compared to two in the group receiving regular sunlight). All non-vertebral fractures were nearly four times more frequent in the sunlight-deprived group (11 in the sunlight-deprived group compared to three fractures in the sunlight-exposed group).

### OEP Comment on Study

The vitamin D level increased 2.2-fold in the sunlight-exposed group of Alzheimer's patients reaching an average level of 20.8 ng/mL. Despite the fact this is below the therapeutic threshold of 32 ng/mL, fracture reduction was impressive.

In this study the number of “fallers” was reduced by 50 percent in the sunlight-exposed group and by 27 percent in the sunlight-deprived group. Fewer falls likely helped reduce hip fracture incidence in these cases. Muscle strength doubled in the sunlight-exposed group and decreased in the sunlight-deprived group. This study suggests fractures among severely vitamin D-deficient Alzheimer’s patients can be dramatically decreased with even a sub-optimal level of vitamin D supplementation.

### Informed Approximation of the Fracture Reduction Potential of Therapeutic Levels of Vitamin D Supplementation

The Osteoporosis Education Project estimates that supplementation with therapeutic levels of vitamin D could result in an overall 50- to 60-percent reduction in low-trauma osteoporotic fractures. This figure, double that of current meta-analyses, is consonant with the expert opinion of others, including noted vitamin D researchers William Grant, Cedric Garland, and Michael Holick. In a 2005 article on the economic burden of insufficient vitamin D, they state, “For osteoporotic fractures, data from clinical studies was used, with an estimate of 50-70 percent of such fractures considered to be due to insufficient vitamin D from all sources.”<sup>53</sup>

A recent report from the Women’s Health Initiative study provides interesting insights into the link between low vitamin D status and hip fracture. In a case-controlled study of the Women’s Health Initiative Observational Study Cohort, women with the lowest levels of vitamin D (less than 19 ng/mL) were found to have a 77-percent higher risk of hip fracture than women with the highest vitamin D level (average 28 ng/mL).<sup>54</sup> In this study of 800 healthy, mostly Caucasian women, those with the highest vitamin D levels averaged only 28 ng/mL.

### Conclusion: A Call for Universal Vitamin D Testing and Repletion

Osteoporotic fractures represent a growing economic and social concern in many areas of the world today. While the factors contributing to fragility fractures are varied, vitamin D deficiency/insufficiency clearly represents a significant factor; it is also an easy factor to correct. For the billion or more people worldwide

who are vitamin D deficient/insufficient,<sup>36</sup> achievement of vitamin D sufficiency should be seen as the first-line intervention for fracture prevention. As the most valid vitamin D trials suggest, this simple intervention could reduce common osteoporotic fractures by an estimated 50-60 percent. Such a significant fracture-reduction potential rivals that of popular anti-resorptive osteoporosis medications. In many of these clinical trials vitamin D and/or calcium are given along with the anti-resorptive bone medications; thus, the effectiveness of the drugs alone is unknown.

In the interest of near universal bone health, vitamin D repletion from sunlight exposure and/or supplementation is now clearly dictated. For fracture prevention, vitamin D serum levels should be restored to at least 32 ng/mL, the level now shown to optimize calcium absorption and normalize PTH. Given significant biochemical individuality in the need for supplemental vitamin D and variation in response to vitamin D therapy, pre- and post-testing of individual vitamin D status is highly recommended.

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