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High-Dose Vitamin D: Helpful or Harmful?

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Abstract

If the optimal serum 25(OH)D level for skeletal health is ≥ 30 ng/mL, then vitamin D insufficiency is widespread, affecting approximately 75% of adults based on a recent survey of over 20,000 Americans. However, after a comprehensive analysis of existing research studies, the Institute of Medicine recently concluded that nearly all individuals are vitamin D replete when their 25(OH)D levels are ≥ 20 ng/mL. Furthermore, two recent publications challenge the belief that 25(OH)D levels > 30 ng/mL are optimal for bone health. In a randomized, placebo-controlled trial, high-dose once yearly vitamin D therapy increased fractures and falls. The second study reported that high-dose vitamin D did not reduce levels of parathyroid hormone or bone resorption among adults with 25(OH)D levels < 32 ng/mL at baseline. It is time to question whether serum 25(OH)D levels ≥ 30 ng/mL are necessary for all individuals.

Keywords

calcium absorption; vitamin D; fractures; falls; Institute of Medicine; meta-analysis

Introduction

Vitamins are organic compounds that cannot be synthesized by an organism, but must be obtained, most often by ingestion, to maintain good health. Very few foods contain vitamin D₂ or vitamin D₃ and therefore, unlike other vitamins, humans primarily obtain vitamin D through sun exposure. Ultraviolet light converts cutaneous 7-dehydrocholesterol to previtamin D₃, which is rapidly converted by liver 25-hydroxylase to 25(OH)D, considered the storage form of vitamin D [1]. Renal conversion of 25(OH)D to 1,25(OH)₂D is tightly regulated, with parathyroid hormone promoting and fibroblast-like growth factor and 1,25(OH)₂D suppressing this conversion step [1].

1,25(OH)₂D binds to the vitamin D receptor and acts as a transcription factor that influences gene expression [1]. The classic target tissues for vitamin D include bone, intestine and kidney. In the intestinal tract, 1,25(OH)₂D promotes calcium and phosphorus absorption. In the renal tubule cells, 1,25(OH)₂D suppresses 1- α -hydroxylase enzyme activity to decrease 1,25(OH)₂D production. Likewise, 1,25(OH)₂D enhances 24-hydroxylase enzyme activity to promote the breakdown of 1,25(OH)₂D into inactive metabolites. In the skeleton, 1,25(OH)₂D can enhance the differentiation of osteoclasts from monocyte-macrophage stem cell precursors and at high doses, can increase osteoblast production of receptor activator of NF- κ B ligand (RANKL), leading to increased osteoclastic bone resorption and release of calcium into the bloodstream [2, 3].

In modern times, adults generally spend little time outdoors, due to a shift from an agricultural to an industrial and technological vocation. Increased sunscreen use and

decreased outdoor activities have contributed to what some experts describe as an epidemic of vitamin D insufficiency [4]. Indeed, in a recent NHANES survey of over 20,000 Americans, approximately 75% of adults had serum 25(OH)D levels <30 ng/mL [4]. Inadequate vitamin D stores have been linked to a decline in calcium absorption, lower serum ionized calcium levels and subsequent higher risk of secondary hyperparathyroidism. High parathyroid hormone (PTH) levels can, in turn, increase bone resorption and eventually lead to a decline in bone mineral density, contributing to the development of osteoporosis or osteomalacia and subsequent fractures.

Patients with vitamin D deficiency osteomalacia frequently complain of muscle weakness and exhibit a waddling gait. In one small study, the number and size of type II muscle fibers increased with vitamin D therapy, in association with improved muscle strength and gait [5]. The effect of vitamin D on muscle health might occur directly via the vitamin D receptor, or indirectly through favorable effects on intracellular calcium levels [1]. Cross-sectional research studies linked low vitamin D levels to a greater risk of falls [6]. Authors of a recent meta-analysis concluded, based on existing clinical trials data, that vitamin D supplements reduce the risk of falls in older adults [7]. The United States Preventive Services Task Force conducted a systematic review of trials published by February 2010 and concluded that vitamin D reduced falls by 17% (95% confidence interval, 11% to 23%) during 6 to 36 months of follow up [8].

In the past decade, commercial 25(OH)D assays became widely available, permitting researchers to easily measure vitamin D stores in subjects. Subsequently, a large number of research studies were published and indicated that higher 25(OH)D levels were associated with greater calcium absorption efficiency [9, 10], a lower risk of secondary hyperparathyroidism [11], higher bone mineral density [12], and a lower risk of fracture and falls [13]. Thus in 2005, six experts evaluated the literature and published a document stating that the optimal vitamin D level for bone health was ≥ 30 ng/mL (75 nmol/L) [14]. Although others declared that a 25(OH)D level ≥ 20 ng/mL (50 nmol/L) was adequate [11, 14, 15], nevertheless laboratories across the country embraced 30 ng/mL as the new threshold indicating normal vitamin D stores. Clinicians likewise sought to achieve serum 25(OH)D levels ≥ 30 ng/mL in their patients.

Institute of Medicine Recommendations on Vitamin D Intake

In 1997, the Institute of Medicine (IOM) published recommendations for an adequate intake of vitamin D [16]. At that time, the IOM concluded that insufficient data existed to determine a recommended daily allowance of vitamin D [16]. However, the IOM determined the “adequate intake” or vitamin D dosage needed to prevent vitamin D deficiency rickets or osteomalacia among individuals with uncertain sun exposure and vitamin D stores. The estimated adequate intake was rounded to the nearest 50 IU and then doubled, as a safety factor to meet the needs of all individuals regardless of sun exposure. Table 1 summarizes the 1997 vitamin D adequate intake determined for individuals in different life stages.

In 2009, following the publication of numerous studies on vitamin D and health outcomes, the IOM decided to update its recommendations on vitamin D intake. To prepare for the update, the committee reviewed the 2007 National Institute of Health Evidence Report on vitamin D by Cranney et al. [17], commissioned an independent systematic literature review by the Tufts Evidence-Based Practice Center [18], and undertook their own comprehensive literature review of vitamin D and health outcomes [1]. The committee met several times between 2009 and 2010 with the aim of reaching consensus regarding the recommended

daily allowance of vitamin D, an intake needed to meet or exceed the nutritional requirements of 97.5% of the general population of the United States and Canada.

In November 2010, the Institute of Medicine released the 2011 Dietary Reference Intakes for calcium and vitamin D. After review of the skeletal health outcomes related to vitamin D status including calcium absorption, parathyroid hormone (PTH) levels, bone mineral density and fracture risk, the IOM decided to increase its recommended intake of vitamin D for individuals across all life stages (Table 1). Recommended daily allowances assumed a setting of minimal sun exposure. However, the recommended increases in vitamin D intake were modest, compared to those suggested by others [19, 20]. In summary, the IOM recommended vitamin D 400 IU per day for individuals between the ages of 0 and 1 year old, 600 IU per day for individuals between 1 and 70 years of age (including pregnant and lactating women), and 800 IU per day for individuals over 70 years of age. The IOM further concluded that the available data did not support a causal relationship between vitamin D status and extra-skeletal health outcomes such as the risk of malignancy or autoimmune disease.

The IOM committee carefully appraised the literature in order to recommend a target serum 25(OH)D level for optimal skeletal health outcomes across life stages. The committee concluded that individuals were at risk of vitamin D deficiency when their serum 25(OH)D levels were <12 ng/mL (30 nmol/L). They also stated that some, but not all, persons were at risk of vitamin D inadequacy when their serum 25(OH)D levels were between 12 and 20 ng/mL (30 and 50 nmol/L). In contrast to other groups [14], the IOM asserted that practically all persons were vitamin D replete when their serum 25(OH)D levels were ≥ 20 ng/mL and expressed concern that individuals with serum 25(OH)D levels >20 ng/mL might be classified as deficient and treated with high-dose vitamin D.

Evidence that 25(OH)D levels ≥ 20 ng/mL indicate vitamin D sufficiency comes from a number of recent studies related to measurement of health outcomes including calcium absorption, PTH, bone mineral density and fracture risk. Below, the literature supporting this contention is summarized. Additionally, two recent studies are highlighted, in which authors reported the effect of high-dose vitamin D on PTH [21], falls [22] and fractures [22].

Vitamin D Levels that Maximize Calcium Absorption

Calcium absorption occurs passively by diffusion between intestinal cells and actively, via vitamin D-mediated upregulation of cellular events leading to transport of calcium across the intestinal cell. In states of high calcium intake, an individual's vitamin D status is less important, as passive absorption of calcium can occur in the absence of vitamin D. This was demonstrated in a recent randomized trial of 256 women ages 70–90 years old with 25(OH)D levels <24 ng/mL at study entry [23]. Women were assigned to take calcium 1,000 mg/day and were randomized to receive 1,000 IU of vitamin D₂ per day or placebo for one year. Although subjects' 25(OH)D levels rose by 14 ng/mL in the group assigned to vitamin D, fractional calcium absorption decreased significantly in both groups, with no significant between-group differences in absorption [23]. Although one study [9] reported a 3% increase in fractional calcium absorption in association with a rise in 25(OH)D levels from 22 ± 4 ng/mL to 64 ± 21 ng/mL following high-dose vitamin D₂, the study was not placebo-controlled, enrolled only eighteen women, and measured changes in absorption over approximately one month. In a cross-sectional study of 492 women ages 20–80 years old, calcium absorption was unrelated to serum 25(OH)D levels [24]. Based on review of these and other studies, the IOM concluded that calcium absorption reaches a maximal fraction in children and adults when their 25(OH)D levels are between 12 ng/mL and 20 ng/mL (30 and 50 nmol/L).

Vitamin D Levels that Minimize Parathyroid Hormone

There is no doubt that vitamin D therapy can lower PTH levels and associated bone resorption [1]. Therefore the serum 25(OH)D level that minimizes PTH is relevant to skeletal health, particularly among individuals with normal renal function. Some authors concluded that the risk of secondary hyperparathyroidism was minimized when serum 25(OH)D levels exceeded ~30 ng/mL [1, 14]. However, much of the data driving this conclusion came from cross-sectional studies graphing the relationship between PTH and 25(OH)D levels. Of note, in a trial [11] of 35 patients with 25(OH)D levels <25 ng/mL at baseline, administration of 1,000–1,500 mg of calcium and vitamin D₂ as 50,000 IU weekly for 8 weeks did not reduce PTH levels significantly in the subset of seven subjects with 25(OH)D levels ≥20 ng/mL at baseline. Authors of this study therefore concluded that the risk of secondary hyperparathyroidism was minimized when 25(OH)D levels were ≥20 ng/mL. Similarly, in a post-hoc analysis of data collected during a trial of raloxifene [25], Lips et al. determined that vitamin D and calcium therapy had minimal effects on PTH levels in subjects with baseline 25(OH)D levels ≥20 ng/mL.

In July 2010, Aloia et al. published another study [21] challenging the belief that 25(OH)D levels >30 ng/mL are necessary to minimize the risk of secondary hyperparathyroidism and attendant bone resorption. Researchers randomized 99 healthy adults with vitamin D insufficiency (25(OH)D <32 ng/mL) to three months of therapy with one of four regimens; double placebo tablets, calcium 600 mg twice daily and placebo vitamin D tablets, placebo calcium tablets and vitamin D₃ 2,000 IU twice daily, or both calcium and vitamin D₃ twice a day. Changes in PTH and bone turnover (C-telopeptide or CTX and procollagen-1 N-terminal propeptide or P1NP) were evaluated after three months of therapy. Authors reported data for the 78 subjects who completed the study.

Demographic characteristics, dietary intake of calcium, vitamin D and protein, bone mineral density and adherence to study medication were similar across treatment groups. Mean 25(OH)D levels increased from 26.6 ng/mL to 44.8 ng/mL ($p<0.0001$) among subjects randomized to vitamin D with or without calcium, with no significant changes in 25(OH)D levels in the other two treatment arms. Surprisingly, subjects randomized to vitamin D experienced increased P1NP values ($p<0.06$) with no significant changes in CTX or PTH. By contrast, subjects randomized to calcium experienced significant declines in CTX ($p<0.0001$) and P1NP ($p<0.0001$). Authors concluded, “The lack of any effect of vitamin D supplementation on PTH or bone markers does not support the proposal of achieving a serum 25(OH)D concentration that is greater than 75–80 nmol/L [30–32 ng/mL] to prevent secondary hyperparathyroidism and bone loss.”

In its recent report, the Institute of Medicine concluded that PTH values could not be used to develop vitamin D Dietary Reference Intakes [1]. The committee noted that studies evaluating the relationship between PTH and subsequent bone mineral density and fracture risk showed inconsistent results across different racial groups. Moreover, PTH values normally increase during puberty, with increasing age, and with a decline in renal function, leading to uncertainty regarding normal PTH values across life stages. Finally, several other factors were noted to influence PTH values including the assay utilized, diurnal variation, and individuals’ dietary intake of calcium and phosphorus. In consideration of these multiple issues, the IOM concluded that optimal vitamin D intake could not be determined using PTH values.

Vitamin D Levels that Maximize Bone Mineral Density

Bone mineral density is an important health outcome related to vitamin D status. The 2007 Evidence Report by Cranney et al. [17] concluded there was good evidence that vitamin D

and calcium supplementation resulted in small increases in spine, hip and total body bone mineral density. However the authors stated it was less certain whether vitamin D alone had beneficial effects on bone mineral density. The 2009 Tufts Evidence Report [18] concurred with the conclusions of Cranney et al.

One recent study suggests that, at least in older men, declines in hip bone mineral density are minimized when serum 25 (OH)D levels are ≥ 20 ng/mL. MrOS is a multi-center longitudinal study evaluating the factors that influence bone mineral density and fracture rates among nearly 6,000 men ≥ 65 years old. The relationship between 25(OH)D levels and changes in hip bone mineral density was evaluated in a subset of 1279 men [26]. Researchers found that men in the lowest 25(OH)D quintile (<19.1 ng/mL) had the highest rates of hip bone loss over a mean $\pm$ standard deviation of 4.4 ± 0.8 years, whereas men in the other four quintiles experienced similar rates of hip bone loss, with no significant difference between quintiles two through five.

The IOM noted discordance between observational studies and randomized controlled trials, regarding the relationship between 25(OH)D levels and bone mineral density in adults. Based on observational studies, the IOM concluded that there was fair evidence to support an association between 25(OH)D levels and bone mineral density at the femoral neck. Data from a longitudinal study supports the IOM conclusion that 25(OH)D levels ≥ 20 ng/mL reflect values optimal for bone mineral density.

Vitamin D Status and Fractures

Fractures signal skeletal fragility, and are widely recognized as the most vital skeletal health outcome related to vitamin D status. Thus, the IOM committee evaluated the vitamin D dose and/or serum 25(OH)D level that minimized the risk of fractures across life stages. Their conclusions regarding the relationship between vitamin D intake and fracture risk contributed to the final Dietary Reference Intakes for vitamin D.

Since 2007, five meta-analyses have evaluated the effect of vitamin D on fracture rates in older adults (Table 2) [17, 27–30]. The 2007 Evidence Report by Cranney et al. [17] concluded that there was inconsistent evidence to support an association between 25(OH)D levels and the risk of fracture among individuals >50 years old. The same report concluded that vitamin D, when combined with calcium supplementation, significantly decreased the risk of non-vertebral and hip fractures. However this benefit predominated in older individuals living in an institutional setting, with inconsistent benefits noted among community-dwelling older adults. The 2009 Tufts analysis [18] incorporated three randomized controlled trials that were published after the 2007 report. However, the new data did not alter authors' conclusions regarding the relationship between vitamin D and fracture, which were identical to those reported in the 2007 analysis.

Authors of four meta-analyses [17, 27–29] of vitamin D fracture trials concluded that vitamin D reduces fractures only when co-administered with calcium (Table 2). In contrast, one group [30] asserted that vitamin D reduced fractures, independent of calcium therapy. The group [30] also concluded that higher achieved serum 25(OH)D levels were associated with a reciprocal decrease in the risk of hip and non-vertebral fracture (Figure 1, with permission). However, this statement was based on limited data, as only ~5% (2,062 of 42,279) of subjects participating in vitamin D fracture trials underwent 25(OH)D measurements during the trials. In the Figure illustrating the relationship between 25(OH)D levels and hip fracture risk, only one study [31] demonstrated a statistically significant reduction in fracture based on the 25(OH)D level achieved during the trial. This study reflected yearly 25(OH)D measurements obtained from only 1.6% (52 of 3270) of participants in a randomized, placebo-controlled trial of tricalcium phosphate and vitamin D

in elderly women residing in long-term care facilities in France [31]. Calcium and/or phosphorus supplementation might have influenced the fracture rate in this trial.

Recently, a large clinical trial raised concern about the safety of high-dose vitamin D. In May 2010, Sanders et al. [22] published the results of a randomized, placebo-controlled trial in which 2256 community-dwelling women ages 70 years and older were randomized to 500,000 IU of vitamin D₃ or matching placebo by mouth each fall or winter for three to five years. Falls were determined by self-report, whereas fractures required radiographic confirmation. Approximately 7% of subjects (n=150) underwent measurement of 25(OH)D and PTH levels during the study. In this subset of subjects, median 25(OH)D levels were 19.6 ng/mL at baseline and in the vitamin D₃ arm, rose to 48 ng/mL and remained above 30 ng/mL one year after dosing. By contrast, subjects randomized to placebo therapy experienced continued vitamin D insufficiency throughout the year.

Unexpectedly, subjects randomized to high-dose vitamin D₃ experienced more falls and more fractures. With respect to falls, 837 women in the vitamin D arm fell 2892 times, providing a falls rate of 83.4 per 100 person years. By contrast, 769 women in the placebo arm fell 2512 times, providing a falls rate of 72.7 per 100 person-years. Thus, the incidence falls rate ratio was 1.15 in the vitamin D arm (95% confidence interval (CI) 1.02–1.30, p=0.03). Interestingly, a temporal relationship between vitamin D₃ dosing and falling was observed, with a falls rate ratio of 1.31 in the first three months after vitamin D₃ ingestion and a rate ratio of 1.13 in the following nine months (test for homogeneity, p=0.02).

Of greater concern, subjects randomized to high-dose vitamin D₃ experienced more fractures. In the vitamin D arm, 157 women sustained 171 fractures, providing a fracture rate of 4.9 per 100 person years. By contrast, 125 women in the placebo arm sustained 135 fractures, providing a fracture rate of 3.9 per 100 person-years. Thus, the incidence fracture rate ratio was 1.26 in the vitamin D arm (95% CI 1.00–1.59, p=0.047). The fracture rate was higher in the first three months after vitamin D₃ ingestion, but the p-value for the temporal association was not significant.

Interestingly, a 2007 study by Smith et al. [32] also demonstrated that high-dose once yearly vitamin D₂ increased the risk of fracture. In that randomized, double-blind, placebo-controlled trial, 9440 men and women over age 75 years were administered 300,000 IU of intramuscular vitamin D₂ or a matching placebo injection each fall for three years. Study drug was administered when subjects received their yearly fall influenza vaccination. Subjects in the vitamin D arm had a higher rate of hip fracture (1.49, 95% CI 1.02–2.18, p=0.04). However, there was no significant difference between treatment arms for first fracture, wrist fracture, or falls.

In a post-hoc analysis of the Smith trial, women randomized to vitamin D₂ experienced a 59% increase in the risk of hip or wrist fractures, compared to women randomized to placebo (p=0.003), leading the authors to speculate that gender might influence the negative effect of high-dose vitamin D on fracture risk. Unfortunately, only 43 subjects (0.5%) underwent measurement of 25(OH)D during the trial and these subjects enjoyed excellent vitamin D stores at baseline (mean 25(OH)D 57 ng/mL); merely 25% of these subjects had initial 25(OH)D levels <30 ng/mL. Increases in 25(OH)D levels occurred among subjects randomized to vitamin D₂, but not among those randomized to placebo, based on measurements taken at baseline, 1, 4, 8, 12, 13 and 16 months of study participation.

In summary, authors of most meta-analyses (Table 2) have concluded that vitamin D does not reduce the risk of fracture, unless combined with calcium therapy. Two randomized placebo-controlled trials testing a once yearly high-dose vitamin D regimen reported that such therapy increased fractures [22, 32], with one study also reporting increased falls [22].

Thus, it seems appropriate to question both the safety, and the necessity, of high-dose vitamin D.

How might high-dose vitamin D increase the risk of fracture? Animal studies suggest that high-dose vitamin D might increase bone resorption. In one study [33], researchers fed rats a low calcium diet and administered vitamin D₃ for seven days as 0.2 µg/kg/day, 1 µg/kg/day and 5 µg/kg/day. Despite a decline in PTH levels, rats in the high-dose vitamin D₃ arm demonstrated increased serum calcium levels, an increase in Tartrate-Resistant Acid Phosphatase (TRAP) levels in the tibial epiphyses, and a dose-proportional decline in serum RANKL levels. Presumably, the low calcium diet prevented vitamin D-mediated increases in calcium absorption, so that any observed increments in serum calcium resulted from increased bone resorption. Authors concluded that short-term, high-dose vitamin D negatively impacted skeletal integrity by causing excess bone resorption.

In another study [34], high-dose vitamin D₃ increased 1,25(OH)₂D metabolism. Rats consuming a normal calcium diet were randomized to high-dose vitamin D₃ (25,000 IU three times a week) or a control dose of vitamin D₃ (200 IU three times per week). Compared to rats receiving lower vitamin D₃ doses, the rats receiving high-dose vitamin D₃ experienced a significant increase in renal vitamin D receptor concentrations, a 43-fold increase in levels of renal 24-hydroxylase enzyme, and a significant decline in 1,25(OH)₂D levels. The authors concluded that high-dose vitamin D caused greater metabolic clearance rate of 1,25(OH)₂D.

How might high-dose vitamin D increase the risk of falls? Since the precise mechanism whereby vitamin D appears to influence muscle health is uncertain [1], this author can only speculate on a biologically plausible explanation for this finding. Based on a rodent study cited above, high-dose vitamin D therapy might trigger a feedback loop in which the organism avoids hypercalcemia by increasing 1,25(OH)₂D metabolism. Lower 1,25(OH)₂D levels could theoretically decrease the calcium available to muscle cells, thereby negatively influencing muscle cell contraction and relaxation and subsequent global muscle function.

Conclusion

Two recent randomized placebo-controlled clinical trials in which serum 25(OH)D levels >30 ng/mL were achieved with vitamin D therapy led to surprising findings. In one study [21], high-dose vitamin D therapy did not decrease PTH or bone resorption in subjects with vitamin D insufficiency. In a placebo-controlled trial [22], high-dose once yearly vitamin D therapy with subsequent 25(OH)D levels >30 ng/mL led to a higher number of fractures and falls. Interestingly, a 2007 randomized placebo-controlled trial by Smith et al. [32] also reported higher rates of fracture with once yearly high-dose vitamin D. Though the mechanism by which high-dose vitamin D might increase fracture is uncertain, these two large clinical trials raise concern regarding the safety of high-dose vitamin D leading to a 25(OH)D level >30 ng/mL. Finally, the Institute of Medicine undertook a comprehensive review of existing literature on health outcomes related to vitamin D status, and concluded that nearly all individuals are vitamin D replete when their 25(OH)D level is ≥20 ng/mL. This author concludes that serum 25(OH)D levels >30 ng/mL are not necessary, nor optimal, for all individuals.

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Figure 1. Relationship Between Achieved 25(OH)D Level and Relative Risk of Hip Fracture [30] Data from the study in which subjects achieved a serum 25(OH)D level of 105 nmol/L (42 ng/mL) reflects measurement of levels in a subset of 52 of 3270 subjects randomized to placebo or tricalcium phosphate and vitamin D [31]. The authors used a competitive binding assay to measure serum 25(OH)D levels. The assay works by displacing [^3H]25(OH) D_3 from the plasma vitamin D binding protein, and thus the assay can overestimate serum 25(OH)D levels due to interference from other substances that are co-extracted when preparing the sample for analysis [1].

Table 1

Summary of Changes to the Institute of Medicine Daily Vitamin D Dietary Reference Intakes [1, 16]

Life Stage Group	1997 Vitamin D Adequate Intake	2011 Vitamin D Recommended Daily Allowance
0–1 year	200 IU [†]	400 IU
1–50 years	200 IU	600 IU
51–70 years	400 IU	600 IU
>70 years	600 IU	800 IU
Pregnant or Lactating	200 IU	600 IU

[†] Please note that “IU” denotes international units. One international unit (IU) is equal to 0.025 micrograms of vitamin D. The intakes above assume a setting of minimal sun exposure.

Table 2
Recent Meta-Analyses Evaluating the Effect of Vitamin D on Incident Fractures

Meta-Analysis	Subjects Included	2007 Smith Trial Included	Conclusions
2007, Cranney et al. [17]	Postmenopausal women and men ≥ 65 years old	No	Vitamin D without calcium does not reduce fractures. Vitamin D with calcium reduces total and hip fractures, but in subgroup analysis this benefit is only evident in trials of institutionalized elderly.
2007, Boonen et al. [27]	Postmenopausal women and men ≥ 50 years old in which hip fracture was the study outcome	No	Vitamin D without calcium does not reduce hip fractures. Vitamin D with calcium reduces the risk of hip and non-vertebral fractures. An exploratory analysis of trials using 700–800 IU of vitamin D reveals a slightly greater reduction in risk for hip fracture.
2009, Bischoff-Ferrari et al. [30]	Men and women ages ≥ 65 years old except for women in Women's Health Initiative study who were included if >60 years old	No	Fracture prevention is dose-dependent. The anti-fracture efficacy of vitamin D increases with higher vitamin D dose and higher achieved 25(OH)D levels.
2009 Cochrane analysis by Avenell et al. [28]	Men ≥ 65 years old, postmenopausal women	Yes	Vitamin D alone is unlikely to reduce new fractures, but vitamin D with calcium does reduce hip fractures.
2010, DIPART analysis by Abrahamsen, et al. [29]	Trials of 1,000+ subjects in which individual subject level data was provided to the authors	Yes	Vitamin D without calcium at doses of 400 to 800 IU daily does not reduce fractures. By contrast, concomitant calcium and vitamin D reduce hip fractures and total fractures, regardless of age, gender or previous fractures.