The effect of vitamin D on bone and osteoporosis

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The main effect of the active vitamin D metabolite 1,25(OH)2D is to stimulate the absorption of calcium from the gut. The consequences of vitamin D deficiency are secondary hyperparathyroidism and bone loss, leading to osteoporosis and fractures, mineralization defects, which may lead to osteomalacia in the long term, and muscle weakness, causing falls and fractures. Vitamin D status is related to bone mineral density and bone turnover. Vitamin D supplementation may decrease bone turnover and increase bone mineral density. Several randomized placebo-controlled trials with vitamin D and calcium showed a significant decrease in fracture incidence. However, very high doses of vitamin D once per year may have adverse effects. When patients with osteoporosis are treated with a bisphosphonate, they should receive a vitamin D and calcium supplement unless the patient is vitamin D replete. These subjects are discussed in detail in this review.

Finally, the knowledge gaps and research agenda are discussed.

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Introduction

Vitamin D status influences the overall mineralization of the skeleton, the rate of bone turnover and the occurrence of fractures. Epidemiological studies show relationships between vitamin D deficiency and lower bone mineral density, higher bone turnover and higher fracture incidence than in case of a vitamin D replete state. Vitamin D supplementation studies resulting in an improvement of vitamin D status have demonstrated an increase of bone mineral density, a decrease of bone turnover and a decrease of fracture
incidence. This paper will give an overview of the available data from epidemiological and intervention studies, and identify gaps in knowledge and a research agenda for the coming years.

**Pathophysiology of bone loss in vitamin D deficient patients**

The active vitamin D metabolite 1,25(OH)2D opens up calcium channels in the gut, stimulates the formation of calcium binding protein in the intestinal cell, and thereby stimulates the absorption of calcium and phosphate from the gut. In this way, optimal circumstances for bone mineralization are created. Mineralization in itself is a passive process, once sufficient calcium and vitamin D are available. In case of vitamin D deficiency, the 1,25(OH)2D concentration may drop and less calcium will be available for bone mineralization. The parathyroid hormone (PTH) level will increase, stimulating the hydroxylation of 25(OH)D in the kidney to 1,25(OH)2D. The increased serum PTH stimulates bone turnover, leading to bone loss.\(^1\) In the new steady state, serum 1,25(OH)2D is within the normal reference range and calcium absorption is restored, at the expense of increased bone resorption. In periods of protracted vitamin D deficiency bone loss is increased and this may lead to osteoporosis (Fig. 1). High turnover bone contains more osteoid tissue (not yet mineralized bone), because more remodeling occurs on the bone surface than in normal circumstances. In addition, the mineralized bone contains less mineral, because the mean age of the osteons is less, and mineral is accumulating up to two years after formation of the osteon. In case of longstanding severe vitamin D deficiency the volume of the osteoid tissue accumulates to more than 5%, leading to osteomalacia. In a series of 119 bone biopsies of patients with hip fracture, overt osteomalacia was not detected, but high bone turnover was observed in 20% of the patients.\(^2\) About 80% of the patients in this series had a serum 25(OH)D lower than 25 nmol/l. Hyperosteoidosis was observed in 0–37% in 19 series of patients with hip fracture, but criteria were very different, including osteoid volume, osteoid thickness, osteoid surface and number of osteoid lamellae. When osteoid thickness was used as main criterion, osteomalacia ranged from 0 to 12%.\(^1\) While high turnover is quite common in older persons, especially in patients with hip fracture, it is surprising that biopsies in patients with hip fracture and severe vitamin D deficiency often do not show signs of vitamin D deficiency. The bone loss in patients with vitamin D deficiency is mainly due to secondary hyperparathyroidism and is for a large part irreversible.\(^3\)

Vitamin D deficiency is associated with increased serum PTH, but the correlation coefficient between serum 25(OH)D and serum PTH does not exceed 0.35, indicating a moderate relationship. Of course, other important determinants of serum PTH in the aged population are renal function and immobility. Serum PTH increases when creatinine clearance drops below 60 ml/min, and immobility suppresses serum PTH. A high calcium intake also may suppress serum PTH.

Relationships between serum 25(OH)D and serum PTH, bone turnover and bone mineral density exist in patients with vitamin D deficiency and insufficiency, but are not observed in a vitamin D replete state. Threshold serum 25(OH)D levels may be established for these outcomes.

![Fig. 1. The pathophysiologic pathways from vitamin D deficiency to osteoporosis, osteomalacia, falls and fractures.](image-url)
Vitamin D status and bone mineral density

Vitamin D status is related to bone mineral density (BMD), not only in vitamin D deficient subjects, but also in vitamin D insufficient subjects. In cross-sectional studies, relationships between serum 25(OH)D and bone mineral density of the hip have been observed. The Amsterdam Vitamin D Study showed a relationship between serum 25(OH)D and bone mineral density of the femoral neck up to a serum 25(OH)D of 30 nmol/l.\textsuperscript{4} In the NHANES III study, a relationship between serum 25(OH)D and BMD of the hip was observed in younger (20–49 yr) and older adults (≥50 yr) up till a threshold of 90 nmol/l.\textsuperscript{5} Thresholds were also studied in the Longitudinal Aging Study Amsterdam (LASA). The BMD in the total hip and in the trochanter increased up till a serum 25(OH)D of 50 nmol/l and then leveled off (Fig. 2).\textsuperscript{6} A global study on vitamin D status and BMD in 7441 postmenopausal women with osteoporosis showed a significant positive relationship between serum 25(OH)D and BMD in the trochanteric area of the hip with a threshold below 50 nmol/l. However, BMD still showed some increase above 50 nmol/l.\textsuperscript{7}

![Fig. 2. Relationships between serum 25(OH)D and PTH, bone turnover markers, BMD of total hip and trochanter and physical performance as determined by LOESS plots. Data are from the Longitudinal Aging Study Amsterdam. Arrows indicate suggested threshold values of serum 25(OH)D for these outcomes. For serum PTH there is no clear threshold. Adapted from Kuchuk et al. J Clin Endocrinol Metab 2009 (ref 6) with permission of the Endocrine Society.](image-url)
Many randomized placebo-controlled clinical trials were performed to study the effect of vitamin D on BMD, and these are summarized in Table 1. Several of these were performed as part of larger trials to study the effect of vitamin D on fracture incidence. In most trials, calcium was given together with vitamin D in doses between 500 and 1200 mg/d. The increase of BMD was usually observed in the femoral neck or the total hip, but sometimes in total body calcium. In most studies the increase of BMD was 1–2.5% in the first year and very little in the second year. The first study in severely deficient nursing home residents with a mean age of 84 years showed an increase in BMD of 7%, but this may be due to a coexisting mineralization defect. When vitamin D and calcium supplements were discontinued the gain in BMD disappeared in about two years.

### Vitamin D and bone turnover

Vitamin D deficiency causes secondary hyperparathyroidism and high bone turnover. Bone turnover and serum 25(OH)D was studied at baseline in a clinical trial on the effect of bazedoxifene in 7441 postmenopausal women with osteoporosis. With increasing serum 25(OH)D from <25 nmol/l to > 75 nmol/l, mean serum osteocalcin decreased from 34.1 to 30.8 ng/ml, and mean CTX decreased from 0.56 to 0.52 ng/ml ($P < 0.001$) in parallel with the increase of bone mineral density of both spine and hip. In the LASA study, serum osteocalcin, a marker of bone formation, and urinary deoxypyridinolin excretion, a marker of bone resorption, were elevated when serum 25(OH)D was low. Both markers decreased with increasing serum 25(OH)D up to a level of 40 nmol/l when a plateau was reached (Fig. 2). A placebo-controlled intervention study with vitamin D 400 IU/d in 330 older women led to a small decrease of serum osteocalcin. Vitamin D3 1000 IU/d in combination with calcium 1500 mg/d caused a decrease of urinary N-telopeptide of 50%, a decrease of serum osteocalcin of 20%, and a decrease of alkaline phosphatase of 10%. A similar decrease of urinary C cross-linked telopeptide of 40% after 3 and 50% after 6 months was obtained after 3 and 6 months vitamin D$_3$, 800 IU/d combined with calcium 1000 mg/d in older women. When calcium and vitamin D are discontinued, bone turnover markers again increase to the pretreatment level.

### Vitamin D for the prevention of fractures

Fractures may occur in children with rickets and in adult patients with osteomalacia. Rickets and osteomalacia only occur with severe vitamin D deficiency, i.e. serum 25-hydroxyvitamin D below 15 nmol/l. In less severe vitamin D deficiency, the mineralization defect is more subtle, but bone turnover is high due to secondary hyperparathyroidism, and bone loss occurs leading to osteoporosis and fractures. Epidemiological studies show a relationship between vitamin D deficiency and fractures. In the Longitudinal Aging Study Amsterdam, the incidence of fractures was higher when serum 25(OH)D was lower than 30 nmol/l. This may be partly explained by a higher fall incidence, as a lower vitamin D status also is related to falls.

Many intervention studies have been performed in older persons to investigate whether vitamin D supplements with or without calcium can decrease the incidence of fractures. Eighteen of these are

#### Table 1

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Vit D dose</th>
<th>Calcium dose mg/d</th>
<th>BMD increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy 1992</td>
<td>56 f</td>
<td>800 IU/d</td>
<td>1200</td>
<td>Total hip + 7%, $p &lt; 0.001$</td>
</tr>
<tr>
<td>Ooms 1995</td>
<td>348 f</td>
<td>400 IU/d</td>
<td>–</td>
<td>Femoral neck + 2.2%</td>
</tr>
<tr>
<td>Dawson-Hughes 1995</td>
<td>247 f</td>
<td>700 IU/d</td>
<td>500</td>
<td>Femoral neck + 1.5%, $p &lt; 0.01$</td>
</tr>
<tr>
<td>Dawson-Hughes 1997</td>
<td>318 m + f</td>
<td>700 IU/d</td>
<td>500</td>
<td>Femoral neck + 1%, $p &lt; 0.001$</td>
</tr>
<tr>
<td>Chapuy 2002</td>
<td>114 f</td>
<td>800 IU/d</td>
<td>1200</td>
<td>Femoral neck + 2.5%, $p = 0.09$ + 3%</td>
</tr>
<tr>
<td>Harwood 2004</td>
<td>150</td>
<td>800 IU/d</td>
<td>1000</td>
<td>+ 3%</td>
</tr>
<tr>
<td>Jackson 2006</td>
<td>2431 f</td>
<td>400 IU/d</td>
<td>1000</td>
<td>Total hip + 1%</td>
</tr>
<tr>
<td>Zhu 2008</td>
<td>120 f</td>
<td>1000 IU/d</td>
<td>1200</td>
<td>Total hip + 2%</td>
</tr>
<tr>
<td>Kärkkäinen 2010</td>
<td>593 f</td>
<td>800 IU/d</td>
<td>1000</td>
<td>Total body + 0.7, $p = 0.01$</td>
</tr>
<tr>
<td>Moschonis 2010</td>
<td>66 f</td>
<td>900 IU/d</td>
<td>1200</td>
<td>Total body + 1–2%</td>
</tr>
<tr>
<td>Jorde 2010</td>
<td>421 m + f</td>
<td>20,000–24,000 IU/d</td>
<td>500</td>
<td>hip NS</td>
</tr>
</tbody>
</table>
summarized in Table 2. Five of these showed a decrease of fracture incidence in the intention-to-treat analysis.8–18 One study showed a borderline significant decrease of fracture incidence,19 and one other (Women’s Health Initiative) showed a significant decrease of hip fracture incidence in the per protocol analysis.20 Nine studies did not show significant changes in fracture incidence. Two studies showed an increase in fracture incidence.21,22 These two clinical trials both used a very high dose of vitamin D once per year. In the first study in 9440 older persons, vitamin D 300,000 IU vs placebo was given once per year21 and this led to an increase of hip fractures of 20%. In the Australian study22 vitamin D 500,000 IU were given orally vs placebo to 2256 women leading to an increase of fall (+15%) and fracture incidence (+26%). The increase of falls was mainly seen in the first three months after the vitamin D dose, when the serum 25(OH)D rose to over 120 nmol/l (Table 2).

Vitamin D as additional treatment in patients with osteoporosis

Most patients with osteoporosis are currently treated with bisphosphonates. Calcium and vitamin D are added for several reasons. In a patient with severe vitamin D deficiency, bisphosphonate treatment may induce symptomatic hypocalcaemia. In addition, all randomized clinical trials on bisphosphonates have been performed with calcium and vitamin D as basic treatment. Some investigators have questioned the possible gain in bone mineral density with additional treatment with calcium and vitamin D. A Japanese group treated 52 postmenopausal women with osteoporosis with alendronate 5 mg/d for 6 months without any supplement.23 The increase of lumbar spine BMD was significantly lower in the patients with a serum 25(OH)D < 62.5 nmol/l (25 ng/ml), than in those with serum 25(OH)D ≥ 62.5 nmol/l (3.3% vs 6.8%, P = 0.027). In Italy, 1515 women with postmenopausal osteoporosis treated with bisphosphonates or raloxifene were classified as vitamin D deficient or vitamin D replete. The mean annualized BMD increase in the lumbar spine was 0.22% in vitamin D deficient patients versus 2.11% in vitamin D replete patients (P = 0.002). Similar differences were observed in the hip.24 The odds ratio for incident fractures was 1.7 (P = 0.004) in vitamin D deficient compared with vitamin D replete patients. These data confirm that the addition of vitamin D and calcium to anti-osteoporotic treatment is necessary, unless the patient is vitamin D replete (serum 25(OH)D > 50 nmol/l all year round) and has a dietary calcium intake of 1200 mg/d. Anyhow, the recent recommendation of the

Table 2
Results of randomized clinical trials of vitamin D (and calcium) with fracture as outcome criterion.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Patients</th>
<th>Vit D dose</th>
<th>Calcium dose mg/d</th>
<th>Obtained 25(OH)D Dnmol/l</th>
<th>Fracture risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy 19928</td>
<td>3270</td>
<td>800 IU/d</td>
<td>1200</td>
<td>71</td>
<td>hip:−43%, non-vert:−32%</td>
</tr>
<tr>
<td>Heikinheimo 1992 15</td>
<td>799</td>
<td>150,000–300,000</td>
<td>–</td>
<td>–</td>
<td>hip:−24%</td>
</tr>
<tr>
<td>Lips 1996 34</td>
<td>2578</td>
<td>400 IU/d</td>
<td>–</td>
<td>54</td>
<td>hip: NS, non-vert: NS</td>
</tr>
<tr>
<td>Dawson-Hughes 1997 16</td>
<td>389</td>
<td>700 IU/d</td>
<td>500</td>
<td>99</td>
<td>non-vert: P = 0.02</td>
</tr>
<tr>
<td>Chapuy 2002 19</td>
<td>583</td>
<td>800 IU/d</td>
<td>1200</td>
<td>80</td>
<td>non-vert: P = 0.07</td>
</tr>
<tr>
<td>Meyer 2002 35</td>
<td>569</td>
<td>400 IU/d</td>
<td>–</td>
<td>74</td>
<td>non-vert: −22%</td>
</tr>
<tr>
<td>Trivedi 2003 17</td>
<td>2686</td>
<td>100,000 IU/4</td>
<td>–</td>
<td>1000</td>
<td>non-vert: −22%</td>
</tr>
<tr>
<td>Larsen 2004 18</td>
<td>9605</td>
<td>400 IU/d</td>
<td>1000</td>
<td>47</td>
<td>non-vert: −16%</td>
</tr>
<tr>
<td>Harwood 2004 20</td>
<td>150</td>
<td>800 IU/d</td>
<td>1000</td>
<td>52</td>
<td>non-vert: NS, falls −52%</td>
</tr>
<tr>
<td>Grant 2005 36</td>
<td>5292</td>
<td>800 IU/d</td>
<td>1000</td>
<td>62</td>
<td>hip:NS, non-vert: NS</td>
</tr>
<tr>
<td>Porthouse 2005 37</td>
<td>3454</td>
<td>800 IU/d</td>
<td>1000</td>
<td>62</td>
<td>hip:NS, non-vert: NS</td>
</tr>
<tr>
<td>Jackson 2006 20</td>
<td>36,282</td>
<td>400 IU/d</td>
<td>1000</td>
<td>62</td>
<td>hip:NS, total fr: NS (hip:per protocol: −29%)</td>
</tr>
<tr>
<td>Flicker 2005 38</td>
<td>625</td>
<td>1000 IU/d</td>
<td>600</td>
<td>80</td>
<td>non-vert:NS, falls −27%</td>
</tr>
<tr>
<td>Lyons 2007 39</td>
<td>3440</td>
<td>100,000 IU/4</td>
<td>–</td>
<td>80</td>
<td>non-vert:NS</td>
</tr>
<tr>
<td>Smith 2007 21</td>
<td>242</td>
<td>800 IU/d</td>
<td>300,000 IU/yr</td>
<td>84</td>
<td>hip +20%</td>
</tr>
<tr>
<td>Pfeifer 2009 40</td>
<td>2256</td>
<td>500,000 IU/yr</td>
<td>–</td>
<td>120</td>
<td>non-vert:NS, falls −27%</td>
</tr>
<tr>
<td>Sanders 2010 22</td>
<td>3195</td>
<td>800 IU/d</td>
<td>1000</td>
<td>75</td>
<td>fracture +26%, falls +15%</td>
</tr>
</tbody>
</table>

hip = hip fracture; non-vert = non-vertebral fracture; NS = not significant; * = p < 0.05.
Institute of Medicine for vitamin D is 600–800 IU/d depending on age.25 The Dutch Health Council recommends 800 IU/d for all patients with osteoporosis. The addition of calcium should not be exaggerated, as a recent meta-analysis suggested that very high intakes might increase the risk of cardiovascular disease.26

Gaps in knowledge

Randomized clinical trials have demonstrated that vitamin D with or without calcium can increase BMD, decrease bone turnover and decrease fracture incidence. It is not known whether vitamin D is effective only in vitamin D deficient or insufficient older persons, or in the complete older population. Some studies suggest that it is more effective in the institutionalized. It is not known whether the response can be increased by higher doses of vitamin D, in other words whether there is a dose-response relationship. An important problem is the addition of calcium. Some meta-analyses show that calcium should be added to vitamin D in order to be effective.27 However, a meta-analysis of calcium supplementation studies suggested that calcium supplementation may increase the risk for cardiovascular disease.26 Another question is whether vitamin D should be prescribed to all elderly or targeted to risk groups.22 In addition, the optimal dose may differ between individuals, i.e. in case of different genetic polymorphisms, chronic diseases and co-medication.

Research agenda

There is a need for large scale double-blind randomized clinical trials on the effect of different doses of vitamin D3 with and without calcium on fall and fracture incidence. Such trials should be done in different ages including the oldest old, in different populations with different vitamin D status and with regard to the effect of genetic profile, chronic disease, co-medication on response to treatment.

References


*22. Sanders KM, Stuart AL, Williamson EJ et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *The Journal of the American Medical Association* 2010; **303**: 1815–1822.


