

# THE ROLE OF VITAMIN D IN BONE METABOLISM AND BEYOND



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## Abstract

Vitamin D regulates bone metabolism and is an important factor in bone health. Vitamin D deficiency is associated with decreased bone mineral density, an increased fracture risk, and an increased risk of falls. Over the past decade, there has been a rising interest in the non-skeletal effects of vitamin D. While there has been some proposed benefit on cardiovascular health, cancer prevention, and inflammation, evidence is limited. Measurement of serum 25-hydroxy vitamin D levels is a contentious issue, with considerable variability between guidelines regarding testing strategies. Additionally, the optimal dose of vitamin D continues to be debated. This article reviews the evidence around both the skeletal and non-skeletal effects of vitamin D use, and the current guidelines about serum 25-hydroxy vitamin D testing and dosing.

## Résumé

La vitamine D contrôle le métabolisme osseux et contribue de façon importante à la santé osseuse. Le déficit en vitamine D est associé non seulement à une diminution de la densité minérale osseuse et à un risque accru de fractures, mais aussi à un risque plus élevé de chutes. Au cours de la dernière décennie a surgi un intérêt croissant envers les effets non-osseux de la vitamine D. Des effets bénéfiques sur la santé cardiovasculaire ont été évoqués, ainsi que des effets positifs dans la prévention du cancer et le contrôle de l'inflammation. Néanmoins, les preuves de ces effets semblent limitées. Les recommandations quant à la mesure de la vitamine D 25-hydroxylée sont sujets à controverse étant donné la variabilité des lignes directrices à cet effet. De plus, la dose optimale de vitamine D n'est toujours pas déterminée. Cet article révisé les données probantes sur les effets osseux et extra-osseux de la vitamine D et les lignes directrices actuelles concernant le dosage sérique de la vitamine D 25-hydroxylée ainsi que la posologie recommandée.

**V**itamin D is an important regulator of bone metabolism. It regulates calcium, the main mineral component of the skeleton, by controlling its entry into the intestine, its exit through the kidney, and its storage in bone.<sup>1</sup>

Due to its role in the bone metabolism and mineralization, vitamin D deficiency is a major cause of bone loss (Figure 1). Vitamin D deficiency causes decreased gut absorption of calcium and phosphate, leading to suboptimal bone mineralization and eventually osteomalacia. It also stimulates production of the parathyroid hormone (PTH), which causes increased bone turnover and therefore bone loss. In many elderly patients, poor renal function also increases production of PTH, therefore further driving this accelerated bone loss.<sup>1</sup>

Considering the multiple pathways by which vitamin D affects bone, it is not surprising that vitamin D status is of clinical significance. Vitamin D deficiency (serum 25-OH D <25 nmol/L) and insufficiency (serum 25-OH-D 25–75 nmol/L) have both been correlated with decreased bone mineral density (BMD). A large prospective study in older adults has shown a correlation between serum vitamin D levels >50 nmol/L (normal >75 nmol/L)<sup>2</sup> and an increase in BMD. Another cohort study found that there were increasing gains in BMD at vitamin D levels >50 nmol/L.<sup>3</sup> In terms of where these gains of BMD occur, a randomized control trial in which subjects took both 800 IU of vitamin D and 1.2 g of elemental calcium daily showed that a BMD increase occurred primarily in the femoral neck or total hip, with an increase

## Vitamin D: A regulator of bone metabolism

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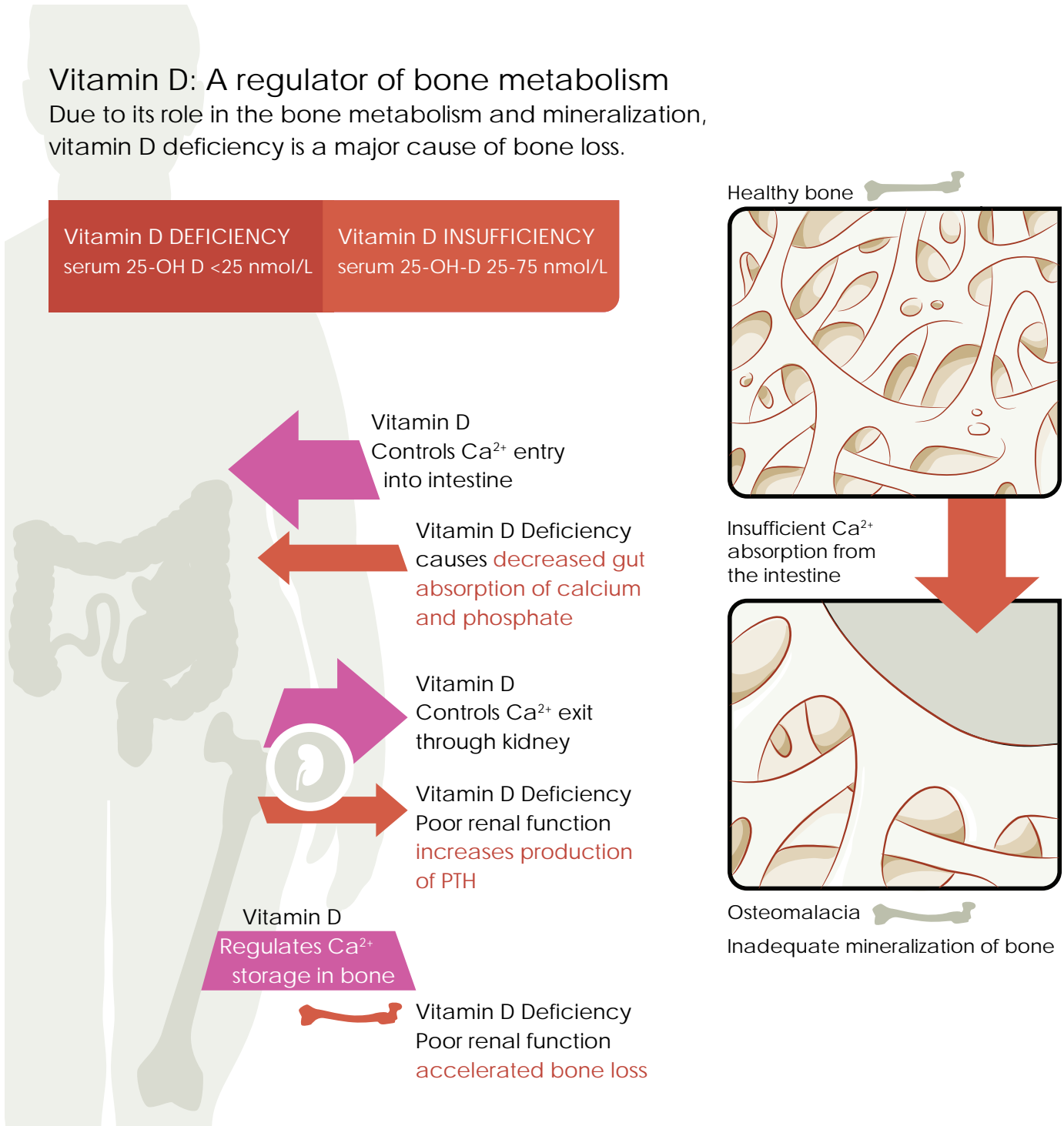


Figure 1. Vitamin D and bone metabolism. PTH = parathyroid hormone.

of 1–2.5% in the first year up to a maximum of 7% in severely deficient patients.<sup>4</sup> All subjects had low-normal 25 (OH)D levels at baseline, and supplementation resulted in a 162% increase in these levels.<sup>4</sup> Another randomized control trial in which subjects were treated with 700 IU of vitamin D plus 500 mg of calcium citrate daily found that gains in BMD disappear by about 2 years after the discontinuation of supplementation at study doses.<sup>5</sup> Subjects in this study were not taking medications known to affect bone metabolism (including vitamin D and calcium) prior to randomization, but baseline vitamin D levels were not tested.<sup>5</sup>

It is important to know how this positive effect of vitamin D on BMD translates to clinical outcomes. In the Longitudinal Aging Study Amsterdam, the relationship between serum vitamin D levels and fractures was examined in a cohort study of 1,311 community-dwelling seniors. Subjects with serum vitamin D levels <30 nmol/L were found to have a higher incidence of fractures.<sup>6</sup> A meta-analysis of randomized clinical trials on the relationship between vitamin D supplementation and fractures showed a relative risk reduction of 26% for hip fractures and 23% for all non-vertebral fractures in both ambulatory and institutionalized patients taking a dose of 700–800 IU of cholecalciferol, either with or without concurrent calcium supplementation. Daily doses of 400 IU were not sufficient to decrease fractures rates.<sup>7</sup> Interestingly, randomized controlled trials using high doses of vitamin D (>300,000 IU) given yearly resulted in an increased fracture risk of more than 20%.<sup>8,9</sup> These high doses of vitamin D also resulted in a 15% greater risk of falls within the first 3 months, with some of the excess fractures associated with the falls and others occurring independently of the falls.<sup>9</sup> Trials using the same total dose divided throughout the year (100,000 IU every 4 months) did not show an increased risk of fracture.<sup>10–12</sup> It is therefore postulated that high serum vitamin D levels (>120 nmol/L) and the subsequent decrease in levels over the course of the year may be the cause of increased risks of fractures and falls.

Large annual doses of vitamin D have been associated with an increased risk of falls, whereas more frequent, regular dosing (i.e., daily, weekly, or monthly dosing) has been associated with a reduced risk of falls. A recent systematic review and meta-analysis of 26 trials demonstrated a significant decrease in falls in those on vitamin D supplementation, with the greatest benefits seen in elderly females, those with baseline vitamin D deficiency, and those taking concurrent calcium supplementation.<sup>12</sup> The mechanism postulated for this decreased risk of falls includes improved muscle strength and changes in the central and peripheral nervous systems.<sup>13</sup>

This effect of vitamin D on the nervous system is among the non-skeletal effects that have been associated with vitamin D in recent years. Because 25-hydroxy-vitamin D (calcidiol) can be converted into the active form, calcitriol, in many different tissues and can regulate cell proliferation and apoptosis, much research is now being targeted to its role in other organ systems.<sup>14</sup> Vitamin D deficiency may potentially lead to hypertension, due to the presence of vitamin D receptors in vascular smooth muscle and its effects on renin activity.<sup>15</sup> Vitamin D has also been shown to have significant immunomodulatory effects, which may explain the observed relationship between low vitamin D levels and systemic lupus

erythematosus, inflammatory bowel disease, multiple sclerosis, and type 1 diabetes.<sup>16</sup> Furthermore, the increased incidences of the metabolic syndrome, type 2 diabetes, and overall mortality in those who are vitamin D deficient have been attributed to its anti-inflammatory properties.<sup>16</sup> The role of vitamin D in cancer prevention is among the most robustly studied of these non-traditional roles of vitamin D, with studies showing benefits in colon, breast, and prostate cancers.<sup>16</sup> While these non-skeletal benefits of vitamin D are encouraging, most of the research is in the form of observational studies and therefore must be interpreted with caution until more controlled, interventional data are available.

Measurement of serum 25-hydroxy vitamin D levels also remains a contentious issue. Due to increasing evidence for the benefits of vitamin D, more physicians have been ordering serum vitamin D level measurements. Vitamin D testing in British Columbia has increased 10-fold in the past 5 years, which, at \$93.63 per test, has resulted in \$3 million dollars annually for outpatient vitamin D testing.<sup>17</sup> While measuring serum the vitamin D level is the best indicator of sufficiency, routine monitoring is currently not recommended in the latest Canadian guidelines.<sup>14</sup> These guidelines suggest that monitoring should only be done in “high-risk” patients and only after 3 months of supplementation.<sup>14</sup> Because the proposed non-musculoskeletal effects of vitamin D have not yet been verified in randomized controlled trials, it is still premature to justify the cost of testing those who are not at significant risk of falls and fractures.<sup>18</sup> Although routine testing for the general population is not feasible, there remains quite a lot of discrepancy about the frequency at which we should be testing patients who *are* most at risk of vitamin D deficiency. The current Canadian guidelines do not comment on how often testing should be done in high-risk patients<sup>14</sup> and, on review of the literature, it is clear that there is currently no evidence to support a particular testing strategy. A paper by Pepper et al. in 2009 described 36 different protocols for the repletion of vitamin D levels,<sup>19</sup> with some recommending yearly testing<sup>18</sup> and others recommending twice-yearly testing, once in spring for the nadir and the other at summer’s end for the peak.<sup>20</sup> A study in veterans hospitals across the southeastern United States found that there is great variability in both the frequency of serum vitamin D testing and in the follow-up of abnormal results. Not surprisingly, those centres that did more frequent testing had higher

### Key Points

- *Vitamin D is a key contributor to the maintenance of bone health.*
- *Vitamin D deficiency is common in the elderly and is associated with bad outcomes such as low bone mineral density, fractures, and falls.*
- *Evidence is lacking on the extra-skeletal benefits of vitamin D.*
- *Measurement of serum 25-hydroxy vitamin D is costly, and current Canadian guidelines recommend testing in high-risk patients only. The appropriate frequency at which testing should be performed remains uncertain.*
- *Canadian guidelines recommend vitamin D supplementation for all adults at a dosage of 400–1,000 IU/d; however, there is still much debate about the optimal dosage and the upper tolerable dosage.*

outpatient costs; but interestingly these same centres had lower in-patient costs. Furthermore, those who had follow-up vitamin D testing had 30% fewer in-patient hospitalizations and shorter lengths of stay when hospitalization occurred.<sup>21</sup> This suggests that, when guidelines are eventually developed for testing frequency for vitamin D, there are economic factors other than just the cost of the test itself that must be considered, and that perhaps more regular monitoring may lead to better outcomes from both a patient and an economic perspective in the long term.

One last caveat that must be considered regarding serum vitamin D testing is that, due to the overwhelming increase in vitamin D testing, the precise, laborious radioimmunoassay for measuring serum 25-hydroxy vitamin D levels has been replaced by quicker, less sensitive automated tests. Multiple automated methods currently exist, leading to substantial variability of results between laboratories.<sup>18</sup> It is therefore imperative that when levels are being drawn serially, patients use the same laboratory to ensure consistency.

Much has been learned about the positive effects of vitamin D in the past 10 years, yet there are still several gaps in our knowledge. In addition to the paucity of high-quality studies on its non-skeletal effects, data are also lacking on the effectiveness of vitamin D across different races and ages. More research is also required to better define the minimum required dose, as well as the tolerable upper limit.<sup>14</sup> The necessity of the addition of calcium supplementation is also in question, especially with new evidence pointing to increased cardiac events with calcium supplementation.<sup>22</sup> With these and other questions still unanswered, vitamin D will undoubtedly remain a popular topic of research over the next several years.

Although there is still discrepancy in the literature about the optimal dose of vitamin D,<sup>14,23,24</sup> current Canadian guidelines<sup>14</sup> recommend vitamin D supplementation for all adults. The dosing range varies depending on age, with dosages of 400–1,000 IU/d for those under 50 years old and 800–1,000 IU/d for those older than 50.<sup>14</sup> Guidelines also differ in their recommendations regarding the upper tolerable dosage. While Canadian guidelines state that daily dosages of up to 2,000 IU are safe, others consider daily dosages of 4,000 IU<sup>23</sup> to as high as 10,000 IU<sup>24</sup> to be safe. The current Canadian guidelines advise against routine monitoring of serum vitamin D, except in patients at high risk of falls and fractures.<sup>14</sup> In these patients, serial testing performed at the same laboratory may improve outcomes, but an evidence-based approach to testing frequency has yet to be established.

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