



Review Article

Doses and Schemes for Correcting Vitamin D Deficiency: An Update

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Abstract

Vitamin D deficiency is a global problem and vitamin D supplements are used to enhance vitamin D status. There is, however, no agreement on the appropriate dosage and replacement schedule. Current guidelines often recommend doses of 800 IU to 1,000 IU of vitamin D per day in patients at risk for vitamin D deficiency, but in some situations, rapid correction with higher daily doses or single or intermittent dosing schedules are needed. The administration of vitamin D several-fold higher than the current recommended intake was previously suggested, based on its efficacy in correcting rapidly insufficient serum levels of 25(OH)D and its relative safety. Recent clinical trials have, however, shown that very high intermittent dosing schedules have resulted in unfavorable health outcomes.

The purpose of this article is to review the mechanism associated with the toxicities of very high intermittent dosing schedules, and to address the proper correction of vitamin D deficiency.

Key points

- Doses of 800 IU to 1,000 IU of vitamin D per day are recommended in patients at risk for vitamin D deficiency
- Rapid correction schemes for vitamin D deficiency have included high daily doses; as well as single or intermittent megadose boluses administered at variable time intervals
- Vitamin D in high daily doses or intermittent megadose boluses can be chosen for a few weeks until adequate 25(OH)D levels are reached. In the case of intermittent administration, it is recommended that individual doses do not exceed 50,000 IU weekly
- Very high intermittent vitamin D megadose boluses can cause adverse events and must be avoided

Keywords: Vitamin D; Vitamin D Deficiency; Cholecalciferol; Megadose; 25OHD

Introduction

Vitamin D is a steroid hormone essential for regulating mineral metabolism and maintaining bone health. Although the prevalence of vitamin D deficiency has decreased in the last decade compared to the previous one, it is considered to still be high [1]. Vitamin D plays an important role in regulating calcium and phosphorus homeostasis and enables mineralization of newly formed osteoid tissue in bone, thereby preventing rickets in children and osteomalacia in adults. Additionally, it has different extra-skeletal functions, related to the wide tissue distribution of vitamin D receptors (VDR) [2-5].

One of the most important actions of vitamin D is to stimulate the absorption of calcium in the intestine, increasing its availability for adequate bone mineralization and is widely recommended and used in the prevention and treatment of osteoporosis [6]. Additionally, vitamin D may play an important role in the growth of muscle cells and the synthesis of proteins necessary for proper muscle function. These actions are reflected in beneficial effects on bone health and reduction in the risk of falls and fractures [2,7].

Vitamin D₃ is synthesized in the skin from 7-dehydrocholesterol (provitamin D₃), which is photolyzed into pre-vitamin D₃ through exposure to ultraviolet B sunlight (~295-315 nm); and it subsequently undergoes a thermally induced transformation to vitamin D₃ (cholecalciferol). Cutaneous synthesis is the main source of vitamin D in humans, while no more than 20% of the daily requirement of vitamin D is obtained from nutritional sources. The cutaneous synthesis of vitamin D shows seasonal variations depending on the intensity of UV radiation and other factors [2,8-10].

Vitamin D in the bloodstream is transported mainly bound to vitamin D transport protein (VDBP) to the liver, where it undergoes a hydroxylation in position 25, forming the 25(OH) D (calcidiol), mainly by the action of several cytochrome P450 enzymes (CYP2R1, CYP27A1), named as vitamin D₃-25-hydroxylase. Subsequently, 25(OH)D undergoes a second hydroxylation in the proximal tubular cells of the kidney, through the action of 1- α -hydroxylase enzyme (CYP27B1), producing 1,25(OH)₂D, which is the active form of vitamin D known as calcitriol. Hydroxylation in the liver is constitutive, while renal hydroxylation is highly regulated by different factors [7,8,11,12].

Serum calcidiol measurement is considered the test of choice to assess vitamin D status, because it is the circulating metabolite found in the highest concentration in serum and has a longer half-life compared to calcitriol (2-3 weeks versus 4-6 hours respectively) [13,14]. It is considered that the optimal level of

25(OH)D is ≥ 20 ng/mL for the healthy population, but in patients with osteoporosis and in those who are going to start treatment, the recommended level is 30ng/mL [4].

The major pathway for the inactivation of the vitamin D metabolites is via an additional hydroxylation through CYP24A1, a third enzyme belonging to mitochondrial P450 fraction, which degrades calcidiol and calcitriol into 24-hydroxylated products and are excreted through the bile into the feces [2,7]. Vitamin D is mainly found in two forms, D₃ (cholecalciferol) and D₂ (ergocalciferol), the chemical structures of vitamins D₂ and D₃ are similar but not identical. Cholecalciferol is considered the most recommended form of vitamin D, because it has a longer half-life, a greater affinity for vitamin D binding protein and VDR, and has been shown to be more effective in raising 25(OH)D levels compared to vitamin D₂ (ergocalciferol) [10,15].

The importance of adequate supplementation and correction of vitamin D deficiency has been widely reviewed; however, there are several not yet well-defined aspects, such as the appropriate dose and regimen for the correction of vitamin D deficiency and particularly, the use of very high single or intermittent doses of vitamin D. In this article, we review the available scientific information that supports the appropriate correction of vitamin deficiency considering the use of native forms of vitamin (D₃ and D₂), however, we have not considered the use of hydroxylated forms of vitamin D (alfacalcidol, calcitriol, etc.), because clinical studies with very high single or intermittent doses have used native forms of vitamin D.

Definitions Related To Vitamin D Replacement Schemes

It is convenient to clarify some terms commonly used in reference to doses and schedules for vitamin D supplementation. Terms such as high doses, megadoses, bolus dose, and intermittent doses are found in the literature. The National Cancer Institute INH defines the bolus dose as “A single dose of a drug or other substance given over a short period of time. It is usually given by infusion or injection into a blood vessel. It may also be given by mouth” [16]; while megadoses have been defined as “An exceptionally large dose, as of a drug or vitamin” [17].

Additionally, it has been proposed to consider intermittent doses to at least 1-week dosing intervals and high doses refers to an intermittent bolus dose of at least 20,000 IU or a daily dose of 4,000 IU [18]. However, other authors consider that a megadose refers to the administration of boluses of 100,000 IU or more of vitamin D [19], but there is no consensus on this definition.

Based on this clarification, it is understood that boluses refer to a single dose of a nutrient or medication, while megadoses relate to the administration of exceptionally high doses. So, to refer to very high doses (megadoses) administered single or intermittently,

probably the most appropriate term would be megadose boluses (single or intermittent).

Correction of Vitamin D Deficiency

There is significant variability in individual response to vitamin D supplementation; but in general, doses of 800 IU to 1,000 IU of vitamin D per day are recommended in patients at risk for vitamin D deficiency [20]. In certain groups of patients (malabsorption, obesity, bariatric surgery, etc.), higher daily doses are needed. In some situations, rapid correction of vitamin D deficiency is required, such as in patients with severe symptomatic deficiency or osteomalacia and/or 25(OH)D values below 10ng/mL, or when treatment with potent antiresorptive agents (denosumab or intravenous bisphosphonates) is to be initiated [4].

Rapid correction schemes for vitamin D deficiency have included high daily doses or single or intermittent megadose boluses administered at variable time intervals. However, these regimens are associated with a different pharmacokinetic profile, which may affect their efficacy and represent an important variable in determining the therapeutic response [21].

The rationale that justified the use of megadoses in single or intermittent boluses was based on the concept of the storage of vitamin D in fatty tissue and its slow release, which could maintain serum levels [22]. Other arguments in favor were the improvement in adherence compared to daily doses and the additional advantage of not increasing the number of medications in older adults with polypharmacy [18,22,23].

Different studies reported that single bolus doses of 300,000 to 600,000 IU of vitamin D2 or D3 allowed a rapid and safe correction of the deficiency; and were considered convenient and practical regimens for this purpose [24-26], but the safety evaluation was done using biochemical parameters as changes in serum calcium values and in urinary calcium excretion. However, subsequent studies provided contrary information not only about the efficacy of megadose boluses, but also about the potential risks of adverse events associated with their use [18].

Effect of Different Vitamin D Replacement Schemes

Correcting deficient vitamin D levels and keeping them in stable physiological ranges is the goal of replenishing the deficiency. In clinical situations that warrant rapid correction of the deficiency, the administration of megadose boluses (single or intermittent) or high daily doses for a few weeks can be chosen. However, it is important to consider that these regimens have different pharmacokinetic characteristics, which could impact their efficacy and safety.

In the Kearns study, the efficacy of a single oral megadose of 250,000 IU of vitamin D3 versus placebo was evaluated. On the 5th

day after administration, 25(OH)D values rose significantly in the group that received vitamin D3 but returned to the baseline value on day 90; with similar concentrations at this time in comparison with the placebo group [28]. These results showed a transient and non-sustained elevation of 25(OH)D due to the effect of the single megadose bolus. In two previous studies that used single-dose boluses of 100,000 IU and 300,000 IU of vitamin D3 respectively, 25(OH)D values rose significantly, but with a tendency to return to baseline after 2 to 3 months [29,30].

In Välimäki's study, two doses of vitamin D3 (100,000 and 200,000 IU) were administered every 3 months versus placebo. Both vitamin D doses were associated with a rapid increase in 25(OH)D concentrations. The proportion of patients who achieved values $\geq 30\text{ng/mL}$, when all the measurements at week 1 after dosing were combined, was 68.9% and 76.1% with the doses of 100,000 IU and 200,000 IU respectively; but 3 months later, these percentages decreased to 32.4% and 40.8% respectively [22]. In this study, the rapid rise in 25(OH)D levels was followed by a pronounced decrease, with marked fluctuations in 25(OH)D levels [22,31].

Pekkarinen evaluated the effectiveness of a total annual dose of 292,000 IU of vitamin D3, but it was administered in two different schedules: daily doses of 800 IU or doses of 97,333 IU (oil) every 4 months. All patients who received the daily dose and 67% of those who received the four-monthly dose had 25(OH)D values above 20ng/mL at the end of the study; and 47% and 28% respectively achieved 25(OH)D values $\geq 30\text{ng/mL}$ at the end of the study. However, 21% and 56% of patients who received daily or quarterly doses, respectively, had 25(OH)D values below 20ng/mL on at least one occasion. The authors concluded that daily doses were more effective than quarterly doses in terms of improving serum 25(OH)D concentration [32].

Fassio evaluated three vitamin D replacement regimens: (1) 10,000 IU daily for 8 weeks, followed by 1,000 IU for 4 weeks, (2) 50,000 IU weekly for 12 weeks and (3) biweekly doses (100,000 IU every other week for 12 weeks). All 3 treatment schedules (at equivalent doses) were effective in correcting the deficiency, but the daily dosing schedule was slightly more effective than weekly administration, which in turn was more effective than biweekly dosing. Based on these results, the authors suggest that longer loading phases are probably unnecessary [33].

When comparing cumulative equivalent doses administered as daily doses or in megadose boluses, the former has been shown to be more effective in restoring and maintaining the 25(OH)D levels [21]. Additionally, megadose boluses produced a rapid but transient elevation of 25(OH)D, with large fluctuations in serum 25(OH)D and a tendency to return to the baseline value around 3 months after administration. In the first weeks after the

administration of a megadose bolus, serum 25(OH)D levels can exceed physiological values, but rapidly dropping even below the desired values [21,22].

It is important to comment that large seasonal fluctuations in 25(OH)D were associated with deleterious effects on bone metabolism. A positive and significant relationship has been found between seasonal variations in 25(OH)D with serum levels of PTH, CTX and NTX. Subjects with wider seasonal fluctuations in 25(OH)D showed higher levels of PTH, CTX and NTX, which would indicate an increase in bone resorption with probable deleterious effects on bone [31,34,35].

Vitamin D Megadoses Bolus and Compensatory Mechanisms

The unexpected increase in falls and fractures reported in a clinical trial associated with the intermittent administration of vitamin D megadose boluses raised concerns and was the subject of an extensive review to explain this paradoxical event, as well as the probable mechanisms involved [36].

In 2010, Sanders, in a group of 2,256 women ≥ 70 years of age, evaluated the efficacy of annual doses of 500,000 IU of cholecalciferol for 3 to 5 years compared to placebo, in reducing the risk of falls and fractures. Contrary to what was expected, an increase of 15% (CI 95: 1.02-1.30) in falls and 26% (CI: 1.00-1.59) in fractures was found in the group that received active treatment compared to those who received placebo. A temporal pattern of increased risk for falls and fractures in the first three months following the annual dose was observed, suggesting a relationship with the high serum levels of 25(OH)D or other metabolites [36].

In a previous study, Smith in 2007 evaluated a group of 9,440 men and women aged ≥ 75 years, who received 300,000 IU of intramuscular vitamin D2 or placebo annually for 3 years. In men, no effect on fractures was observed, but in the women group, a 59% increase in the fracture risk of the proximal femur or distal forearm was found in those who received vitamin D compared to placebo. No effect of vitamin D on fall risk was found, but this was a secondary objective of the study [37].

The results of the Sanders' study were the subject of an extensive discussion. Some hypotheses based on clinical and observational studies proposed that the beneficial effect of vitamin D in reducing chronic pain, reducing the rate of respiratory infections and improving physical performance and mood in older adults, would be responsible for an increase in mobility, a reduction in periods of physical inactivity and a greater tendency to adopt risky activities or behaviors, which would be the cause of the increased risk of falls and fractures [27,38,39].

The role of countervailing factors triggered by megadose boluses of vitamin D on mineral homeostasis has also been implicated [19,40] such as up-regulation of 24hydroxylase (CYP24A1), that results in

downregulation of 1,25(OH)2D and stimulating fibroblast growth factor 23 (FGF23), which suppresses 1 α -hydroxylase (CYP27B1) [40,41].

Owens compared weekly administration of 35,000 or 70,000 IU of vitamin D3 for 12 weeks, and this was followed by an additional 6 weeks without supplementation (total 18 weeks). Both doses were associated with a significant increase in 25(OH)D and 1,25(OH)2D3. However, with the 70,000 IU weekly doses, an increase in 24,25(OH)2D was observed at weeks 6 and 12, which persisted after stopping supplementation and until week 18. The authors concluded that high-dose vitamin D3 supplementation (70,000 IU) can inhibit the bioactivity of 1,25(OH)2D3; that would persist even after rapid discontinuation of high-dose vitamin D supplementation [42].

Another study in lactating mothers compared the administration of a single bolus of 150,000 IU of vitamin D3, with the administration of 5,000 IU daily for 28 days (the same cumulative dose but administered daily). The single bolus produced higher 25(OH)D concentrations over the first 15 days in comparison with the daily doses, but the elevation of 24,25(OH)2D was increased by approximately 50% with bolus dosing and 30% with daily dosing. This increase was maintained for at least 28 days after vitamin D administration [43].

These findings suggest that a single large bolus of vitamin D produces a long-lasting increase in 24-hydroxylase activity as a feedback control response, that results in downregulation of 1,25(OH)2D and its subsequent biological activity [42-44]. Tissue availability of the active 1,25(OH)2D is dependent on the balance between the activating 1 α -hydroxylase (CYP27B1) and the inactivating 24-hydroxylase (CYP24A1). A single megadose bolus of vitamin D can disrupt this tight hormonal control and paradoxically lead to an intracellular deficiency of the active form of vitamin D [44,45]. It has also been suggested that 24,25(OH)2D may act at the VDR as a "blocking molecule" binding to the VDR with subsequent reduction in 1,25(OH)2D biological activity [42].

Additionally, high doses of vitamin D increase fibroblast growth factor (FGF23) concentrations which impair the 1-alpha hydroxylation of 25(OH)D. A meta-analysis of 9 clinical studies found that vitamin D supplementation in deficient patients significantly elevated serum concentration of intact FGF23 (iFGF23), but the elevation in the C-terminal fraction of FGF23 (cFGF23) was not significant. Most of the clinical studies included in this meta-analysis focused on the measurement of iFGF23 and a few on the cFGF-23 [46].

Zitterman, in a meta-analysis of 23 clinical studies, found that vitamin D supplementation dose-dependently increases FGF23 levels. The effect was significantly greater with daily doses $> 3,000$ IU or when active vitamin D metabolites were used, while daily

doses of up to 3,000 IU did not result in a substantial change in FGF23. The FGF23 increment was also higher if baseline 25(OH) D concentrations were low (<20ng/mL) and in patients with end-stage kidney/heart failure. A limitation of this meta-analysis was the inclusion of studies that measured different forms of FGF23, but the majority of which measured iFGF23 (18 of 23 studies) [41,47].

FGF23 is a phosphaturic hormone secreted mainly by osteocytes that exert a negative control on 1,25(OH)2D synthesis, through the inhibition of the 1 α -hydroxylase enzyme (CYP27B1). In turn, FGF-23 increases the expression of the 24-hydroxylase enzyme (CYP24A1), the function of this last enzyme is precisely to prevent the accumulation of toxic levels of 1,25(OH)2D and 25(OH)D, by promoting the 24hydroxylation [12,40,48,49].

In addition to the association of FGF23 with faster progression of CKD (chronic kidney disease), left ventricular hypertrophy, and increased cardiovascular mortality, several studies reported an

association of FGF23 with increased risk of frailty and falls [50-52]; which, at least theoretically, could contribute to the increased risk of falls and fractures reported with the use of vitamin D megadose boluses.

Expert Consensus Statement on Correction of Vitamin D Deficiency

Vitamin D3 (cholecalciferol) is considered the most recommended form of vitamin D. Only some guidelines recommend using either (vitamin D3 or D2), but none of them recommend using only vitamin D2.

The recommended doses of vitamin D in patients at risk of vitamin D deficiency are around 800 IU to 1,000 IU daily, accompanied by sufficient calcium intake, mainly through diet or with pharmaceutical supplements when necessary [20]. However, the positions of different international guidelines recognize that in certain clinical situations the use of higher doses is required for rapid correction of vitamin D deficiency. See table 1.

Institution	Recommendation
AACE/ACE (2020) [53]	Adults who are vitamin D insufficient or deficient [serum 25(OH)D 20 to 29 or <20ng/mL, respectively] may be treated with 5,000 IU vitamin D3 daily for 8 to 12 weeks to achieve a 25(OH)D blood level >30ng/mL. Regimen should be followed by maintenance therapy of 1,000 to 2,000 IU of vitamin D3. Only in uncommon clinical situations is there a need to prescribe high dose (e.g., 50,000 IU)
GRIO (2020) [31]	In vitamin D deficiency or Insufficiency: Start with a loading phase: 50,000 IU of vitamin D3 per week for 8 weeks in patients whose 25OHD is <20 ng/mL; or 50,000 IU of vitamin D3 per week for 4 weeks in patients whose 25OHD is between 20 and 30ng/mL. After this loading phase, prescribe long-term supplementation: 50,000 IU of vitamin D3 per month
GCC (2020) [54]	For severe vitamin D deficiency (25(OH)D<10ng/mL): 50,000 IU loading dose weekly for 6 weeks
SEIOMM (2021) [55]	In patients with severe osteoporosis [25(OH)D<10ng/mL]: Cholecalciferol: 50,000 IU/week for 6-8 weeks. Subsequently continue with the recommendations for vitamin D insufficiency [25(OH)D 1030ng/mL]: Cholecalciferol: 50,000 IU/month or 1,000-2,000 IU/day
ESCEO Working Group (2022) [56]	In specific indications (Low 25-hydroxyvitamin D levels, need for a rapid correction of vitamin D deficiency, after bariatric surgery, etc.) loading dose (25,000 or 50,000 IU/week for 4–6 weeks) is recommended, followed by the maintenance dose (800–1000 IU)
SIOMMMS (2022) [4]	In patients with symptomatic osteomalacia and/or serum 25(OH)D<10ng/mL, or in patients starting bone anti-resorptive therapy with intravenous bisphosphonates or denosumab with serum 25(OH)D<20ng/mL. An initial loading dose of 3,000 - 10,000 IU/day (average 5000 IU/day) of vitamin D3 for 1-2 months, or in a single dose of 60,000 to 150,000 IU, followed by the maintenance dose (2,000 IU/day)
Central and Eastern European Expert Consensus Statement (2022) [56]	If a rapid correction of vitamin D deficiency is indicated, a regimen with a higher initial vitamin D dose (6,000 IU per day, and in certain cases, even up to 10,000 IU per day) for 4-12 weeks (depending on the severity of vitamin D deficiency), followed by a maintenance dose with 800 to 2,000 IU per day is recommended
UK clinical guideline for osteoporosis (2022) [57]	Routine intermittent administration of large doses of vitamin D (e.g.≥60,000 IU), is not advised

Table 1: Vitamin D supplementation schemes recommended by different societies.

AACE/ACE: American Association of Clinical Endocrinologists/American College of Endocrinology; GRIO: Groupe de Recherche et d'Information sur les Ostéoporoses; GCC: Gulf Cooperation Council; SEIOMM: Sociedad Española de Investigación Ósea y del Metabolismo Mineral; ESCEO: European Society of Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; SIOMMMS: Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases

Rapid replacement regimens include high daily doses or megadose boluses of vitamin D for a few weeks, followed in both cases by maintenance doses. The recommended high daily doses range between 3,000 IU and 10,000 IU depending on each particular guide. Most guidelines - with few exceptions - recommend not using weekly vitamin D boluses greater than 50,000 IU. Recent guidelines suggest the use of megadose boluses of 50,000 IU [53,55], or 25,000 to 50,000 [20] but avoiding doses higher than 60,000 IU [57].

This last recommendation is important to avoid triggering the compensatory mechanisms already described. It is important to consider that boluses of 70,000 IU of cholecalciferol can evoke compensatory mechanisms aimed at avoiding excessive elevation of 1,25(OH)₂D [42]; and the administration of 100,000 IU quarterly at least in one clinical study has not demonstrated efficacy in maintaining stable levels of 25(OH)D [22,31].

Conclusions

Doses of 800 to 1,000 IU of vitamin D per day are recommended for adult patients at risk of vitamin D deficiency, in order to ensure a sufficient vitamin D status. The use of intermittent regimens with large doses is not recommended for this purpose. In situations where rapid correction is required, vitamin D in high daily doses or intermittent megadose boluses can be chosen for a few weeks until adequate 25(OH)D levels are reached. In the case of choosing megadose boluses, it is recommended that individual doses do not exceed 50,000 IU weekly.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Disclosures and declarations

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