Chapter

An Evidence-Based Review of Efficacy and Safety of Dietary, Natural Supplements and Sunlight in Vitamin D Deficiency

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Abstract

There have been recent concerns about the propensity of calcium and vitamin D supplementation to cause cancer. In osteoporotic patients, this has led to increasing recommendations advocating the replacement of calcium supplementation with dietary or other means. Around the world, the problem of vitamin D deficiency remains, being a large contributor of rickets and osteomalacia in the developing world and osteoporosis in post-menopausal women and people dependent on long-term corticosteroid treatment. We review the alternatives of vitamin D supplementation through dietary, other natural supplements as well as sunlight therapy, in an evidence-based manner. We will also review the safety aspect of each modality.

Keywords: vitamin D deficiency, osteoporosis, rickets, bone health, diet, natural supplements

1. Introduction

Vitamin D is a fat-soluble vitamin utilised by human beings for normal bone development; maintenance by increasing the absorption of calcium, magnesium and phosphate; as well as potential pleiotropic effects on the prevention of cancer, heart disease, autoimmune disease, type 2 diabetes and depression [1].

A circulating level of 25-hydroxyvitamin D greater than 30 ng/mL (50 nmol/L) is considered a healthy level of vitamin D to maintain. About 1 billion people in the world have vitamin D deficiency, ranging from children (leading most notably to rickets), pregnant and lactating women, certain racial groups, post-menopausal women and the elderly (leading to osteoporosis) [2].

Vitamin D deficiency arises from multiple causes including inadequate dietary intake and inadequate exposure to sunlight. About 50–90% of vitamin D is absorbed through the skin via sunlight, whilst the rest comes from the diet.

Vitamin D clinical trials have increased over the past decade. Despite these trials, studies (including meta-analyses) have provided inconsistent conclusions. Some meta-analyses make the assumption that vitamin D is a pharmacological agent, and not as a nutrient. Bolland [3, 4] and Zhao's [5] findings suggest that vitamin D supplementation does not prevent fractures or falls (and in fact one study suggested it may contribute to falls in community-dwelling older women at higher dosages [6],

Figure 1.
In many countries, there is an abundance of sunlight throughout the entire year. Ironically, the sun-protective messages for the primary prevention of skin cancers become stronger than those of the moderate benefits of sunlight.

or have clinically meaningful effects on bone mineral density, and suggested 'little justification to use vitamin D supplements to maintain or improve musculoskeletal health'). A recent umbrella review did conclude that most RCTs have been carried out in populations that are not vitamin D deficient and, because of this, possible beneficial effects from vitamin D supplementation cannot be excluded [7].

Further, complementary medicine supplementation receives less stringent regulation for approval to the general public. For example, in Australia, vitamin D or other supplements which claim that it 'may' improve bone health and general well-being are approved on the Therapeutic Goods Administration as an ARTG [8] compared with vitamin D as a medication.

Given the urgent need for the general population, clinicians and consumers will benefit from the latest evidence for vitamin D supplementation (through diet, extraneous supplementation and sunlight therapy), including its efficacy and potential harm (**Figure 1**).

2. Epidemiology

Vitamin D deficiency is a major global public health problem in all aged groups, particularly in the Middle East. There is striking lack of data in infants, children and adolescents worldwide and in most countries of South America and Africa [9].

Of concern, even in countries where there is sun exposure all year-round, reports of deficiency is common in infants (90% in Turkey, 46% in black Americans, 96% in Kuwait and 99% in Indian), in children (58% in Belgium, 72% in Malaysia and 95% in Afghanistan), in adolescents (50% of non-whites in Canada, 46% in China and 45% in the United Arab Emirates) and in adults (52% of women in New Zealand, 97% in 62% in Korea and 77% in Brazil).

3. Pathophysiology

Vitamin D is crucial in calcium and vitamin D metabolism, as its absence around 15% of dietary calcium and 60% of phosphorus is absorbed. 1,25-Dihydroxyvitamin D interacts with the vitamin D receptor which increases

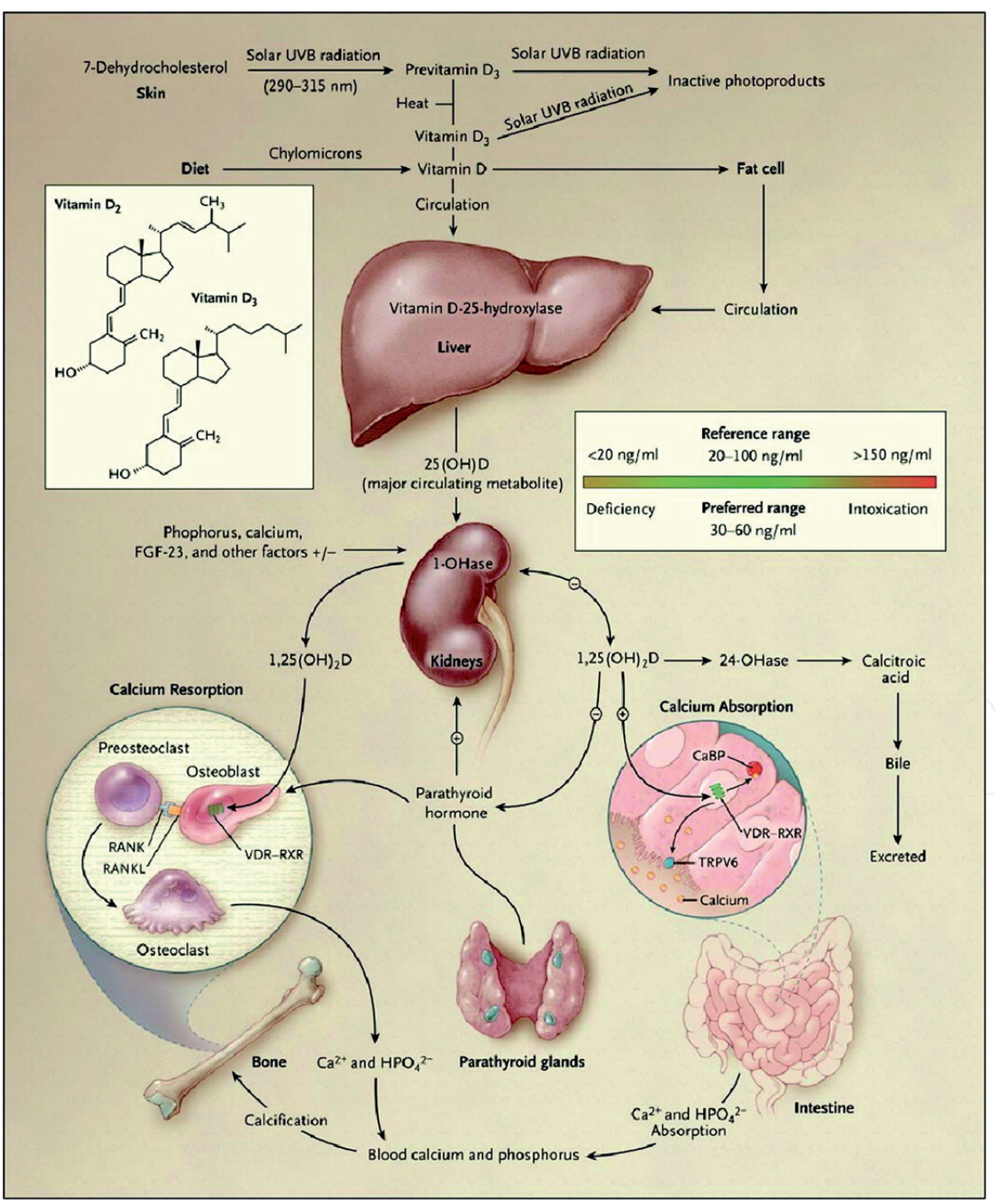


Figure 2.
Vitamin D Metabolism (From Horlick [10]).

the intestinal calcium absorption to 40% and phosphorus to 80% (**Figure 2**, [10]). Vitamin D is transformed for activation through two hydroxylations in the body. Among the metabolic products or modified versions of vitamin include calcitriol (1,25-dihydroxyvitamin D3); the active form of vitamin D, with a 15-hour half-life; and calcifediol (25-hydroxyvitamin D3) with a 15-day half-life [10]. Vitamin D is bounded to specific receptors located throughout the body. Whilst serum 25(OH) D levels do not indicate the amount of vitamin D stored in body tissues, it is the best indicator of vitamin D status.

When the level was 30 ng/mL or less, there was a significant decrease in intestinal calcium absorption that was associated with increased parathyroid hormone [10]. Further, there is strong support from reports that maternal vitamin D deficiency leads to overt bone disease (congenital rickets) from before birth to post-natal life [11]. Throughout the world, there has been widespread debate as to the serum 25(OH)D concentrations associated with deficiency (e.g. rickets), for optimal bone health and optimal overall health, and most cut points have not been developed by an agreed mutual scientific process. The US Institute of Medicine concluded that individuals are at risk of vitamin D deficiency at serum 25(OH)D concentrations <30 nmol/L (<12 ng/mL). However, some individuals are potentially at risk for inadequacy even at levels ranging from 30 to 50 nmol/L (12–20 ng/mL). The committee agreed with sufficient levels at ≥50 nmol/L (≥20 ng/mL) and that 50 nmol/L is the serum 25(OH)D level that covers the majority of needs of the population (97.5%) [12].

Further, hypovitaminosis D in its mild but especially in severe forms can exacerbate symptomatic hypocalcaemia following intravenous bisphosphonate (zoledronic acid) [13]. Even though this is rare, associated hypocalcaemia may be life-threatening and require immediate resuscitation and evaluation, often requiring hospitalisation to prevent additional morbidity and mortality risk from tetany, refractory hypotension, seizures or arrhythmias. Therefore it makes good sense to optimise vitamin D levels prior to administration of these agents [14].

Vitamin D toxicity can occur when blood 25(OH)D levels are 88 ng/mL or greater [15]. Symptoms may include sleepiness, vomiting, weakness, headache, nausea and constipation, and acute toxicity may cause hypercalcaemia and hypercalciuria.

4. Evidence-based review

Whilst there have been several treatment guidelines published, they are consensus-based rather than evidence-based [16–19]. This review seeks to address this issue and identify any gaps in research for vitamin D replacement, listing the types available including dietary, other supplementation and sunlight, for bone health (rickets, osteoporosis) as well as to address safety and efficacy in an evidence-based manner.

Systematic search of MEDLINE, CINAHL and EMBASE for articles published rom September 2015 to August 2019 and the Cochrane Database of Systematic Reviews (most recent issue searched—Issue 2, 2019) was conducted by the author. Randomised controlled trials, meta-analyses and reviews of all aspects of vitamin D supplementation in humans were reviewed. Articles pertaining to osteoporosis in a specific condition (e.g. epilepsy) were excluded.

All studies were reviewed independently by the author, who recorded individual study results, and an assessment of study quality and treatment conclusions was made according to evidence-based protocols.

Out of a total of 211 articles from PUBMED for vitamin D supplementation and osteoporosis, we found 22 articles satisfying the research criteria. Out of a total of 54 articles from PUBMED for vitamin D supplementation and rickets, we found 22 articles satisfying the research criteria. Of the 76 reviews from Cochrane Database of Systematic Reviews, there were 4 suitable review articles [20–23].

5. Vitamin D replacement in diet

Human beings require and source vitamin D from diet, dietary supplements and exposure to sunlight.

Whilst in particular for older people and those with restriction in diet, a diet rich in oily fish (which can theoretically improve 25-OHD levels and prevent vitamin D deficiency), in reality this is a challenge to achieve [24]. Only a few foods are a good source of vitamin D. These include fortified dairy products and breakfast cereals, fatty fish, beef liver and egg yolks.

Apart from the flesh of fatty fish (such as salmon, tuna and mackerel) and fish liver oils, very little foods contain vitamin D. Trace amounts of vitamin D can be found in egg yolks, cheese and beef liver. These foods contain vitamin D3 and its metabolite 25(OH)D3 [25]. Vitamin D2 is contained in some mushrooms [26, 27].

In the standard Western diet, fortified foods provide most of the vitamin D [26]. For example, US milk is fortified with 100 IU/cup. (In Canada, by law its milk is fortified with 35–40 IU/100 mL and its margarine at ≥530 IU/100 g.) However, other dairy products derived from milk, such as ice-cream and cheese, are generally not fortified. Some ready-to-eat cereals for breakfast often contain small amounts of added vitamin D, as do some brands of orange juice and yogurt. Some plant-based alternatives to mild (such as drinks made from oats, almond or soy) are sometimes fortified with vitamin D to the amount (about 100 IU/cup) found in fortified cow's milk. Several countries of the developed world (e.g. United States, Canada and Australia) mandate the fortification of infant formula with vitamin D, 40–100 IU/100 kcal in the United States and 40–80 IU/100 kcal in Canada; however, this is not practical especially in those who breastfeed and those countries which do not mandate fortification of their milk formulas.

6. Sunlight for vitamin D replacement

Most people meet at least some of their vitamin D needs through exposure to sunlight [28]. Solar ultraviolet B radiation crosses the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3. Excessive sunlight exposure does not cause intoxication because any excess previtamin D3 or vitamin D3 is destroyed by sunlight, and in the skin there is reversible conversion to inactive sterols [24].

In residential aged care, practical attempts for therapeutic sunlight therapy have produced only mild 25(OH)D3 improvements and depended on the season of exposure [29]. On a practical level, excessive exposure to ultraviolet is the primary cause of skin cancer, including squamous cell carcinoma, basal cell carcinoma and cutaneous malignant melanoma [30], so this is not a pragmatic approach from a public health perspective. Essentially, people with limited sun exposure require good dietary sources of vitamin D or take a supplement to achieve recommended intake levels.

Besides increasing sun exposure, the best way to get additional vitamin D is through supplementation.

7. Natural supplements for vitamin D

In fortified foods and supplements, vitamin D is also available in two forms, vitamins D2 (ergocalciferol) and D3 (cholecalciferol), that differ in their side-chain structure only. Vitamin D2 is manufactured by the UV irradiation of ergosterol in yeast, and vitamin D3 is manufactured by the irradiation of 7-dehydrocholesterol from lanolin and the chemical conversion of cholesterol [10]. Both forms effectively raise serum 25(OH)D levels [28, 31]. It appears that at nutritional doses vitamins D2 and D3 are equivalent, but at high doses vitamin D2 is less potent.

The recent increase in vitamin D interest by the general public has fuelled a big rise in sales of over-the-counter vitamin D preparations. Additionally, products with progressively increasing content of over-the-counter vitamin D preparations are becoming increasingly prevalent. Many types of pharmaceutical preparations for vitamin D supplementation are commercially available, including oily drops, capsules and tablets [31].

Individuals at high risk for deficiency should have a vitamin D blood test first; a dosage of up to 3000–4000 IU may be required to restore blood concentrations. In the Middle East and African countries, vitamin D doses ≥2000 IU/day may be needed to reach the target 25(OH)D level ≥20 ng/ml [32].

Whilst for pregnant women and children (1000 IU daily is safe) [33], there are very few concerns regarding vitamin D complications; in the elderly and especially those who are vitamin D replete, there has been some concerns about increased falling risks (especially at high doses) [34]. A 1-year, double-blind, randomised clinical trial conducted in Switzerland of 200 community-dwelling men and women 70 years and older with a prior fall, randomised to receiving monthly 24,000 IU (low-dose), 60,000 IU of vitamin D3 and 24,000 IU of vitamin D3 plus 300 μg of calcifediol, found that the higher-dose groups increased vitamin D levels more effectively but did not improve lower extremity function (over 12 months) and indeed increased fall incidence slightly [35]. Whilst this is not a cause for alarm, the study does confirm the popular scientific idiom 'Too much of a good thing is bad thing'. Bischoff-Ferrari [36] advocates against regular high-dose bolus or monthly moderate doses of vitamin D for fracture prevention. Indeed Zhao [5] in a meta-analysis of 33 randomised trials involving 51,145 participants found no benefit of supplements containing calcium, vitamin D or both compared with places in fracture prevention among community-dwelling older adults (over 50 years); however, it is noted that the research is limited by the lack of reporting of whether participants had osteoporosis, osteopenia or low bone mass, as well as participants mainly from Europe and the United States.

In contrast, research on vitamin D replenishment in the mild to moderate vitamin D-deficient elderly population following a hip fracture showed that a single loading dose of cholecalciferol (250,000 IU vitamin D3, the REVITAHIP (Replenishment of Vitamin D in Hip Fracture) strategy) or placebo, both receiving daily vitamin D (800 IU) and calcium (500 mg), was able to improve vitamin D levels and reduce falls (**Figure 3**) and pain levels [14]. The REVITAHIP investigators adopted a similar loading dose vitamin D followed by maintenance vitamin D at 800 IU (and calcium) daily supplied to the participants, due to the very high rates of vitamin D deficiency noted in the HORIZON Recurrent Fracture study (observed in the first 385 patients [37]). The investigators found that virtually all participants in the active treatment group reached target vitamin D (>50 nmol/L) at weeks 2 and 4 compared with the placebo group (**Figure 4**).

Interestingly, Smith [38], in a group of elderly women (mean age 66 years) with hypovitaminosis D (<50 nmol/L), demonstrated that vitamin D followed

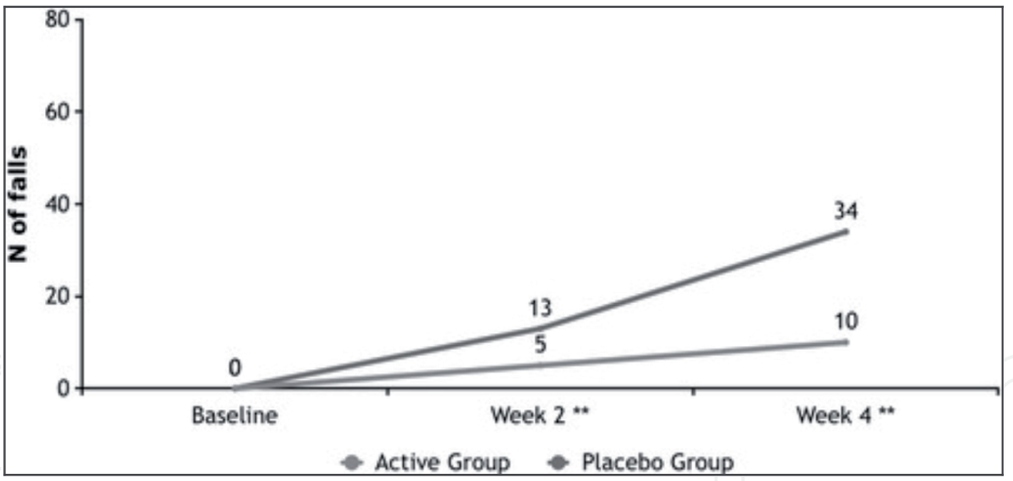


Figure 3.
REVITAHIP Active Vitamin D Protocol (initial 250,000 IU followed by 800 IU Vitamin D3 and 500 mg Calcium Daily at 4 weeks shows significance in reducing falls.

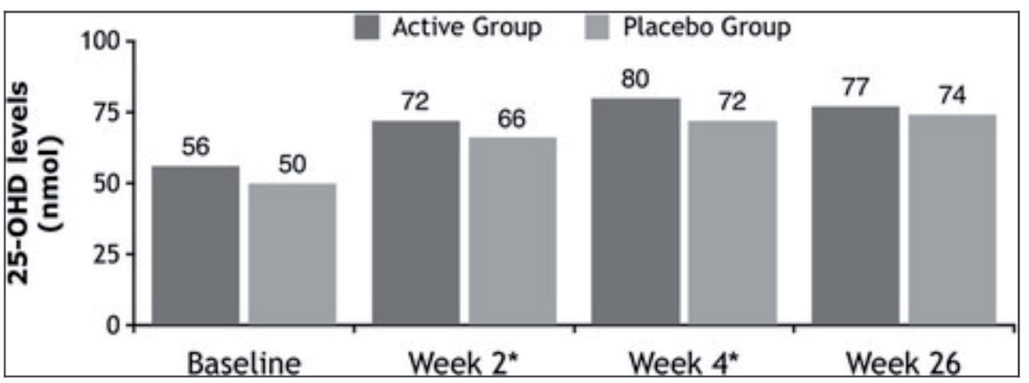
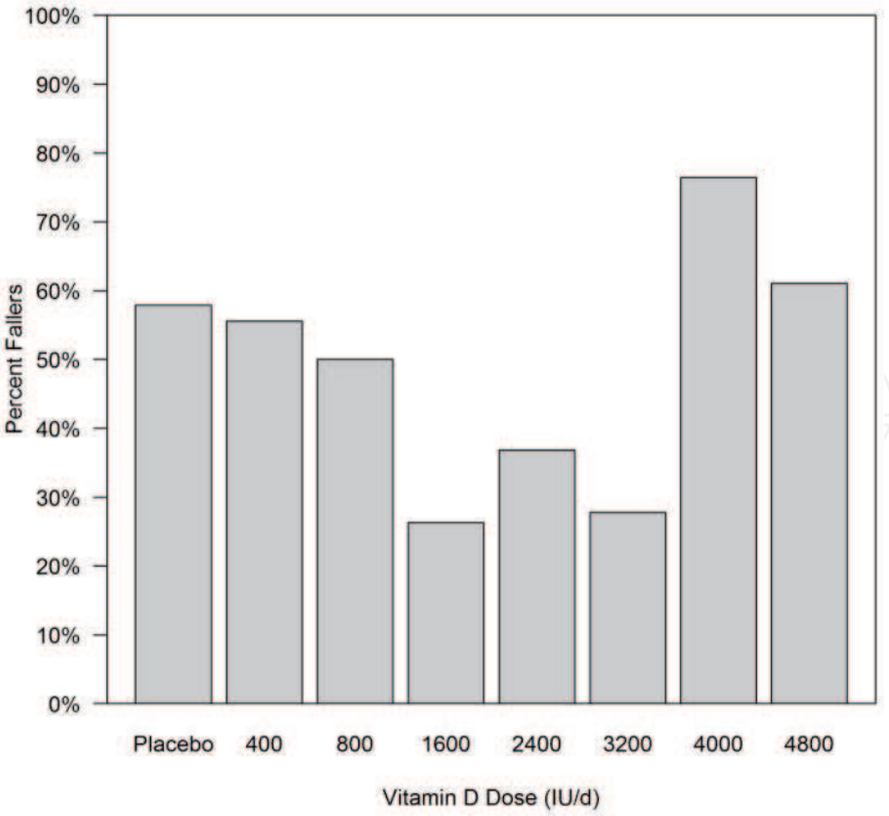


Figure 4.
REVITAHIP Active Vitamin D Protocol (initial 250,000 IU followed by 800 IU Vitamin D3 and 500 mg Calcium Daily at 2, 4 and 26 weeks showed significant 25-OHD levels improvements compared with the placebo group.

a U-shaped curve on falls whether analysed by serum dose or serum 25(OH)D3 levels. The investigators found no decrease in the incidence of falls on low vitamin D doses (400, 800 IU), a significant decrease in falls on medium doses (1600, 2400, 3200 IU) ($p = 0.020$). Counterintuitively, Smith found no decrease on high doses (4000, 4800 IU) compared to placebo ($p = 0.55$). The rate of falls was 60% in the lowest quintile <25 ng/ml (<50 nmol/L), 21% in the low middle quintile 32–38 ng/ml (80–95 nmol/L), 72% in the high middle quintile 38–46 ng/ml (95–115 nmol/L) and 45% in the highest quintile 46–66 ng/ml (115–165 nmol/L). A similar U-shaped pattern in the subgroup with a previous fall history was noted among the quintiles of 25(OH)D3 levels (**Figure 5**, [38]).

Conglomerating the results from Bischoff-Ferrari, Lyles, Smith and Mak, there does not appear to be any justification in having regular high-dose vitamin D supplements at monthly intervals, due to the risk of vitamin D toxicity, hypercalcaemia and perhaps oversaturation of vitamin D receptors on skeletal muscles, leading to a propensity to falls. The author would recommend the REVITAHIP strategy of initial single loading dose bolus (250,000 IU) followed by regular 800 IU daily [14, 37], or 24,000 IU monthly [35], supplementation but would recommend to be cautious with the Smith approach of medium daily dosages, probably up to 1600 IU daily without a bolus [38], for high-risk populations, and would support that larger monthly doses of 100,000 IU need further evaluation with respect to efficacy and safety.



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8. Conclusions

Vitamin D is an essential fat-soluble hormone with multiple positive pleiotropic effects on the human bodies besides the optimisation on bone health. The evidence for ensuring high-risk groups such as pregnant women, children and those from the Middle East and African countries is vitamin D replete with either dietary, sunlight or combination with appropriate vitamin D supplements at moderate doses. For community-dwelling older adults with a history of falls, osteoporosis and/or fractures, there is still evidence for a good safety profile for moderate dosages (either through an initial single-dose bolus followed by daily low-dose or regular moderate daily or monthly dosages). The author does not recommend regular high-dose bolus (>500,000 IU bolus) or greater than 50,000 IU monthly given its possible increased risk of falls and associated fractures.

Author Note

The author dedicates this chapter to his eldest son Johann, for his constant bravery, courage, diligence and dedication to his sport, studies and in life, and to his mother Demi, for her constant reminder to strive for perfection.

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