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# Vitamin D Physiology, Deficiency, Genetic Influence, and the Effects of Daily vs. Bolus Doses of Vitamin D on Overall Health: A Clinical Approach

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**Abstract:** Vitamin D is a pleiotropic hormone that plays a vital role in regulating bone growth, maintaining calcium and phosphate homeostasis, modulating immune function, and a wide range of other pleiotrophic actions in humans, which have increased the attention for its clinical applications. Despite its importance, vitamin D deficiency is prevalent worldwide and is related to a range of pathophysiological conditions, including an increased risk of osteoporosis and chronic and autoimmune diseases. The recommended daily doses of vitamin D vary depending on genetics, age, sex, and health status, with specific doses recommended for infants, children, adults, and those at increased risk of deficiency or specific health conditions. Maintaining adequate vitamin D levels is essential for optimal health, and together with sun exposure, appropriate supplementation strategies can help achieve this goal. Vitamin D supplementation is commonly used to maintain adequate levels, and the optimal administration strategy, such as a daily dose vs. a bolus, is still being investigated. This review aims to understand vitamin D physiology and the impact of relevant vitamin D polymorphisms and to evaluate the role of a daily dose versus a bolus in maintaining optimal vitamin D levels and clinical health outcomes. It also provides suggested clinical guidelines for clinicians based on the most recent scientific evidence.

**Keywords:** vitamin D; daily dose; bolus; vitamin D deficiency; immune systems; osteoporosis; health outcome



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## 1. Introduction

Vitamin D is an ancient, evolutionary, pleiotropic, and latitudinal hormone that plays a "vital" role in almost all human physiological processes, including calcium and phosphate homeostasis, bone growth, cardiometabolic, and immune function [1]. Recently, emerging research highlights the key role of vitamin D in modulating the composition and activity of the gut microbiota and vice versa [2]. Vitamin D is primarily synthesized in the skin when exposed to UVB radiation or obtained from dietary sources or supplements. Before being usable by the human body, vitamin D undergoes two main enzymatic transformations in the liver and kidneys to obtain its active form, calcitriol, which can then reach target cells through binding to transport proteins and perform its functions. To date, more than 200 genes are regulated by vitamin D [3]. However, despite this crucial role, vitamin D deficiency is prevalent worldwide, and low vitamin D levels have been associated with numerous pathologies. This is linked to multiple factors, including migrations of people from sunnier locations to more northern regions and a lack of daily sun exposure due to

an increase in time spent working indoors [4]. Supplementation of vitamin D has thus become an important tool to combat this deficiency, and two main regimens are normally recommended by healthcare professionals: daily doses and weekly or monthly bolus doses. Although to date, numerous clinical studies and meta-analyses have sought to understand which is the most appropriate mode of administration, the optimal regimen for vitamin D supplementation remains controversial [5]. This review aims to evaluate the role of a daily dose vs. a bolus in maintaining optimal vitamin D levels and related health outcomes. Together with clinical evidence, the influence of genetic polymorphisms on vitamin D kinetics and dynamics are analyzed to understand the most appropriate mode of administration and consequently the development of appropriate personalized supplementation strategies to promote optimal health outcomes.

## 2. Physiology of Vitamin D

Vitamin D is a fat-soluble hormone that naturally occurs in two main forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) (Figure 1). Vitamin D2 is produced by plants, specifically produced by the ultraviolet irradiation of the yeast and fungi sterol, ergosterol, which is found in some types of mushrooms and yeasts [6]. Vitamin D3 (cholecalciferol) is synthesized in the skin epidermis through a series of chemical reactions that occur when 7-dehydrocholesterol, a type of cholesterol present in the skin, is exposed to sunlight UVB radiation. The UVB radiation transforms 7-dehydrocholesterol into pre-vitamin D3, which then undertakes a thermal isomerization process, converting it into cholecalciferol (Figure 2) [3].

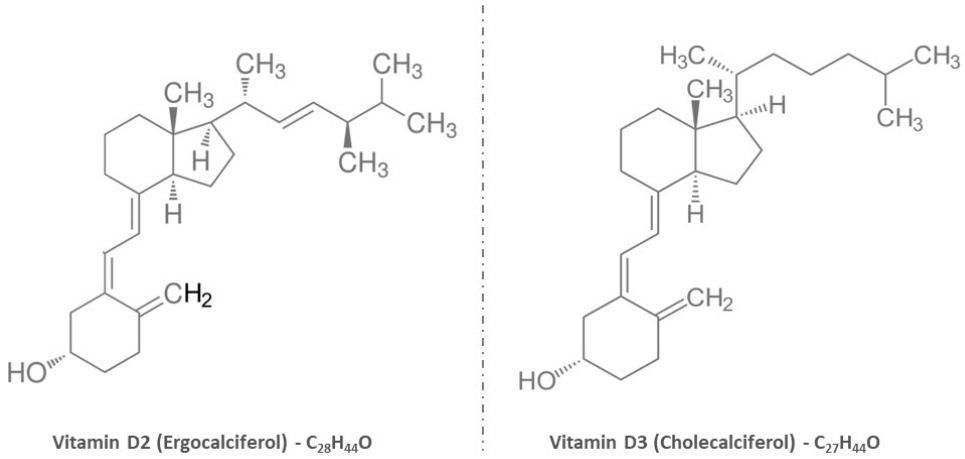


**Figure 1.** Chemical structure and molecular formula of vitamin D2 and vitamin D3.

Vitamin D can be consumed through natural sources, such as fatty fish and egg yolks, or through fortified foods like UV-irradiated mushrooms and supplements like fish oil. When vitamin D is consumed in the diet, digestive enzymes such as trypsin and pepsin take part in vitamin D absorption by clearing vitamin D binding proteins that are present in food to allow its release. Moreover, in the duodenum, other digestive enzymes, like amylase, lipase, and protease, facilitate the release of vitamin D from the food matrix, favoring the absorption in the small intestine (Figure 3) [7].

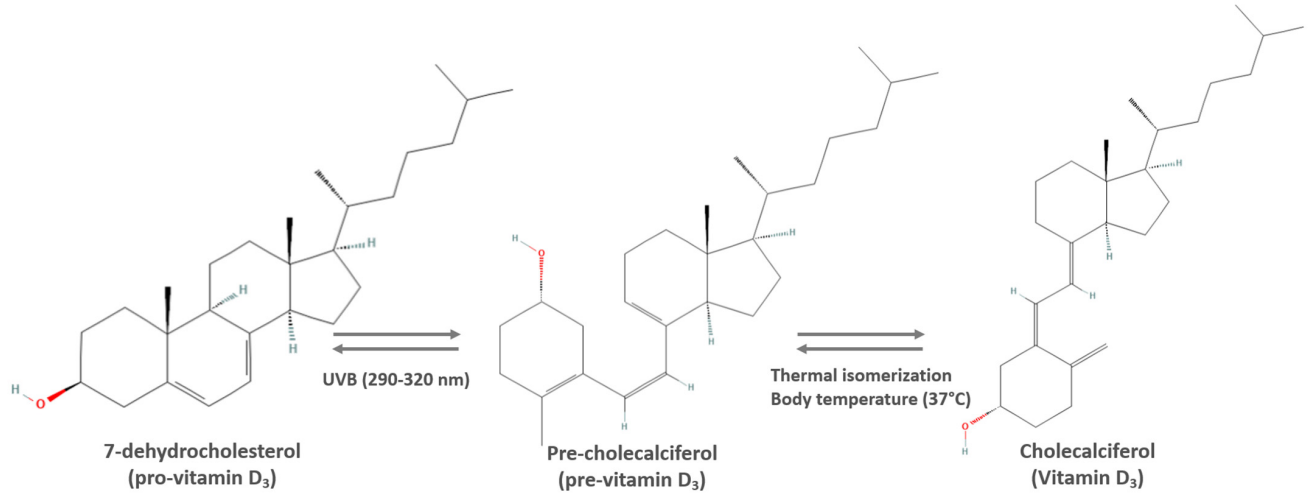


**Figure 2.** Conversion of 7–dehydrocholesterol to cholecalciferol in the skin.

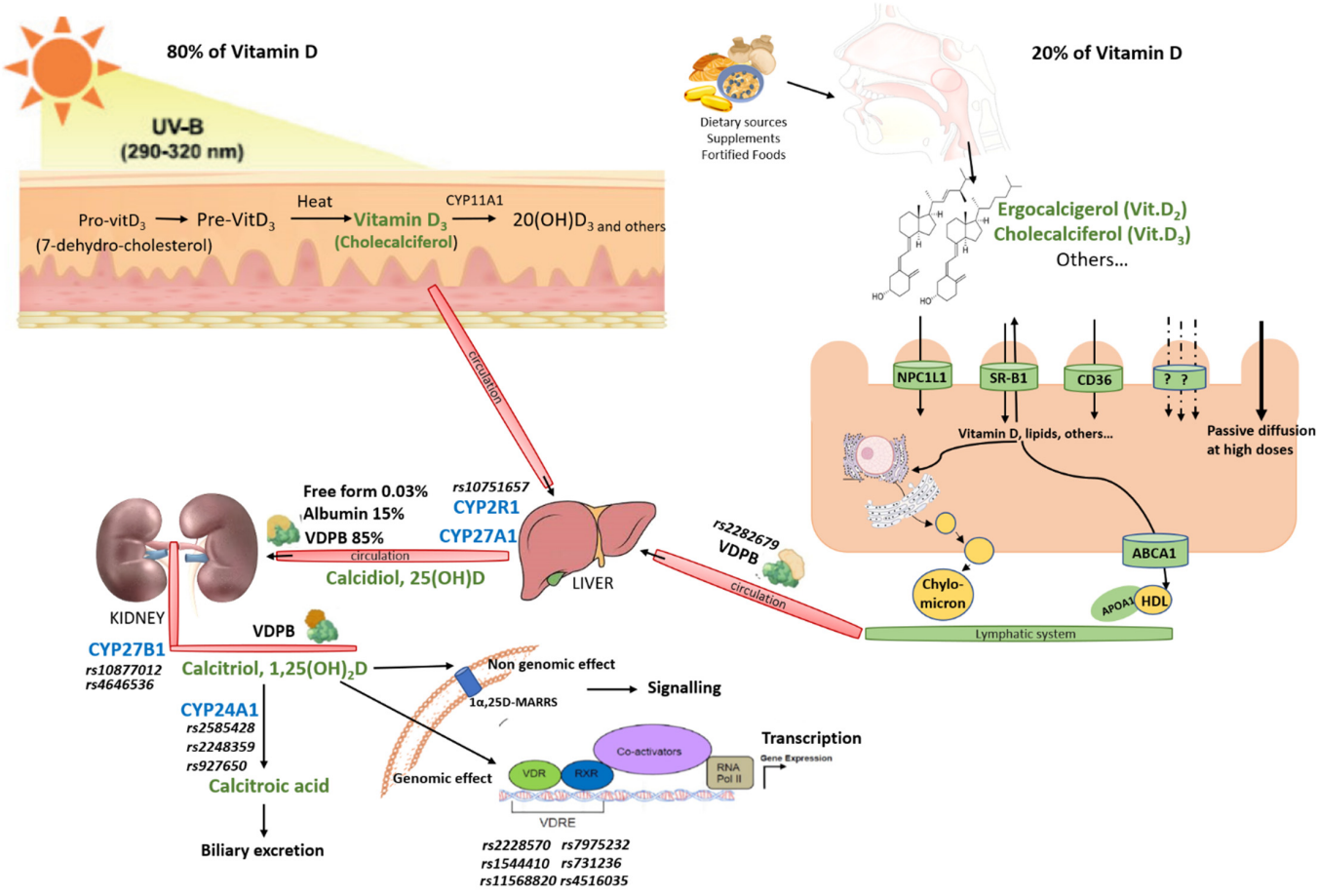


**Figure 3.** Clinical physiology of vitamin D and relevant SNPs.

### *2.1. Vitamin D Absorption*

Dietary vitamin D absorption is dependent on the consumed amount of dietary fat, as vitamin D is a fat-soluble hormone. A study published in 2015 found that the absorption of vitamin D was increased when taken with high-fat foods [8]. Once reaching the small intestine, vitamin D is incorporated into micelles and transported across the apical membrane of enterocytes by various transporters, including NPC1L1, SR-BI, and CD36. These transporters facilitate vitamin D uptake into the enterocytes. Passive diffusion

also has a role in transporting vitamin D into the cell, particularly at higher doses. Once inside the cell, some efflux transporters, such as SR-BI, transport back vitamin D out to the intestinal lumen, while a major portion is incorporated into chylomicrons. Although binding proteins seem to be relevant for the intracellular transport of vitamin D, none have been clearly identified thus far. Ultimately, chylomicrons transport vitamin D in its free form into the lymph using primarily the apolipoprotein B-dependent route. Other secretion pathways, via the HDL and ABCA1 route, may also be involved (Figure 1) [9,10].

### *2.2. Vitamin D Metabolism*

Once absorbed into the enterocytes, vitamin D needs to be transported to various tissues, including the liver, where it undergoes metabolism by vitamin D 25-hydroxylase (CYP27A1 and CYP2R1) to form 25(OH)D3 or calcidiol, which is the primary circulating form of vitamin D in the blood. The kidneys, mainly in the proximal tubule, further metabolize 25(OH)D3 to its biologically active form, 1$\alpha$,25-dihydroxyvitamin D3 or calcitriol, through 5(OH)D 1$\alpha$-hydroxylase (CYP27B1). Calcitriol binds to vitamin D binding protein (VDBP) and is transported to target tissues, like the intestines, kidneys, and bones, where it regulates phosphate and calcium absorption, mobilization, and reabsorption (Figure 1). CYP24A1 (25(OH)D 24-hydroxylase), the major vitamin D inactivating enzyme, tightly regulates calcidiol and calcitriol levels catalyzing the hydroxylation at C-24 and C-23 of both vitamin D derivates, producing biologically inactive biliary excreted calcitroic acid through the 24-hydroxylase biochemical pathway, while the 23-hydroxylase route produces 1,25–26,23 lactone, whose relative activity is species dependent [11]. The transport of vitamin D is facilitated by vitamin D binding protein, which serves as the key transport protein. This protein helps to protect vitamin D from degradation and facilitates its transport in the bloodstream. VDBP is required for efficient intestinal absorption of vitamin D and mutations in the VDBP gene were associated with vitamin D deficiency [12]. VDBP, which is predominantly synthesized in the liver, is regulated by various factors, such as inflammatory cytokines, glucocorticoids, and estrogen, but not by vitamin D itself. Although VDBP has multiple biological functions, its primary function is to regulate the levels of free and total vitamin D in the circulation. Among the different forms of vitamin D, calcidiol is the most extensively studied and is considered the best biomarker to assess vitamin D levels [13]. In a typical, non-pregnant individual, only a small fraction of about 0.03% of calcidiol is present in the free form, with the majority bound to either VDBP (85%) or albumin (15%). According to the free hormone hypothesis, only free calcidiol can enter cells, a principle that applies to other lipophilic hormones as well. However, certain tissues, including the kidney, have a mechanism involving the megalin/cubilin complex that enables them to take up calcidiol that is still bound to VDBP [14]. Nonetheless, most tissues depend on the free fraction of calcidiol for their needs. Measuring only total calcidiol may not be entirely accurate in assessing vitamin D status [12,14,15]. In fact, while calcidiol remains the most used biomarker, recent studies highlight that other analytes, such as bioavailable and free calcidiol, VDBP, the C-3 epimer of calcidiol, calcitriol, and 24,25-dihydroxyvitamin D, could be useful to an individual's vitamin D status characterization [16]. Further research is required to standardize the measurement methods and better understand the impact of these analytes. To date, total calcidiol can be measured in whole blood, serum, plasma, or blood spots, and it is extremely stable under different laboratory preanalytical conditions and long-term storage [17]. It is normally measured using either a ligand-binding assay (such as an immunoassay platform like a competitive enzyme-linked immunosorbent assay (ELISA) or liquid chromatography–tandem mass spectrometry (LC-MS/MS) or a competitive chemiluminescent immunoassay or competitive receptor-binding assays). On the other hand, an assay that targets and quantifies unbound calcidiol (free calcidiol) directly or the measurement of VDBP, calcidiol, and albumin may be useful all together for calculating free and bioavailable calcidiol [14].

### *2.3. Genomic and Non-Genomic Mechanisms of Vitamin D*

Vitamin D exerts its effects by binding to the vitamin D receptor (VDR), a type of ligand-activated transcription factor belonging to the nuclear receptor family, which is present in many different tissues throughout the body, including the intestines, bones, kidneys, immune cells, and various organs. This interaction induces genomic and non-genomic regulation of various downstream targets that are involved in diverse biological functions (Figure 1). When calcitriol binds to the VDR, it forms a complex that can then bind to specific DNA sequences in the nucleus of the cell, thereby regulating the transcription of specific genes. Through this mechanism, vitamin D can regulate the expression of genes involved in calcium and phosphorus metabolism, immune function, and other physiological processes. The VDR controls the expression of over 200 genes and therefore controls over 1000 different physiological processes [18].

In the genomic pathway, the cytosolic VDR is bound by calcitriol, which triggers phosphorylation of the VDR, heterodimerization with the retinoid-X receptor (RXR), and translocation of the complex into the nucleus. Once inside the nucleus, in the promoter region of the target genes, the VDR–RXR–calcitriol complex attaches to vitamin D response elements and collaborates with transcriptional co-repressors or co-activators to regulate mRNA expression, thus controlling various functions, including phosphate and calcium homeostasis (Figure 1) [18]. The non-genomic pathway involves the binding of calcitriol to the membrane-bound VDR, also known as 1,25D-membrane-associated, rapid response steroid-binding protein (1,25D-MARRS). This interaction results in rapid modulation of the calcium cell signaling pathway and mitogen-activated protein kinase signaling via direct binding of intracellular signaling molecules that control specific cellular functions [19].

Interestingly, CYP11A1, also known as P450scc, has been identified as a new vitamin D-metabolizing enzyme. It is expressed in the gastrointestinal tract and in the skin where it can use vitamin D as an alternative substrate to cholesterol. Its products, including 20(OH)D and its hydroxymetabolites, have been shown to have anti-proliferative, differentiation, and anti-inflammatory effects on skin cells. Additionally, they can increase the defense mechanisms against DNA damage and oxidative stress and exhibit anti-cancer activities in a cell line-dependent way.

Vitamin D pleiotropic effects are thus not solely due to the calcitriol–VDR pathway but also to the CYP11A1-derived vitamin D metabolites, which may activate the ROR$\alpha/\gamma$ or VDR pathways [20]. Further studies to fully understand their specific contributions to the various effects of vitamin D on health and disease are needed.

The body tightly regulates the production and utilization of vitamin D to maintain optimal levels in the bloodstream. When vitamin D levels are low, the parathyroid gland produces the parathyroid hormone (PTH), which induces calcium release from bones and calcium reabsorption in the kidneys. This process increases the levels of calcium and vitamin D in the bloodstream. Conversely, when vitamin D levels are high, the body slows down the production of PTH to prevent excessive calcium absorption [21]. This regulatory mechanism reveals that the body can effectively maintain optimal levels of vitamin D in the bloodstream. Taking high doses of vitamin D, such as through bolus doses, can lead to negative consequences. Bolus doses of vitamin D cause a rapid increase in 25(OH)D levels, but this comes at the expense of downregulating the vitamin D active form calcitriol and other immune factors. Conversely, a daily small or moderate dose of vitamin D may have superior intracellular effects, but frequent dosing is necessary due to its half-life of 20 h. Thus, consuming moderate amounts of vitamin D on a daily basis may offer greater benefits for musculoskeletal health, prevention of respiratory infections, and reduction of cancer mortality than using large bolus doses.

### *2.4. Vitamin D Polymorphism of Clinical Relevance*

Vitamin D polymorphisms could have important clinical implications for a range of diseases, including bone health, autoimmune diseases, cancer, and COVID-19 outcomes [22–24]. Identifying individuals with certain genotypes may allow for targeted interventions to reduce

disease risk or improve outcomes. Here described are polymorphisms affecting vitamin D physiology with a level 3 of evidence or very important (VIP) evidence according to the latest research and summarized on the interactive tool, the Pharmacogenomics Knowledge Base (PharmGKB) [25]. The VDR gene is located on chromosome 12 and comprises 9 exons. Several SNPs in the VDR gene have been identified; the most common and of clinical relevance are rs10735810 (TaqI), rs7975232 (ApaI), rs1544410 (BsmI), rs731236 (FokI), rs11568820, and rs4516035 [26]. These SNPs are located in the non-coding regions of the gene or the 5′ untranslated region and are associated with differences in VDR expression and activity [27]. In a recent meta-analysis, a better response to vitamin D supplementation has been associated with those who carry the variant allele (Tt + tt) of the TaqI polymorphism and the FF genotype of the FokI variant [26]. In addition to VDR polymorphisms, polymorphisms in genes involved in vitamin D metabolism, such as VDBP, CYP2R1, and CYP27B1, have also been studied. VDBP is a plasma protein that binds and transports vitamin D metabolites in the blood. Several single nucleotide polymorphisms in the VDBP gene have been identified; in particular, rs2282679, rs4588, and rs7041 are the most commonly studied [28]. These SNPs result in different protein isoforms of VDBP, which have been associated with differences in vitamin D binding affinity and circulating vitamin D levels. The rs7041 SNP results in two protein isoforms of VDBP known as Gc1F and Gc1S. Individuals with the Gc1S isoform have been found to have higher circulating levels of vitamin D compared to those with the Gc1F isoform.

The clinical implications of VDBP polymorphisms are still being investigated. Some studies have suggested that individuals with the Gc1S isoform may have a lower risk of osteoporosis and fractures compared to those with the Gc1F isoform. Other studies have found associations between VDBP polymorphisms and inflammatory bowel disease, cardiovascular disease, and cancer, although the results have been inconsistent.

Overall, while VDBP polymorphisms may have some clinical relevance, more research is needed to fully understand their implications for disease risk and treatment [29].

Several single nucleotide polymorphisms in the CYP2R1 and CYP27B1 genes have been identified, including, respectively, rs10751657, rs2060793, and rs12794714 for CYP2R1 and rs10877012, rs703842, rs4646536, and rs4646536 for CYP27B1, which have been associated with differences in vitamin D metabolism and circulating 25(OH)D levels [28]. The clinical implications of CYP2R1 and CYP27B1 polymorphisms are still being investigated, but some data show a correlation with autoimmune disorders [28,30]. Some studies have suggested that individuals with certain genotypes may have a higher risk of osteoporosis and fracture, while others have found no association. Other studies have investigated the role of CYP2R1 polymorphisms in other diseases, such as multiple sclerosis and cancer, but the results have been mixed. Polymorphisms affecting the CYP24A1 gene, such as rs2585428, rs2248359, and rs927650, have also been linked with some diseases and impaired clinical outcomes [31,32].

## 3. Timing of Vitamin D Assumption and Absorption

The timing of vitamin D supplementation and dietary sources that enhance vitamin D absorption are important considerations in maintaining optimal vitamin D levels. Vitamin D is a type of fat-soluble hormone that requires fat for optimal absorption into the bloodstream [8,33]. Therefore, it is recommended to take vitamin D supplements with meals that contain fat in order to enhance its absorption. Studies have shown that taking vitamin D with the largest meal of the day can increase blood levels of vitamin D by up to 50% after just 2–3 months. In addition, consuming vitamin D with a high-fat meal has been found to increase blood levels of vitamin D by 32% after 12 h compared to a fat-free meal in older adults [8,33]. Foods like nuts, avocados, full-fat dairy products, seeds, and eggs are excellent sources of healthy promoting fats that can boost vitamin D absorption. However, it is important to note that dietary sources may not provide sufficient amounts of vitamin D, and supplementation may be necessary to achieve optimal vitamin D levels. In fact, not many foods naturally contain vitamin D3. The flesh of fatty fish and fish liver oils are the best sources, as reported in Table 1. Cheese, egg yolks, and beef liver contain smaller

amounts of vitamin D, and some mushrooms are sources of vitamin D2. Nowadays, a lot of foods are fortified with vitamin D, like dairy products and cereals [34,35].

**Table 1.** Vitamin D Content of Selected Food * [36].

| Dietary Sources | Serving | Micrograms (mcg) per Serving | International Unit (U.I.) | % Daily Value (DV) |
|---|---|---|---|---|
| Cod liver oil | 1 tablespoon | 34.0 | 1360 | 170 |
| Trout (rainbow), farmed, cooked | 3 ounces | 16.2 | 645 | 81 |
| Salmon (sockeye), cooked | 3 ounces | 14.2 | 570 | 71 |
| Milk, 2% milkfat, vitamin D fortified | 1 cup | 2.9 | 120 | 15 |
| Soy, almond, and oat milks, vitamin D fortified | 1 cup | 2.5–3.6 | 100–144 | 13–18 |
| Sardines (Atlantic), canned in oil, drained | 2 sardines | 1.2 | 46 | 6 |
| Egg ** | 1 large | 1.1 | 44 | 6 |
| Liver, beef, braised | 3 ounces | 1.0 | 42 | 5 |
| Tuna fish (light), canned in water, drained | 3 ounces | 1.0 | 40 | 5 |
| Cheese, cheddar | 1.5 ounce | 0.4 | 17 | 2 |
| Chicken breast, roasted | 3 ounces | 0.1 | 4 | 1 |

* The FDA DV for vitamin D is 20 mcg (800 IU) for adults and children aged 4 years and older [35]. ** Vitamin D is in the yolk.

In general, studies have shown that vitamin D supplements are more effective than fortified foods at increasing serum 25-hydroxyvitamin D levels. This is because supplements can provide a higher and more consistent dose of vitamin D compared to fortified foods, which may vary in their vitamin D content and bioavailability. However, fortified foods can still be a good source of vitamin D if consumed regularly as part of a balanced diet [37,38].

Although there is no scientific evidence to support it, it may be better to take vitamin D in the morning for convenience and better adherence. It is recommended to take vitamin D with a nutritious breakfast, and simple strategies, like using a pillbox, setting an alarm, or storing supplements near the dining table, can be effective reminders to take them. Further, few studies suggest that there is a correlation between vitamin D levels in the blood and sleep quality. Low levels of vitamin D have been linked to a higher risk of reduced sleep duration, poorer sleep quality, and general sleep disturbances [39–41]. However, 1 small study of 40 IFN-β-treated multiple sclerosis patients suggested that a daily intake of 4370 IU of vitamin D levels may be linked to lower melatonin levels in people with multiple sclerosis [42]. In contrast, a study on postmenopausal women found that sleep quality decreased when vitamin D levels were repleted with a daily dose of 2000 IU, but further research is needed to confirm this [43]. Although some anecdotal reports suggest that taking vitamin D at night may negatively affect sleep quality, there is currently no scientific evidence to support this claim [44,45]. Optimal strategies for individuals may be determined through personal experimentation until further scientific studies become available.

## 4. Vitamin D Deficiency

In recent years, vitamin D supplements and testing have significantly increased in the health sectors and markets. However, there is still ongoing debate regarding the optimal vitamin D dose and status, as well as the role of supplementation. This is due to the lack of clear benefits shown by large interventional studies, which may be attributed to limitations in trial design, small sample sizes, consideration of the use of vitamin D-fortified foods, and highly diverse and inconsistent intervention methods [46].

Low levels of vitamin D, indicated by a serum 25-OHD3 (calcidiol) concentration of <50 nmol/L or 20 ng/mL, are associated with a plethora of health problems, such as fractures and bone loss, osteoporosis and osteomalacia in adults, rickets in children, type 2 diabetes, cardiovascular and autoimmune diseases, and certain types of cancer [4,46,47].

Therefore, the primary treatment goal is to maintain a calcidiol level of >20 ng/mL (50 nmol/L), although there is some hint of evidence suggesting a benefit for a higher threshold, especially for cancer prevention and prognosis [48]. Severe vitamin D deficiency, with a calcidiol concentration below <12 ng/mL (30 nmol/L), significantly increases the risk of infections, chronic fatigue, and overall mortality and should be rapidly restored to normal levels [4].

The optimal plasma level of vitamin D is a matter of ongoing debate and research. A panel of experts of the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine (NASEM) reported that people with serum 25(OH)D concentrations less than 12 ng/mL (30 nmol/L) are at risk of vitamin D deficiency. Levels of 20 ng/mL (50 nmol/L) or more are sufficient for most people [49]. Differently, the Endocrine Society indicated that, for clinical practice, a serum 25(OH)D concentration of more than 30 ng/mL (75 nmol/L) is necessary to maximize the effect of vitamin D on bone, calcium, and muscle metabolism [50]. The FNB committee also highlighted that serum concentrations greater than 125 nmol/L (50 ng/mL) may be associated with adverse effects [49]. However, current evidence suggests that a level between 30–50 ng/mL (75–125 nmol/L) is desirable for most people with higher values (close to 50 ng/mL) consistently related to reduced overall mortality [51–53]. A systematic review with a meta-analysis of an observational cohort and randomized intervention studies suggested that there is a moderate yet noteworthy, inverse relationship between circulating vitamin D levels and the risk of all-cause mortality. Specifically, when categorized by type of supplementation, the administration of vitamin D3 alone demonstrated a significant 11% decrease in all-cause mortality. On the other hand, supplementation with vitamin D2 alone did not have a significant effect on mortality [54]. A recent meta-analysis of a retrospective cohort and clinical studies on COVID-19 mortality rates and vitamin D blood levels showed a median of approximately 23.2 ng/mL of vitamin D in the analyzed population and suggested a theoretical point of zero mortality at approximately 50 ng/mL. Moreover, the study highlighted how low vitamin D is a predictor and not a side effect of COVID-19 infection [55]. Despite the compelling evidence indicating that severely deficient individuals may benefit from vitamin D supplementation in terms of mortality and infection prevention, it is not a universal panacea and is likely only beneficial in cases of deficiency. Nevertheless, its rare adverse effects and broad safety range imply that it could be a vital, cost-effective, and safe supplementary therapy for numerous ailments. Additional comprehensive studies are necessary to assess its potential advantages. A global public health intervention that encompasses vitamin D supplementation for specific high-risk groups and systematic fortification of vitamin D in food is crucial to avoid severe vitamin D deficiency.

### *The Latitude Hypothesis and Immigrants*

Despite the best natural source of vitamin D being sunlight, it can also be derived from food. Optimal living conditions for most of the world's population, including temperature, food resources, and UV radiation for vitamin D production, are found between the 20th and 40th parallels north and south. However, Europe is a notable exception, with

almost half a billion people residing between the 40th and 60th parallel north where UV radiation levels are significantly lower. The latitude hypothesis suggests that the lower levels of UV radiation in regions farther from the equator contribute to a higher prevalence of vitamin D deficiency in those areas. Additionally, there has been a segment of the European population, including Greenland, living even further north than the 60th parallel since the time of the Vikings, which among the various hypotheses, seem to have been extinguished due to several factors, including in-breeding, inappropriate diet, and vitamin D deficiency [56]. Non-western immigrants and refugees are more susceptible to vitamin D deficiency and rickets than the native population. Individuals of non-western origin may experience severe vitamin D deficiency, with up to 50% of children and adults exhibiting serum 25-hydroxyvitamin D levels below 25 nmol/L. This can be attributed to a lack of exposure to sunshine, as well as having more pigmented skin and wearing skin-covering clothes due to cultural or religious reasons. A recent study highlighted a small inhibitory effect of melanin on vitamin D3 synthesis. This difference may be sufficient to explain the epidemiological data on the relationship between melanin and vitamin D3 synthesis [57]. The food these individuals consume also typically contains very little vitamin D except for fatty fish. Additionally, many immigrants have a low calcium intake [58].

## 5. Recommendations Regarding Vitamin D Supplementation and Doses

The recommended daily dosage of vitamin D varies depending on a person's age, sex, body weight, genetics, environment, and health status. The vitamin D plasma level should be monitored at least two times a year in winter and springtime to understand its annual fluctuation. In subjects with vitamin D deficiency, it is recommended to measure the vitamin D level until the optimal value is reached and consistently maintained over time [59]. A summary of a possible simplified scheme of vitamin D recommend daily dosages depending on age and plasma level based on the most recent available guidelines [46,60,61] is reported in Table 2.

**Table 2.** Vitamin D supplementation in the general population based on plasma level and age.

| | **Optimal Plasma Level to Achieve (25OHD3)** | **Recommend Daily Dietary Intake with 25OHD3 > 30 ng/mL** | **Recommend Daily Dose with 20 ng/mL < 25OHD3 < 30 ng/mL** | **Recommend Daily Dose with 10 ng/mL < 25OHD3 < 20 ng/mL** | **Recommend Daily Dose with 25OHD3 < 10 ng/mL** |
|---|---|---|---|---|---|
| Pregnancy and breastfeeding | 30–50 ng/mL (75–125 nmol/L). | 800 U.I. | 1000–2000 U.I. | 1000–2000 U.I. | 4000 U.I. |
| Preterm infants | | 400 U.I. | 400 U.I. | 600 U.I. | 1000 U.I. |
| Infants 0–2 | | 400 U.I. | 400–600 U.I. | 800 U.I. | 1000 U.I. |
| Children 3–6 | | 400 U.I. | 600–800 U.I. | 1000 U.I. | 2000 U.I. |
| Children 7–10 | | 600 U.I. | 800–1000 U.I. | 1000 U.I. | 4000 U.I. |
| Adolescents 11–18 | | 600 U.I. | 800–2000 U.I. | 2000 U.I. | 4000 U.I. |
| Adults 19–65 | | 600 U.I. | 800–2000 U.I. | 2000 U.I. | 4000 U.I. |
| Seniors 66–75 | | 800 U.I. | 800–2000 U.I. | 2000 U.I. | 4000 U.I. |
| Elderly >75 | | 800 U.I. | 2000–4000 U.I. | 4000 U.I. | 8000 U.I. |
| | | | *Double the dose in obese individuals* | *Until optimal plasma levels are achieved* | *Until optimal plasma levels are achieved* |

The American Academy of Pediatrics suggests that all breastfed and partially breastfed infants should receive a daily supplement of 400 IU of vitamin D beginning in the first few days of life, monitoring vitamin D3 levels after 4 weeks and every 3–4 months. Never exceed 1000 IU between supplementation and diet [62,63]. The recommended daily intake for children and adolescents is 600–1000 IU per day up to 2000 in obese individuals. For most adults, the recommended daily intake is 800–2000 IU per day, but some health organizations recommend higher doses (up to 4000 U.I.) for certain populations, such as older adults, obese individuals, and people with limited sun exposure or dark skin. For elderly individuals and those with frailty, higher doses of vitamin D supplementation may be required to maintain optimal levels. According to the majority of nutritional guidelines, vitamin D doses of 2000–4000 IU/day were most effective in reducing falls and fractures in these populations [46,63]. According to recommendations from the Endocrine Society, it is advised that women who are pregnant or breastfeeding consume a minimum of 600 IU of vitamin D daily. Additionally, it has been acknowledged that in order to maintain a blood level of calcidiol above 30 ng/mL, a higher intake of at least 1500–2000 IU of vitamin D per day may be necessary [50]. For adult individuals with vitamin D deficiency, higher doses of vitamin D supplementation may be required to achieve adequate blood levels. To attain a blood level of calcidiol above 30 ng/mL, the Endocrine Society advises a daily dosage of 6000 IU of vitamin D2 or D3 or an intake of 50,000 IU of either vitamin D2 or D3 for a duration of 8–12 weeks. After this initial period, a lower dose of 1500–2000 IU is recommended daily for maintenance therapy [50].

Importantly, vitamin D supplementation should be personalized based on a person's specific health status and needs. Moreover, it is important not to exceed the recommended dosages of vitamin D without medical supervision to prevent toxicity that can occur with very high doses. Potential adverse effects, such as hypercalciuria, hypercalcemia, and kidney stones, are rare and typically only occur at high doses of vitamin D. To minimize the risk of adverse effects, it is important to monitor vitamin D levels and calcium status regularly, especially in high-risk populations [64].

Overall, the use of vitamin D supplementation in populations at risk of deficiency or those who require higher doses for therapeutic purposes is recommended by current scientific evidence.

Although dietary supplements can be easily available to consumers and be used on their own, vitamin D supplementation above the threshold allowed by national medicines regulatory authorities (usually >2000 IU/day) should always be prescribed and monitored by a physician or equivalent licensed healthcare professional. Before starting vitamin D supplementation, it is important to consider some health conditions that may affect the metabolism and effect of vitamin D in the body. Some of these conditions include:

Kidney disease: Since vitamin D is metabolized by the kidneys, people with kidney disease may have compromised absorption and utilization of vitamin D.

Liver disease: Vitamin D is transformed in the liver into an active form, so people with liver disease may not be able to produce sufficient amounts of active vitamin D.

Hypersensitivity to vitamin D: Some people may develop allergic or adverse reactions to vitamin D, so it is important to consult a doctor before starting supplementation.

Autoimmune diseases: Some autoimmune diseases, such as systemic lupus erythematosus and multiple sclerosis, may be influenced by vitamin D supplementation and therefore require careful medical evaluation before starting supplementation.

Inflammatory bowel diseases: Some inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, may affect the absorption and utilization of vitamin D.

Vitamin K2 and magnesium are relevant bioactive molecules in bone metabolism. In particular, vitamin K2 supplementation might reduce fracture risk in osteoporotic patients by improving bone quality, potentially increasing the efficacy of vitamin D and calcium supplementation [65,66].

In any case, it is always important to consult a doctor or qualified healthcare professional before starting vitamin D supplementation or any other dietary supplement. In particular, it

may be useful to contact a physician expert in personalized medicine to genetically type the entire vitamin D pathway and define a personalized nutraceutical strategy.

Before starting supplementation, the likelihood of hypersensitivity to vitamin D should be monitored if feasible (hypercalciuria, hypercalcemia, nephrocalcinosis, CYP24A1 gene mutation, nephrolithiasis, SLC34A1 gene mutation, or history of other hypersensitivities to vitamin D during the family anamnesis). This recommendation should be applied to all age groups and groups at risk for vitamin D deficiency. In patients with bone deformities, bone pain, a history of fragility fractures, or other skeletal symptoms, it is recommended to evaluate calcium–phosphate metabolism [alkaline phosphatase activity, PO4, Ca, PTH, urinary Ca/creatinine ratio,] and possibly bone mineral density [50,63].

## 6. Daily Dose vs. Bolus

Two main regimens for vitamin D supplementation are daily doses and bolus doses. Daily doses involve the intake of a fixed amount of vitamin D on a daily basis, whereas bolus doses involve the intake of a large dose of vitamin D at intervals ranging from weekly to annually. There is an ongoing debate about which method (daily dose or bolus) is more effective in terms of clinical outcomes. Daily vitamin D supplementation is a typical approach to improve vitamin D plasma levels and prevent deficiency-related health problems. Several studies have investigated the use of daily vitamin D supplementation in different populations and clinical contexts (Table 3) [67–69]. Bolus vitamin D therapy was also assessed in various populations, including patients with vitamin D deficiency, chronic kidney disease, and osteoporosis [5,70–72].

Several studies have investigated the effectiveness of vitamin D daily doses versus bolus doses in maintaining optimal vitamin D levels and health outcomes, but the results are mixed and often dependent on the specific population and dosing regimen studied. [5,73].

**Table 3.** Clinical trials of daily versus bolus dose of vitamin D supplementation.

| Year | Dose | Principal Effect | Outcome | Ref. |
|---|---|---|---|---|
| 2022 | Bolus dose 100,000 IU with 10,000 IU/week | Increase in serum calcidiol levels | Positive | [74] |
| 2011 | Daily dose (1600 IU or once-monthly (50,000 IU) | Increase in serum calcidiol levels | - | [75] |
| 2008 | Daily dose (1500 IU), weekly bolus dose (10,500 IU), or monthly bolus dose (45,000 IU) | Increase in serum calcidiol levels | - | [76] |
| 2017 | Daily dose (1000 IU), weekly dose (7000 IU), or monthly dose (30,000 IU) | Increase in serum calcidiol levels | - | [77] |
| 2020 | Daily dose, weekly dose, or bi-weekly dose | Increase in serum vitamin D levels | - | [78] |
| 2017 | Daily dose | Increase and maintenance of serum 25(OH)D levels | Positive | [79] |
| 2019 | Bolus dose | No reduction in total cancer mortality | Negative | [80] |
| 2022 | Daily dose | Reduction in total cancer mortality | Positive | [81] |
| 2022 | Bolus dose | No improvement in COVID-19 outcomes | - | [82] |
| 2018 | Daily dose or bolus dose | Increase in 25(OH)D3 levels and less diversion to 24,24(OH)2D3 | - | [83] |
| 2021 | Bolus dose | Downregulation of 1,25(OH)2D levels | - | [5] |

A recent randomized, triple-blind, controlled trial investigated the use of an oral bolus of 100,000 IU vitamin D3 or a placebo on 34 healthcare workers to analyze the change from the baseline in serum calcidiol and the proportion with vitamin D sufficiency (25(OH)D $\geq$ 75 nmol/L) at the endpoint. The results showed that vitamin D supplementation safely and rapidly increased calcidiol plasma levels, reaching sufficient levels [74].

Another study conducted in a university clinical research study randomly assigned 64 community-dwelling adults age 65+ to receive daily (1600 IU) or once-monthly (50,000 IU) vitamin D2 or vitamin D3 for 1 year. At baseline, 40% of subjects had serum calcidiol levels less than 30 ng/mL. Despite compliance of more than 91%, after 12 months of vitamin D dosing, 19% of subjects had still low vitamin D levels. Moreover, vitamin D2 supplementation increased 25(OH)D2 but produced a decline in 25(OH)D3. Overall, vitamin D3 was slightly but significantly more effective than vitamin D2 to increase serum calcidiol despite both daily and weekly bolus doses of vitamin D supplementation being equally effective in raising serum vitamin D levels over 12 weeks with similar safety profiles, highlighting how not all the subject could benefit from the same vitamin D regime [75]. A randomized, controlled trial in 48 women aged 81 $\pm$ 8 years old who had undergone hip fracture surgery randomly assigned to receive vitamin D3 supplementation at 1500 IU daily, 10,500 IU weekly, or 45,000 IU every 28 days with the primary outcome to measure the serum calcidiol concentration attained. Daily, weekly, and monthly bolus doses of vitamin D supplementation were equally effective in increasing serum vitamin D levels after two months of treatment [76].

A prospective, randomized clinical trial aimed to compare the efficacy and safety of daily 1000 IU, weekly 7000 IU, and monthly 30,000 IU doses of vitamin D3 for 3 months in 64 adults with vitamin D deficiency (calcidiol < 20 ng/mL). The study found that all groups had a dose response for increases in serum calcidiol statistically equivalent in terms of efficacy and safety profiles [77].

A recent study examined the safety and effectiveness of 3 different cholecalciferol supplementation schedules (daily, weekly, or bi-weekly) on healthy individuals with low calcidiol levels (<20 ng/mL) over a 12-week period. The doses administered were 10,000 IU/day for 8 weeks followed by 1000 IU/day for 4 weeks, 50,000 IU/week for 12 weeks, and 100,000 IU/every other week for 12 weeks. All subjects achieved normalized vitamin D levels rapidly and safely with similar calcidiol serum levels [78]. Overall, the analyzed literature consistently demonstrated how either a bolus dose of vitamin D or a daily dose can increase vitamin D plasma levels.

Interestingly, the healthy outcomes related to the use of daily versus bolus doses of vitamin D supplementation will be now analyzed.

A meta-analysis of 25 randomized, controlled trials involving 11,321 participants found that daily vitamin D supplementation was more effective than bolus doses in raising and maintaining serum 25-hydroxyvitamin D (25(OH)D) levels over a period of 2 to 24 months. The study concluded that daily doses of vitamin D were more effective in maintaining the optimal vitamin D status and preventing acute respiratory infections [79].

Another meta-analysis of randomized, controlled trials found that vitamin D supplementation was related to a significant reduction in total cancer mortality only with the daily dosing of vitamin D but not with the bolus doses [80]. Consistent with these results, a recent meta-analysis of randomized, controlled trials analyzing the relation between vitamin D supplementation and total cancer outcomes has highlighted for vitamin D supplementation, only daily dosing but not large-bolus dosing reduces total cancer mortality. Moreover, bolus dosing did not reduce the risk of total cancer incidence, and the benefits of daily dosing were limited to normal-weight individuals [81].

The COVID-VIT-D trial, a multicenter, open-label, randomized, international clinical trial conducted over 1 year in 543 patients older than 18 years, investigated if an oral bolus of cholecalciferol (100,000 IU) administered at hospital admission influences the outcomes of moderate–severe COVID-19 disease. Patients were followed from admission to discharge or death and the results showed no improvement in the outcomes of the

COVID-19 disease. Interestingly, in the cohort analyses, patients who had the highest serum calcidiol (>25 ng/mL) at admission presented a lower percentage of pulmonary involvement and better outcomes [82].

An interesting study on lactating mothers compared the effect of daily versus bolus vitamin $D_3$ dosing on vitamin $D_3$ catabolism. A single high dose of vitamin D resulted in higher production of 24,25(OH)2D3 compared to daily vitamin D supplementation with the effect persisting for at least 28 days after administration following a 14-day lag. This is likely due to the induction of the 24-hydroxylase enzyme (CYP24A1), which results in the downregulation of 1,25(OH)2D. However, in the long term, a daily dose of vitamin D may be more effective at increasing 25(OH)D3 levels and result in less diversion of 25(OH)D3 to 24,25(OH)2D3 compared to larger bolus dosing [83].

In fact, when vitamin D is present in excess, CYP24A1 is induced. This enzyme converts both 25-hydroxyvitamin D (25(OH)D) and 1,25(OH)2D to inactive metabolites. The upregulation of CYP24A1, therefore, results in a decrease in the concentration of active 1,25(OH)2D, which can have important consequences for immune function and other biological processes. This downregulation of 1,25(OH)2D is thought to be a feedback mechanism that prevents excessive vitamin D activation and calcium absorption, which can lead to hypercalcemia (high calcium levels in the blood) and other adverse effects. The downregulation of 1,25(OH)2D also has implications for the efficacy of vitamin D supplementation, particularly with bolus doses, which can cause a rapid but temporary increase in serum 25(OH)D levels followed by a decrease in 1,25(OH)2D levels due to the induction of CYP24A1 [5].

The concept that emerges from the provided information is that the use of large bolus doses of vitamin D may not always be beneficial and may even be counterproductive. On the contrary, lower or moderate daily doses of vitamin D may be more effective in improving musculoskeletal health, preventing respiratory infections, and reducing cancer mortality [83]. Furthermore, the use of bolus doses of vitamin D may be motivated by convenience and the presumed advantages in adherence compared to daily administration. However, this approach may be based on a misunderstanding of how vitamin D is activated and regulated in the body. Specifically, bolus doses of vitamin D may produce a rapid increase in 25(OH)D levels, but at the cost of downregulating cellular activation and immune factors. Conversely, a small or moderate daily dose of vitamin D may have superior intracellular effects and require frequent dosing due to its half-life of 20 h [83–85]. In conclusion, to achieve the best results for musculoskeletal health, prevention of respiratory infections, and reduction of cancer mortality, it may be necessary to consider lower or moderate daily doses of vitamin D instead of large bolus doses. Additionally, avoiding frequent use of bolus doses based on a misunderstanding of vitamin D regulation in the body may be helpful [83]. Overall, a bolus dose of vitamin D appears to be faster in increasing plasma vitamin D levels in some studies, although both modes lead to an increase in vitamin D after a certain interval of time. However, some evidence has shown that a daily dose is better at maintaining a healthy state and reducing the risk of disease, avoiding toxic effects or excessive induction of vitamin D catabolic enzymes.

## 7. Conclusions

Vitamin D is an indispensable nutrient with multifaceted roles in maintaining optimal health. Vitamin D deficiency is a widespread concern and has been linked to various pathologies. Whether daily or bolus doses are the most effective regimen for vitamin D supplementation remains a matter of ongoing debate. The evidence regarding the efficacy of daily vitamin D supplementation versus bolus doses is mixed despite the majority of nutritional guidelines recommending daily doses. While some studies have found daily doses to be more effective in maintaining optimal vitamin D levels and improving health outcomes, others have found bolus doses to be more effective in raising vitamin D levels, at least in the short term. Bolus therapy also has some limitations. One potential limitation is the risk of toxicity, as high doses of vitamin D can lead to hypercalcemia,

hyperphosphatemia, and other adverse effects. Another limitation is the potential for rebound hypovitaminosis D where vitamin D levels decrease rapidly after the bolus dose is administered. Additionally, the optimal dose and timing of bolus vitamin D therapy are not well established and may vary depending on the population and clinical context. Collectively, bolus vitamin D therapy can be an effective approach to rapidly improve vitamin D status in certain populations. However, its use should be carefully considered, and its limitations, including the potential for toxicity and rebound hypovitaminosis D, should be taken into account.

Another crucial point is whether 25-hydroxyvitamin D (25(OH)D), the main metabolite of vitamin D found in circulation commonly used as a biomarker to assess vitamin D status, requires additional associated measurements. In fact, other metabolic pathways are acknowledged to play a significant role in vitamin D function, and measuring additional metabolites may become necessary in the future. It is also relevant to further evaluate the usefulness of free 25(OH)D instead of total 25(OH)D.

The available evidence suggests that both daily and bolus doses of vitamin D supplementation can effectively raise serum vitamin D levels. However, the optimal dosing regimen may depend on the specific clinical outcome being targeted. For long-term maintenance of vitamin D levels and disease risk reduction, daily dosing may be preferable, while bolus dosing may be more suitable for rapidly increasing vitamin D levels in certain populations due to its convenience and effectiveness. It is critical to note that excessive vitamin D supplementation, regardless of the dosing regimen, can cause toxicity and adverse effects. Therefore, monitoring vitamin D levels and seeking advice from a healthcare professional before initiating any vitamin D supplementation regimen is essential.

Therefore, further research is needed to establish the most effective and appropriate vitamin D biomarkers to be measured and the optimal supplementation strategy. A daily dose may collectively represent an optimal regimen for vitamin D supplementation with limited adverse effects and good compliance. A personalized daily dose considering all genotypic and phenotypic influencing factors is thus crucial to promote optimal vitamin D status and overall health.

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